Micronutrient Intervention Effects on Cognitive Outcomes in Post-Acute Traumatic Brain Injury

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2. None of the material contained in the thesis has been used in any other submission for an academic award.

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Abstract

Traumatic brain injuries result in a complex pathophysiological cascade that includes neuroinflammation, cellular energy dysregulation and axonal injury (Werner & Engelhard, 2007). Nineteen essential vitamins and minerals, along with omega-3 polyunsaturated fatty acids, are required by the body for competent cellular function. These cannot be synthesized by the body and must therefore be ingested either as part of the diet or through supplementation. Previous research has highlighted a relationship between micronutrient (vitamins, minerals, omega-3) levels and cognition in a range of neurological conditions (Bitarafan et al., 2014; Moore et al., 2012; Veronese et al., 2016), however there is very little research in post-acute traumatic brain injury (TBI). The aims of this thesis were to investigate the effects of micronutrient supplementation on cognition in both a normative and a TBI population, while also gaining an insight into the levels of micronutrients present in the diets of these participants. In the TBI population the hypothesis was that by nutritionally supporting these individuals this would improve cellular functioning and neuronal repair following injury, reducing the effects of ongoing secondary cascade mechanisms, with improved cognitive function as the outcome. Study one (normative study) demonstrated significant improvements in cognition, specifically memory and executive functions, following a relatively short eight-week intervention period, particularly in those taking a broad-spectrum multimicronutrient. Study two (TBI population) used a cross-over study design (omega-3 and multimicronutrient) with parallel placebo group. The omega-3 intervention consistently resulted in improved learning, attention, processing speed and set shifting, whereas improvements following the multimicronutrient intervention were more limited. Analyses of food diaries from participants in both studies indicated that levels of fat-soluble vitamins, some B vitamins, and minerals are below recommended intake in diet. Results of these studies indicate that micronutrient interventions can result in cognitive improvement in a relatively short period of time. This evidence provides a solid foundation for future micronutrient research in TBI populations which have the potential to serve as an adjunct to traditional rehabilitation strategies.

Table of Contents

Chapter One

Chapter Two

Chapter Eight

List of figures

List of Tables

Preface

Traumatic brain injuries (TBI) have life-long consequences for an individual's ability to successfully maintain aspects of daily life including education, work, and inter-personal relationships (Ponsford et al., 2012). These cognitive-behavioural changes can be partially attributed to initial injury severity but are also dependent upon a wide range of other factors including age, pre-injury cognitive ability, psychosocial coping style, plus the secondary biochemical cascade (Ponsford, 2013). The secondary cascade consists of a complex interplay of metabolic crises, including excitotoxity, oedema, neuroinflammation, oxidative stress, and axonal injury (Giza & Hovda, 2014). The function of this response is to isolate the region of damage preventing spread of toxic material and to recruit reparative mechanisms (Finnie, 2013). When these mechanisms are protracted (secondary cascade processes may be active up to 17 years post-injury - Ramlackhansingh et al., 2011), additional damage is caused to brain tissues, with the possibility that cognitive and behavioural functions are negatively affected. The extended nature of the secondary cascade however offers clinicians the opportunity to intervene to potentially reduce negative outcomes by diminishing or halting secondary cascade mechanisms.

Biochemical processes underlying normal neuronal functioning, including cellular energy production and myelin maintenance and repair, require adequate intake of micronutrients (vitamins, minerals, and omega-3 polyunsaturated fatty acids) from diet or supplements. Following TBI metabolic rate increases utilizing micronutrient stores; it is therefore important that nutritional intake is sufficient to meet increased demands to replace depleted stores and to support on-going reparative processes. Research investigating the nutritional requirements of individuals in the acute phase following TBI has contributed to improved patient outcomes. There is, however, a lack of research investigating nutritional factors in recovery from TBI in the post-acute period. This is despite research in animal models of TBI and in other neurodegenerative conditions (e.g. dementia, multiple sclerosis) indicating that supplementation with micronutrients has neuroprotective and neuroreparative effects. There have also been calls from a number of areas including the US military, health professionals, head injury charities, and academics to conduct micronutrient research in TBI populations. Supplementing micronutrient intake in TBI offers the potential for a low-cost adjunct to traditional rehabilitation

strategies, supporting neuronal recovery and as a consequence potentially improve cognitive outcomes.

This programme of doctoral research investigates the use of vitamin, mineral and omega-3 supplements in post-acute TBI with the intention of identifying potential improved cognitive functions. Prior to the clinical study a normative study was undertaken to provide a comparative baseline and to inform methodology with both studies using an eight-week supplementation period. Both studies used test/retest of a broad battery of cognitive measures to identify effects of supplementation on task performance. The TBI study had a matched placebo group to account for any learning or spontaneous recovery effects in the TBI population. A crossover study design was utilised for the clinical study with a washout period between intervention periods and a placebo group running in parallel. Participants completed food diaries during intervention periods to gain an insight into dietary micronutrient intake of participants to allow for comparison between groups regarding daily intake levels.

The literature review of this thesis, Chapter One, will explore the epidemiology of TBI and the mechanisms underlying the initial brain injury, the secondary biochemical cascade and cell death. Chapter Two will review the thirteen essential micronutrients and omega-3 PUFAs important for neuronal function. The methodology and procedure for the normative study will be presented in Chapter Three with the results and summary of the normative study in Chapter Four. Chapter Five will describe the TBI patient demography followed by the methodology and procedure of the TBI study in Chapter Six and findings and summary of this research in Chapter Seven. Finally, Chapter Eight will discuss the overall conclusions arrived at from this programme of research with a reflection on limitations before ending with a discussion of future directions for the research.

Chapter One: Traumatic Brain Injury and Cellular Function

1.1. Traumatic Brain Injury

Traumatic brain injuries (TBI) arise as the result of a sudden force impacting the head; in 2016-2017 there were 156,000 admittances to accident and emergency departments with a diagnosis of TBI in the United Kingdom with males one and a half times more likely than females to sustain a traumatic injury (Headway, 2020). Similarly, in 2014, approximately 2.8 million people were seen in hospital emergency departments in the United States following a TBI, either as an isolated injury or in combination with other trauma (Centres for Disease Control and Prevention, 2019). Epidemiology statistics for traumatic brain injury, however, are based on varying administrative criteria and it is therefore difficult to obtain an accurate picture of numbers affected, both nationally and worldwide (Roozenbeek et al., 2013). Across Europe the most prevalent causes of TBI are motor vehicle accidents and falls, with assaults and being struck by or against an object other major causes (Peeters et al., 2015; Tagliaferri et al., 2006). Epidemiology is also affected by age, with older persons more likely to sustain a TBI following a fall compared with younger age groups except for children and adolescents (Roozenbeek et al., 2013). Another leading cause of head injury in the general population is sports participation, with research indicating that between 15% to 21% of head injuries are sports related (Beck & Kerr, 2011; Theadom et al., 2014). The greater body of sports research focus has been on contact sports, for example American football, rugby and boxing (Asplund & Best, 2015; Kirkwood et al., 2015) and the occurrence of delayed neurodegeneration in individuals engaged in these sports. This has led to further research into sports traditionally viewed as non-contact where blows to the head occur (for example football) to ascertain whether repetitive mild concussive or sub-concussive injuries result in neurodegenerative pathology at a later time point (Gandy et al., 2014; Hales et al., 2014; Koerte et al., 2015). Following recent armed conflicts and the increased use of explosive devices by enemy combatants, service personnel are also a population with high incidence of TBI. In large cohort studies 12% to 15% of United States (US) service personnel report mild to moderate head injuries (Hoge et al., 2008; Schneiderman et al., 2008) with over 56,000 US personnel acquiring some level of TBI in field operations during 2008 and 2009 alone (Fischer, 2010). In summary, TBI at all levels of

severity leads to neuropathology resulting in great cost to both the individual and wider society.

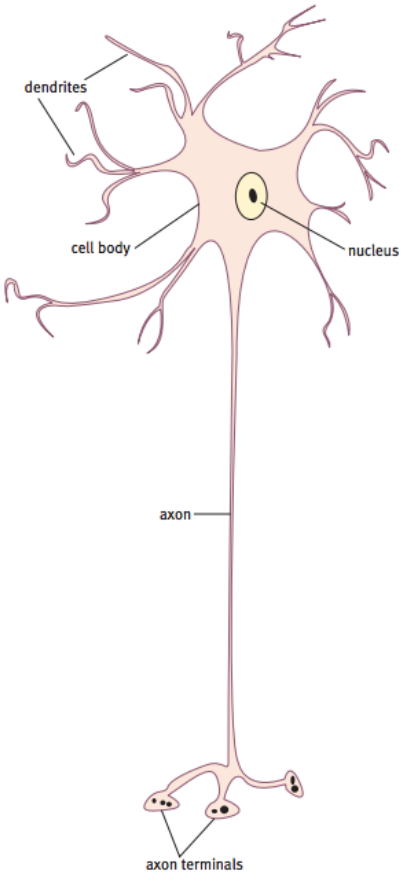
Traumatic insult to the brain leads to a complex pathophysiological chain of events. The immediate consequences of the acceleration and deceleration forces during impact are a combination of translation (coup and contrecoup) and rotation injuries in association with mechanical strain (Ponsford et al., 2012). The resultant primary injury produces a non-uniform distribution of focal and diffuse contusions, lacerations, axonal injury and haematoma (Povlishock & Katz, 2005; Werner & Engelhard, 2007) and severity of primary injury reflects force of impact. These primary injuries initiate a secondary cascade of cellular changes including oedema, neuroinflammation and diffuse axonal injury (Donkin & Vink, 2010; Finnie, 2013; Johnson et al., 2013). This results in an ongoing disease process (Masel & DeWitt, 2010). To fully understand the significance of these pathophysiological changes it is necessary to briefly illustrate normal cellular function.

1.2. Structure of normal neurons and glial cells.

Neurons and glia have organelles common to nearly all cells of the body. These basic cellular structures are enclosed in the soma, or cell body and have been extensively studied. Neurons and glia refer to broad categories of cell differentiated in terms of structure, neurochemistry, and function (Barres, 2008; Masland, 2001; Mountcastle, 1997). Glia constitute at least fifty percent of brain volume providing support, insulation, nourishment, and release of a number of neuromodulatory molecules (Barres, 2008; Fields et al., 2015). Neuronal populations (nodes) interact to process information from the internal and external environment as part of functional networks, formulating and executing responses (Park & Friston, 2013). Analyses of the process of functional integration continues to be investigated in order to gain a more in depth understanding of how they co-ordinate to facilitate cognition. See Figure 1.1 for basic diagram of a neuron.

Figure 1.1

Basic Neuronal Structure [Reprinted from Watson et al., (2010) with permission from Elsevier]



1.2.1. Soma

The cell body (soma) of a typical neuron has a roughly spherical diameter of 20µm. The neuronal membrane acts as a barrier separating the cytosol (a potassium-rich salt solution) and organelles from the extracellular space (Bear et al., 2007). The functional organelles of the neuron include the nucleus, mitochondria, rough and smooth endoplasmic reticulum and Golgi apparatus. Collectively these organelles (minus the nucleus) are referred to as the cytoplasm.

1.2.2. Nucleus

Centrally located within the soma the nucleus is a spherical structure containing tightly packed bundles of deoxyribonucleic acid (DNA), termed chromosomes. The nucleus is surrounded by the nuclear envelope composed of an inner and outer membrane separated by the perinuclear space. The membranes of the nuclear envelope are embedded with nuclear pore complex (NPC) forming channels for the tightly regulated nuclear transport mechanism (Cohen et al., 2011). Within the nucleus is a smaller structure (the

nucleolus) responsible for ribosome[1] production and pre-ribosomal ribonucleic acid (rRNA) assembly (Hetman & Pietrzak, 2012). Chromosomes are responsible for cellular gene expression through the process of transcription. Activator proteins bound to enhancer regions on the DNA sequence come into contact with the initiation complex and release the copying mechanism to synthesise a strand of messenger RNA (mRNA). Messenger RNA is then transported to the cytoplasm through the nuclear envelope to ribosomes for translation into polypeptides (building blocks of proteins) (Cramer et al., 2001). Errors in the transcription process occur regularly and are propagated repeatedly through translation, creating epimutations that generally do not result in long term damage to the individual, due to the transient nature of the mRNA strands (Gordon et al., 2015). Mutations in DNA caused by exogenous (e.g radiation) and endogenous (e.g. attack by reactive oxygen species[2]) factors and normal aging occur under normal physiological conditions and are often repaired. DNA damage has the potential to permanently affect neural function and has implications for neurodegenerative processes (Cornelius et al., 2013).

Although the nuclear transport mechanism is tightly regulated, designed to only allow import of vital cellular proteins and export of mRNA strands, viruses have evolved to take advantage of this process in a number of different ways (Cohen et al., 2011). The human immunodeficiency virus 1 and influenza A disassemble their cellular contents within the cellular cytoplasm. These cellular contents contain protein markers that enable them to be transported through the nuclear envelope where the viral RNA is replicated (Engelhardt & Fodor, 2006). Other more complex viruses, for example herpes viruses, fuse their capsid envelope to the cytoplasm side of the NPC, releasing their DNA into the nucleus where it is replicated (Roizman & Furlong, 1974; Roizman & Zhou, 2015).

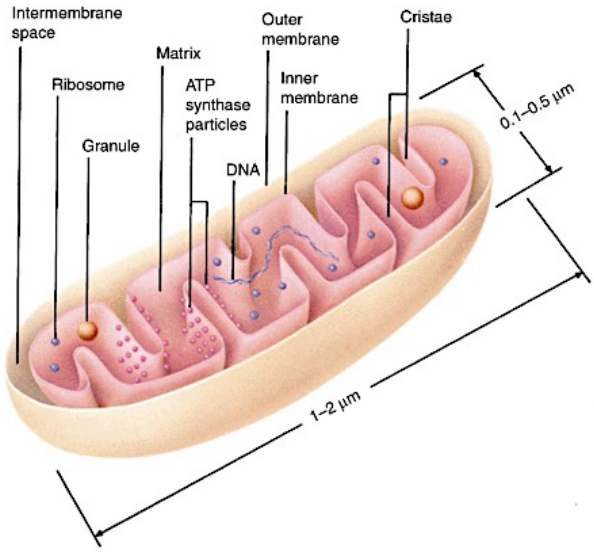
1.2.3. Mitochondria

Mitochondria are one of the most abundant organelles in the cytoplasm and are responsible for cellular respiration (see Figure 1.2).

[1] Organelles responsible for the assembly of cellular proteins
[2] Chemically reactive molecules or ions containing oxygen

Figure 1.2

Structure of Mitochondria [Reprinted from Frey & Mannella (2000) with permission from Elsevier]



Pyruvate, produced during glycolysis, is converted to acetyl-CoA and carbon dioxide (CO_2) via pyruvate decarboxylation. The acetyl-CoA then enters the Krebs cycle (Krebs & Johnson, 1937a; Krebs & Johnson, 1937b) where it is fully oxidized to CO_2 and H_2O, producing nicotinamide adenine dinucleotide hydride (NADH). The NADH is then oxidized to NAD^+ via the electron transport chain within the mitochondrial cell membrane, creating a hydrogen ion gradient across the inner membrane. This proton gradient produces 2.5 adenosine triphosphate (ATP) molecules for every NADH oxidized through oxidative phosphorylation (Chance & Williams, 1955), the chemical energy stored in ATP fuelling most cellular biochemical reactions (Atkinson, 1968). Proteins required for oxidative phosphorylation and for the assembly of transfer RNA (tRNA) and ribosomal RNA (rRNA) are manufactured within the mitochondria from mitochondrial DNA (mtDNA) (Taylor & Turnbull, 2005). The mitochondrial respiratory chain is the major source of components involved in reactive oxygen species (ROS) production within the cell and is protected from damage by antioxidant factors (including vitamins C and E), however under conditions of cellular stress, for example inflammatory processes, antioxidants are not able to maintain levels of protection (Richter, 1995). Mitochondrial DNA is more susceptible to damage by ROS compared to nuclear DNA as it is not packaged with histones (proteins) and is transiently located on the internal mitochondrial membranes in close proximity to ROS production (Richter, 1995). Damage to the structure of the mitochondria or perturbations of the underlying processes within them result in diminished cellular energy production in the form of ATP.

1.2.4. Endoplasmic reticulum

Contiguous with the nuclear envelope is the rough endoplasmic reticulum (rER) formed from interconnected stacks of cisternae and microtubules studded with ribosomes (protein molecules). The quantity of rER found in neurons is much greater than in glia or non-neuronal cells and is the main site of protein synthesis in all cells (Mandon et al., 2013). Messenger RNA (mRNA) carrying RNA transcripts bind to the ribosomes where the instructions are translated and assembled into polypeptides for protein assembly. Major groups of proteins synthesized in the rER include secretory proteins (including many hormones and enzymes), proteins for use within the ER and associated organelles (e.g. Golgi apparatus, nuclear envelope, lysosomes) and integral membrane proteins (Mandon et al., 2013). Soluble proteins for use within the cell cytosol are formed slightly differently, utilising free-floating ribosomes or ribosome strings (polyribosomes) (Lerner et al., 2003).

Maintenance of protein homeostasis (proteolysis) is crucially important for the health of both the cell and the whole organism. The number of possible protein chain conformations is very large, as a consequence folding reactions are complex and heterogeneous. Protein chains longer than 100 amino acids (around 90% of all human cell proteins) are susceptible to collapse into disorganized globular confirmations and therefore require 'chaperones' to guide them into the correct form (Kerner et al., 2005). As these proteins are upregulated during periods of cellular stress they are often referred to as stress proteins (or heat-shock proteins) and are involved in a number of different roles including de novo protein folding, refolding of stress denatured proteins and the degradation of faulty, damaged or surplus proteins through the ubiquitin-proteasome system (Hartl et al., 2011). Chaperone-mediated folding pathways and networks are supported by ATP-dependant and co-factor regulated binding and release cycles (Hartl et al., 2011). During conditions of cellular stress, seen for example in rising levels of unfolded or misfolded proteins in the lumen (the internal space of the rER), the unfolded protein response (UPR) signalling network acts to regain cellular proteolysis (Hetz & Mollereau, 2014). These stress networks switch off on-going protein synthesis, upregulate the production of chaperones, induce apoptosis (programmed cell death) and activate aspects of the inflammatory response (Berridge, 2002) and can prove fatal for the cell.

Similar in appearance to rough ER but without ribosomes, smooth endoplasmic reticulum (smooth ER) is contiguous with rough ER. Composed of a tubular network smooth ER is involved in lipid homeostasis (including the production of arachidonic acid

and metabolites) and hormone production. Smooth ER also has a vital role in many signalling processes, particularly calcium homeostasis. Smooth endoplasmic reticulum extends throughout the neuron, including into dendritic spines (Berridge, 2002; Westrate et al., 2015). Most cellular calcium accumulates within the lumen of the smooth ER as a dynamic store for signalling responding to growth factors, hormones, and changes in the internal cell state including function of the chaperone system and reduction-oxidation reaction (redox) states (Zhang & Kaufman, 2008). As ER stores are finite, signalling depends on an efficient recycling and replenishment mechanism mediated by sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) (Kaufman & Malhotra, 2014). Mitochondria also play a key role in maintenance of calcium homeostasis, acting as a buffer to prevent overload of the cytosol following calcium release, rapidly sequestering and returning it to the ER via mitochondria-associated ER membranes (MAMs; Kaufman & Malhotra, 2014). Imbalance caused by movement of calcium from the ER to the mitochondria results in the initiation of the stress response and also activation of permeability transition pore (PTP) formation, contributing to apoptosis (Berridge, 2002).

1.2.5. Golgi apparatus

In vertebrate cells the Golgi apparatus (or Golgi complex) characteristically comprises flattened membrane discs forming stacks termed cisternae (compact zones) laterally connected by tubulovesicular regions (non-compact zones) to form a continuous ribbon-like structure (Mogelsvang et al., 2004). The Golgi apparatus can be divided into three main compartments; the *cis*-, medial and *trans*-Golgi with movement of cargo[3] in a *cis*- to *trans*- direction (De Matteis & Luini, 2008; De Matteis & Rega, 2015). The Golgi complex is a self-organizing organelle undergoing continual change requiring a constant supply of energy to maintain structure. Without this supply of energy the Golgi complex collapses and rapidly diffuses into the cytoplasm (Karsenti, 2008; Lowe, 2011). The complex is often situated near the nucleus, adjacent to the centrosome[4] and endoplasmic reticulum to facilitate its function as the primary site for post-translational modification, processing and transport of proteins and lipids (Guo et al., 2014) .

Proteins and lipids are transferred from the ER to the *cis*-Golgi via vesicular-tubular clusters (Brandizzi & Barlowe, 2013). The two major classes of lipids processed by the Golgi are glycerophospholipids (GPLs) and sphingolipids (SLs), which transit

[3] Cellular products

[4] Site of cytoskeletal structure production

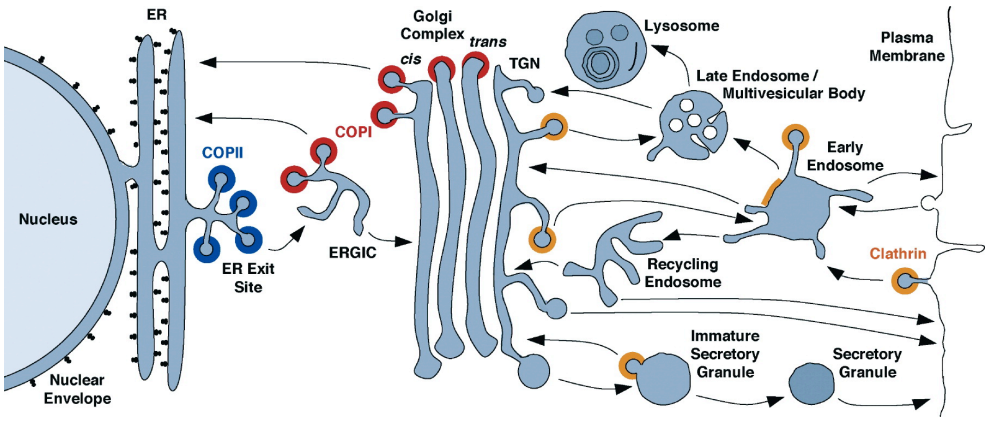
through the Golgi in distinctly different ways. GPLs are synthesized in the ER and are then carried to the Golgi through a forward secretory transport mechanism with a complementary retrograde trafficking route for recycling of products (Bonifacino & Glick, 2004). SLs are synthesised in the Golgi itself, with precursors transferred directly from the ER by a lipid carrier protein (Halter et al., 2007; Van Meer et al., 2008).

Proteins and lipids processed in the Golgi apparatus are sorted and exit the complex via the trans-Golgi network (TGN) (Guo et al., 2014), a tubular and reticular compartment continuous with the *trans* cisternae. During this sorting process coating proteins, often utilizing clatherin or clatherin polymers to form electron dense structures, cover cargo vesicles containing processed proteins and lipids (see Figure 1.3). This vesicle formation results in TGN membrane deformation and budding, the coat structure allowing for directing of proteins and lipids to correct targets for efficient physiological functioning (Guo et al., 2014).

In addition to protein and lipid processing the Golgi complex also plays a role in calcium uptake and storage, storing up to five percent of cellular calcium (Chandra et al., 1991). This role is not fully understood, but the level of calcium seems to be held in a steady state through the combined activity of a ER calcium ATPase (SERCA) and another calcium pump, calcium ATPase (SPCA1; Pizzo et al., 2011).

Figure 1.3

Sorting of Proteins in the Trans-Golgi Network [Reprinted from Bonifacino & Glick (2004) with permission from Elsevier]



All the previous organelles are common to the majority of cells in the human body; neurons and glia however have other more specialised structures specific to the 'excitable' function of these cells.

1.2.6. Neuronal membrane

The outside membrane of the neuron, termed the neuronal or plasma membrane, is a selectively permeable barrier enclosing the cytoplasm with very high electrical resistance and capacitance properties (Alberts et al., 2013; Lehninger, 1968). The membrane is approximately 5 nm thick, composed of a phospholipid bilayer with apposing continuous hydrocarbon chains. These chains are comprised of a hydrophilic polar head in contact with the extracellular fluid and a hydrophobic non-polar tail in contact with the intracellular fluid; on either side of the phospholipid bilayer is a monolayer of protein (Robertson, 1959). The neuronal membrane is studded with lipids and proteins, some of which are configured to form pores involved in the controlled transit of ions (sodium, potassium and calcium) between the intracellular and extracellular environments through either active or passive transport mechanisms (Brini et al., 2014; Gulledge et al., 2013; Jensen et al., 2012; Mosgaard & Heimburg, 2013). Due to differing functions of neuronal sub-compartments the distribution of protein structures varies (Nusser, 2012); dendrites have high aggregations of ligand-gated ion channels for reception and transduction of chemical messengers from other cells (Higley & Sabatini, 2012) whereas myelinated axons have concentrations of voltage-gated ion channels focused on the axon initial segment and at nodes of Ranvier to allow for efficient signal propagation (Yoshimura & Rasband, 2014). Coherence of the neuronal membrane is crucial to maintain integral cell functioning and segregation of internal and external cellular environments. Plasma membrane disruption as a consequence of trauma results in disruption to the regulated ion flux, apoptosis, and oxidative damage, and swift repair is crucial to regain cellular function (Hendricks & Shi, 2014) .

1.2.7. Cytoskeleton

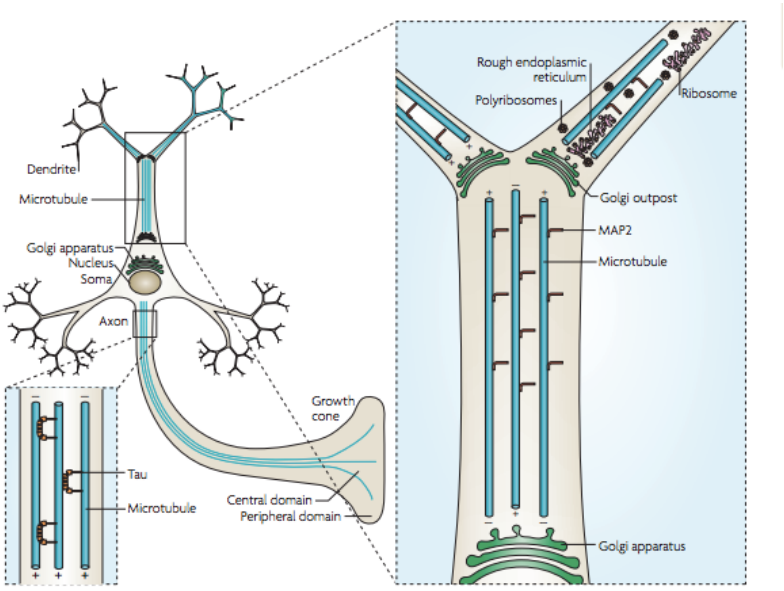
Within neurons are several tube-like support structures; microtubules, microfilaments and neurofilaments. These structures are dynamically regulated, changing in accordance to the needs of the cell.

1.2.7.1. Microtubules.

Microtubules are the largest of these structures formed from interlaced strands of tubulin (Millecamps & Julien, 2013; see Figure 1.4).

Figure 1.4

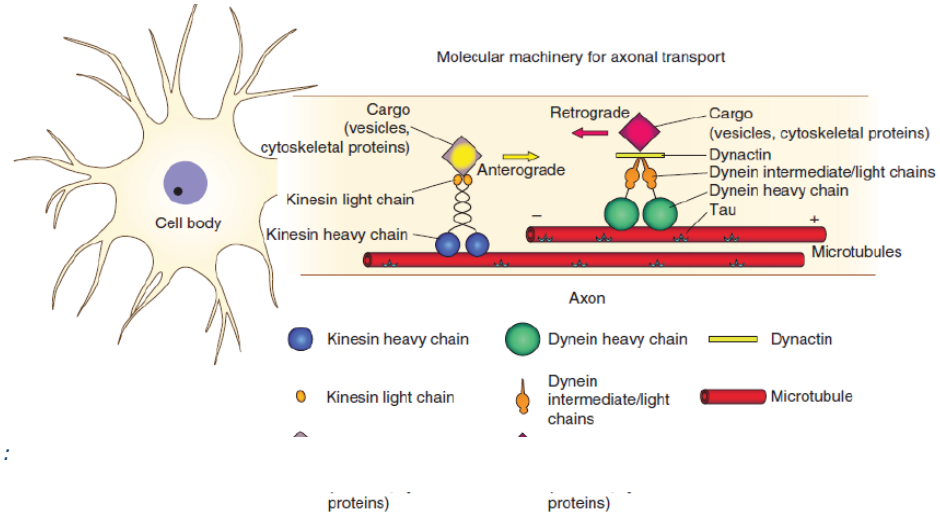
Microtubule Structure within the Axon {Reprinted from Conde & Cácares (2009) with permission from Springer]



The most important role of microtubules is to provide a 'track' for axonal transport of mitochondria, lipids, synaptic vesicles, proteins, and other organelles to and from the neuronal cell body (see Figure 1.5). Axonal transport is also involved in clearance of recycled and misfolded proteins to avoid build-up of toxic products. Microtubules are polarized within axons, with the minus end (slower growing) facing the soma and the positive end (faster growing) facing the end of the axon (Millecamps & Julien, 2013). Cargo is transported via specific axonal motors in anterograde and retrograde directions along microtubules at differing speeds dependent upon contents. Transport occurs as a combination of rapid movements, pauses, and direction shifts, with average speed of transport reliant on length of cargo pauses. The constant movement of transport along microtubules often results in 'traffic jams' where microtubules become clogged with transported materials (Maday et al., 2012; Roy et al., 2000; Wang et al., 2000).

Figure 1.5

Axonal Transport [Reprinted from Roy et al., (2009) with permission from Elsevier]



Axonal transport takes two forms: fast axonal transport responsible for transit of membrane-bound organelles (e.g. vesicles and mitochondria) and slow axonal transport responsible for movement of cytoplasmic and skeletal proteins (e.g. enzymes, microtubules and neurofilaments) (Lasek et al., 1984). Anterograde transport (towards the synapse) conveys proteins, lipids and mitochondria, supporting distal nerve terminal function and neurotransmitter release (Millecamps & Julien, 2013). Retrograde transport (back to the soma) involves transit of misfolded and aggregated proteins, intracellular signals, and the recycling of proteins involved in neuronal transmission, functions essential for maintenance of neuronal homeostasis (Bisby, 1982; Moughamian et al., 2013) .

ATP-powered molecular motors, kinesins (mainly anterograde movement) and dyneins (mainly retrograde movement) facilitate movement of cargo along microtubules. Kinesins attach their two-part motor domain to microtubules and tail regions to cargo, then 'walk' along the microtubules (Hirokawa et al., 2010); one head of the motor domain remains bound to the microtubule, hydrolysing ATP, to allow the other head to move towards the plus end of the microtubule (Millecamps & Julien, 2013). Dyneins, although differing in structure to kinesins, function in a similar way. Dyneins are a multi-subunit complex; an ATPase-utilizing globular motor domain binds to microtubules via coiled-coil stalks, one stalk remaining bound to the microtubule while the other detaches and reattaches to allow the complex to 'walk' along the microtubule (Millecamps & Julien, 2013) with cargo bound to the dynein complex by an extended tail structure (Carter, 2013).

Many viruses hijack these mechanisms to gain access to the nucleus, for example the herpes simplex virus utilizes the microtubule network to move towards the nucleus for transcription and replication. To achieve this the herpes simplex virus capsid has to change polarity, moving by retrograde transport to the centrosome then switching microtubules to move by anterograde transport to the nucleus (McElwee et al., 2013). Following replication, the herpes simplex virus is then carried back to axon terminals (Ibiricu et al., 2011). Other viruses utilize similar pathways to invade the central nervous system including rabies (Gluska et al., 2014) and the human immunodeficiency virus (Berth et al., 2015).

Loss of microtubule structural integrity is a feature of many neurodegenerative tauopathies (for example Alzheimer's Disease, Parkinson's Disease, fronto-temporal dementia), whereby the microtubule-associated protein tau becomes abnormally phosphorylated (Irwin et al., 2013; Spillantini & Goedert, 2013; Wang & Liu, 2008). The mechanism by which this occurs is not universally agreed (Kneynsberg et al., 2017). The current general consensus is that dissociation of tau from microtubules occurs first, resulting in increased sensitivity to the action of microtubule severing proteins that act by removing tubulin subunits. This is thought to cause disassembly of the microtubule, consequently disrupting cellular cargo transport mechanisms (Jean & Baas, 2013; Roll-Mecak & Vale, 2008), and communication between neurons, although this varies for different pathologies (Kneynsberg et al., 2017).

1.2.7.2. Other support structures.

Microfilaments are the narrowest structures of the cytoskeleton, formed into rope-like strands from the polymer actin. A mesh of proteins lines the inside of the neuronal membrane anchoring the microfilaments as they run longitudinally down the neurite. Microfilaments are responsible for formation of all projections from the cell, including axons and phagocytic protrusions[5], and are also able to form contractile bundles providing motility to some classes of organelle (e.g. macrophages [6] and neutrophils [7]). Neurofilaments are hollow and composed of longitudinal coils of a number of different protein strands making them mechanically strong. This strength is used to form bridges within axons and dendrites to control the diameter of the structure, ensuring efficient neurotransmission (Yuan et al., 2012).

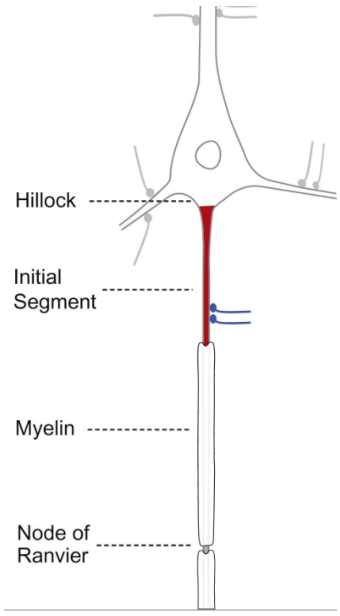
[5] Projections from the cell that surround and dispose of waste or toxins
[6] Engulf and digest cellular debris
[7] One type of white blood cell

1.2.8. Axon

Extending from the neuronal soma is a long process termed the axon, specialised for the transfer of information over distance in the nervous system. Axons vary in length from 1µm to over a metre, with diameters of 1µm to 25µm axonal width related to speed of nerve impulse; the broader the axon the faster the signal (Alberts et al., 2013). Each nerve cell has one primary axon which can branch off into numerous axon collaterals particularly in the reticular formation, a highly interconnected area of the brainstem (Humphries et al., 2006; Palay et al., 1968). The neuronal soma tapers to form the axon hillock, differentiated from the soma by the absence of Nissl staining due to lack of rough endoplasmic reticulum and sparsely dispersed clusters of free ribosomes and polysomes (Palay et al., 1968; see Figure 1.6). Protein synthesis does not therefore take place within the axon and so any required proteins are transported from the soma via axonal transport mechanisms (Lasek et al., 1984).

Figure 1.6

Position of Axon Hillock and Initial Segment *[Reprinted from Kole & Stuart (2012) with permission from Elsevier]*



Between the axon hillock and the start of axon myelination (if present) is the axonal initial segment (AIS). The AIS is characterised by clustering of microtubules from the soma into fascicles (bundles) and the presence of a dense granular layer or undercoating beneath the plasma membrane (Palay et al., 1968). The specific function of this granular layer is not fully understood but is thought to reflect the high density of voltage-gated channels within this segment, in combination with specialised anchoring proteins involved in the generation of action potentials (Kole & Stuart, 2012). The AIS

also plays a key role in regulation of synaptic input integration, intrinsic excitability and neurotransmitter release (Debanne et al., 2011; Rasband, 2010) with concentrations of AIS sodium, potassium and calcium voltage-gated ion channels being highly neuron-type specific (Bender & Trussell, 2012). Action potential generation is initiated in the AIS in most cases; the comparatively narrow diameter of the AIS means that capacitance of this segment is small and so requires less inward current to generate an action potential and is thus able to support rapid membrane potential changes (Kole & Stuart, 2012). Orthodromic signal propagation within the axon travels away from the soma to the axon terminal in a series of action potential spikes. Resting potential of an axon is -70mV, maintained by the sodium/potassium pump moving ions against their concentration gradient (from areas of low concentration to high concentration).

Arrival of a stimulus of sufficient magnitude causes the membrane potential to become more positive, causing voltage-gated sodium channels to open. Voltage-gated potassium channels begin to open at 0mV to +30mV; depolarization occurs as more sodium flows into the axon than potassium moves out. At maximum depolarization (at approximately the same voltage required for full opening of the potassium gates; +30mV) the sodium channels become deactivated and begin to close. Potassium voltage-gated ion channels close more slowly than sodium channels, therefore too much potassium diffuses out, resulting in hyperpolarization. The time period during which the membrane is hyperpolarized is termed the 'refractory period', when no action potential can occur. The membrane is returned to resting potential through the action of the sodium/potassium pump, a metabolically expensive process (Hodgkin & Huxley, 1952). The signal propagation occurs as this process is repeated in the following section of neuron. In myelinated neurons propagation is faster as fatty myelin acts as an insulator for the signal, preventing voltage seepage, the signal regenerated at gaps in myelin termed the nodes of Ranvier (Moolenaar & Spector, 1979).

At the end of the axon the fibre splits into varying numbers of endpoints (an axonal arbour) that terminate in a bulb referred to as the terminal bouton or axon terminal. Terminal boutons end in synapses that fire on dendrites, soma, glial cells and other axons, facilitating communication within the nervous system (Gray, 1959; Schmitz et al., 2001; Shen et al., 2012). The structure of terminal boutons differs in a number of ways from the main body of the axon; the microtubules that extend the length of the axon terminate as the axon swells to form the bouton, mitochondria proliferate to reflect the high energy demands of the processes which occur within this structure (Sheng, 2014), and electrical

impulses transmitted down the axon are converted to a chemical signal in the form of neurotransmitters.

Neurotransmitters in terminal boutons are either transported to the site by axonal transport mechanisms or manufactured within the terminal bouton from precursors and stored in synaptic vesicles, small bubbles of membrane found on the inside surface of the bouton facing the synapse. When an action potential arrives at the synapse the plasma membrane is depolarized causing calcium channels to open, triggering exocytosis of synaptic vesicles and release of neurotransmitter cargo into the synaptic cleft where they are utilized by target membranes (Südhof & Rizo, 2011). Following neurotransmitter release both the vesicles and neurotransmitters are recycled and repackaged for re-use (endocytosis). This process is slower than exocytosis and can result in the synapse becoming 'exhausted' (Eulenburg & Gomeza, 2010; Hori & Takahashi, 2012; Melikian, 2004).

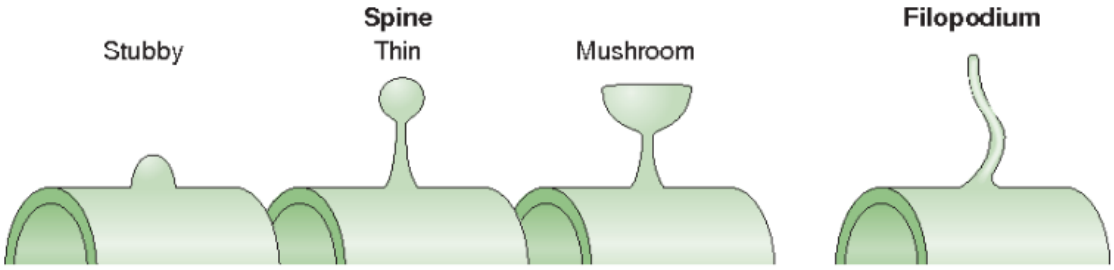
1.2.9. Dendrites

Extending from the neuronal soma are many projections, the dendrites. These can be structurally differentiated from axons, being typically shorter with a tapered shape, rather than keeping the constant diameter seen in axons. Collectively dendrites of a neuron are termed a 'dendritic tree' to reflect the complex branch-like structure with different neuronal types having distinctive dendritic arbours (see Table 1 for neuronal morphologies). Dendrites act as the antennae for the neuron, receiving chemical (neurotransmitter) messages through thousands of synapses and converting them to electrical impulses in the form of an action potential. When neurotransmitters bind with receptors on the dendrite large transient depolarization 'spikes' occur causing either neurotransmitter-gated sodium or potassium ion channels to open. Opening of sodium ion channels lowers the threshold for depolarization of the membrane and is 'excitatory', opening of potassium ion channels conversely increases the threshold for depolarization and is hence 'inhibitory'. If the cumulative effect of spikes travelling across the soma reaches the threshold for depolarization at the axon hillock and AIS an action potential is generated (Hausser et al., 2000). Some types of neuron, including pyramidal neurons of the neocortex, spiny neurons of the striatum, and cerebellar Purkinje cells have protrusions from the dendrites termed 'spines' (Rochefort & Konnerth, 2012). Dendritic spines typically have a narrow 'neck' with a 'head' attached and are classified into three broad types; thin, mushroom and stubby (see Figure 1.7). Individual dendrites can have all spine types of varying densities reflecting functional diversity; the head and neck

morphology ensuring that individual spine synaptic activity is less likely to affect neighbouring spines.

Figure 1.7

Dendritic spine types *[Reprinted from Yuste & Bonhoeffer (2004) with permission from Springer]*



Action potentials generated in the axon can back-propagate to the soma and dendrites in varying degrees of amplitude, depending on neuron type (Hausser et al., 2000; Krueppel et al., 2011; Major et al., 2013). It has been suggested that back-propagation of signals plays a role in morphological changes in dendrites and as a result synaptic plasticity (Fuchs & Flügge, 2014; Perez-Cruz et al., 2009). Dendritic spine structures and densities have the capacity to alter in response to activity-dependent and -independent mechanisms, with increased synaptic activity resulting in spine enlargement. These changes fluctuate over time and are thought to underlie learning and memory (Kasai et al., 2010). Neuronal subtypes in specific brain regions are more plastic than others, for example pyramidal cells in the amygdala and hippocampus – structures thought to be key to memory and emotional processing (Fuchs & Flügge, 2014). Different neuronal (Table 1.1) and glial (Table 1.2) sub-types utilise particular neurotransmitters to fulfil their function (See Table 2).

Table 1.1

Neuronal sub-types within the brain

Categorisation	Structural Features	Function	Location
Pyramidal	Triangular shaped cell body with a single long axon with three to five basal dendrites and a distinctive pyramidal arborisation of apical dendrites. Dendrites have large numbers of dendritic spines, increasing surface area. Vary in size.	Excitatory cortical output neurons.	Outer granule layer, pyramidal layer and ganglionic layer of the cerebral cortex, hippocampus and amygdala.
Stellate/Granule	Short axon and three to four short dendrites in a star-shaped structure.	Interneurons	Outer and inner granule layers, and ganglionic layer of visual and somato-sensory cortices. Cerebellum.
Cells of Marinotti	Long axon that bifurcates with short dendrites.	Interneurons	Pyramidal and ganglionic layers of the cortex.
Fusiform Cells	Axon arises from the side of the soma and dendrites from either end to form a spindle structure.	Interneurons	Multiform layer of the cortex.
Purkinje	Large neuron with a single axon and numerous elaborately branching dendrites.	Only output cells of the cerebellum	Cerebellum.
Basket	Bifurcating axon which cradles the cell body of Purkinje cells.	Interneurons	Cerebellum and hippocampus.

Note: Interneuron = neurons that transmit impulses between neurons

Sources: Andersen et al., 1964; Ferrer et al., 1986; Lim et al., 2018; Markram et al., 2004; Mertz et al., 2000; Spruston, 2008

Table 1.2

Basic glial sub-types within the brain

Categorisation	Structural Features	Function	Location
Protoplasmic Astrocytes	Several stem branches splitting into finer processes	Facilitate neurotransmission	Cortical layers II-VI
Fibrous Astrocytes	Straight processes	Connect with nodes of Ranvier-structural and metabolic support	White matter
Interlaminar Astrocytes	Oblong cell bodies, tortuous processes	Unknown but only found in higher order primates	Pial surface to cortical layers II-IV
Polarized Astrocytes	Varicosities down length of straight processes	Unknown but only found in higher order primates	Cortical layers V-VI
Oligodendrocytes	Processes that wrap around neurons (up to 40)	Myelination of white matter	Throughout central nervous system
Ependymal cells	Cuboid or columnar. Ventricle surface covered in villi	Form part of the blood-brain and brain-cerebrospinal barrier. Maintain cerebrospinal fluid flow.	Lateral ventricles
Microglia	Numerous processes surrounding cell body	Innate immune mechanism of central nervous system.	Throughout the central nervous system

Sources: Bushong et al., 2002; Del Bigio, 2010; Oberheim et al., 2006, 2009, 2012; Olah et al., 2011; Sherman and Brophy, 2005

Table 1.3

Major neurotransmitters of the brain

Neurotransmitter	Function	Regions of activity	Involved in
Adrenaline	Excitatory	Thalamus Hypothalamus Midbrain	Attention, arousal and vigilance.
Acetylcholine	Excitatory (usually)	Interneurons throughout the brain	Sleep and arousal. Acquisition and maintenance of learning, memory and attention.
Glutamate	Excitatory	Hippocampus Amygdala Basal Ganglia	Synapse plasticity and learning
Noradrenaline	Alpha-1 and beta receptors are excitatory. Alpha-2 receptors are inhibitory.	Cerebral cortex Hypothalamus Brain stem Cerebellum	Attention, arousal and vigilance. Hunger and feeding behaviours.
Dopamine	Inhibitory (usually)	Neocortex (particularly prefrontal cortex). Basal Ganglia (Striatum, Substania Nigra & Ventral Tegmental Area). Limbic System. Pituitary Gland. Posterior hypothalamus. Superior and inferior colliculus.	Reward and reinforcement; learning and motivation. Initiation of behaviours.
Gamma-Aminobutyric Acid (GABA)	Inhibitory	Substantia Nigra Globus Pallidus Periaqueductal Grey Matter Hippocampus Cerebellum Interneurons throughout the brain.	Locomotor activity, feeding behaviour, sexual behaviour, aggression, mood, regulation of pain sensitivity, cardiovascular regulation, thermoregulation.
Serotonin (5-Hydroxytryptamine; 5-HT)	Inhibitory	Hypothalamus Limbic System Cerebellum	Emotional state/mood. Body Temperature

Sources: *Boekhoudt et al., 2018; Bromberg-Martin et al., 2010; Coull et al., 1997; Evetts et al., 1972; Gais and Born, 2004; Gubellini et al., 2004; Hasselmo, 2006; Jenkins et al., 2016; Mukherjee and Manahan-Vaughan, 2013; Taber et al., 2012; Wu and Sun, 2015*

1.2.10. Glial cells

There are two broad classes of glia in the central nervous system; the macroglia (including astrocytes, oligodendrocytes and ependymal cells) and the microglia (Dong & Benveniste, 2001). In humans, the average ratio of glia to neurons is 1:1, although this varies depending on brain region and cortical layer. In the cortex, approximately eighty percent of cells are glia, this proportion drops to approximately sixty percent in the grey matter and just twenty percent in the cerebellum (Azevedo et al., 2009). These structures play vitally important roles in the normal functioning of the human brain beyond that of simply being support structures for neurons.

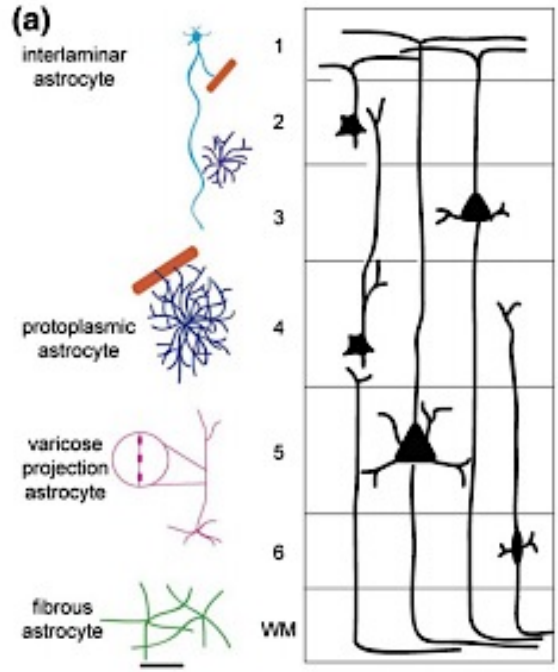
1.2.10.1. Astrocytes.

Traditionally identified through positive staining of glial fibrillary acidic protein[8] (GFAP), astrocytes are the most numerous glia and work in close proximity to neurons and the cerebral vasculature. Staining and analysis techniques have found that the spread of astrocyte processes is much greater than previously thought, underpinning the important function of these cells (Bushong et al., 2002). Astrocytes fill almost all spaces between neurons leaving gaps as small as 20nm wide with little overlap in domains (Koehler et al., 2009). Within the brain astrocytes have traditionally been viewed as support structures for neurons, undertaking functions that include maintenance of the blood-brain barrier (Persidsky et al., 2006), control of extracellular concentrations of water and ion levels (Koehler et al., 2009) and neurotransmitter production and clearance (Anderson & Swanson, 2000; Nedergaard et al., 2003; Volterra & Meldolesi, 2005). The close contact with neurons also facilitates astrocytes' role in axonal regrowth and synaptogenesis in addition to regulation of blood microcirculation and neurogenesis; without the involvement of astrocytes neuronal function would break down (Jiao & Chen, 2008; Pasti et al., 1997; Ridet et al., 1997; Ullian et al., 2004; Zonta et al., 2003). Astrocytes are highly connected to one another and themselves via gap junctions, the function of autocellular gap junctions is not currently clear but may be related to stabilization of cellular processes (Pannasch et al., 2012; Wolff et al., 1998). Compared to rodents (with two sub-types; protoplasmic and fibrous) and lower primates (three sub-types; protoplasmic, fibrous and interlaminar), humans and higher primates brains have four astrocyte sub-types that interact with and facilitate synaptic activity: protoplasmic, fibrous, interlaminar and polarized (varicose) astrocytes (See Figure 1.8).

[8] An intermediate filament protein, forming networks that give strength and support to cells.

Figure 1.8

Astrocyte positions and types *[Reprinted from Vasile et al., (2017) under the terms of the Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/]*



Protoplasmic astrocytes are the most numerous sub-type and associated with the grey matter of cortical layers II-VI. Compared to other mammals, protoplasmic astrocytes are more complex in human brains with longer, more numerous processes (Oberheim et al., 2009). Each protoplasmic astrocyte has several stem branches that split into many finer processes to form a uniform spongiform structure (Sofroniew & Vinters, 2010). Cell bodies of these glia are around 10µm in diameter with processes spanning between 100 and 200µm, enclosing an estimated 140,000 to 2 million synapses, depending on the brain region (Bushong et al., 2002; Oberheim et al., 2006; Oberheim et al., 2009). Protoplasmic astrocytes occupy distinct anatomical domains with little overlap between neighbouring astrocytes and have control over large numbers of synapses and associated vasculature; nearly all endfeet of these astrocytes have contact with blood vessels. The exact number of neurons and blood vessels within each astrocyte domain vary according to cortical layer and cellular density (Oberheim et al., 2006, 2009, 2012). The significance of this domain organization is still unclear but may relate to co-ordination of cerebral blood flow and synaptic activity (Oberheim et al., 2012). Protoplasmic astrocyte processes partially encompass virtually all synapses within cortical layers II-VI (Oberheim et al., 2006; Peters & Palay, 1991). The function of these perisynaptic

membranes is debated, with some positing that they are involved in 'tripartite' synaptic activity (Araque et al., 1999), other alternatively posit that perisynaptic membranes may act as a shield to protect the synapse from 'leak out' neurotransmitter escape and 'leak in' neurotransmitter interference from nearby synapses (Nedergaard & Verkhratsky, 2012). These membranes also maintain the balance of synaptic cleft ion levels and play a vital role in neurotransmitter homeostasis, expressing high levels of transporters for neurotransmitter clearance and recycling (Sattler & Rothstein, 2006; Seifert et al., 2006).

The other sub-type common to mammals, fibrous astrocytes, are similar across species but are comparatively larger in humans. Fibrous astrocytes can be distinguished from protoplasmic astrocytes having fewer, straighter, processes with less branching (Oberheim et al., 2009). Fibrous astrocytes are found in white matter oriented in the same plane as myelinated axonal bundles but are not directly involved in myelination. Unlike the domain organisation of protoplasmic astrocytes, the processes of fibrous astrocytes overlap extensively, however their cell bodies are evenly spaced. Processes of fibrous astrocytes connect with the cerebral vasculature and nodes of Ranvier (Privat & Rataboul, 2012) but are not present at synapses and therefore seem to play the structural and metabolic support role previously ascribed to all glia (Oberheim et al., 2009).

Interlaminar astrocytes are a sub-type only found in humans and primates, with oblong-shaped cell bodies in primates and round cell bodies in humans (~10μm diameter). Interlaminar astrocytes are more numerous in humans, compared to other primates and originate densely packed in layer I of the cortex (Oberheim et al., 2009; Vasile et al., 2017). These astrocytes have two forms of tortuous process; between three and six processes contribute to the astrocytic network near the pial surface and one or two extend in a columnar organization into cortical layers II-IV (Oberheim et al., 2006). These extensions into the neuropil are found within the domains of protoplasmic astrocytes and have end bulbs containing mitochondria. These cortical extensions usually terminate within the neuropil or less frequently in the vasculature (Colombo & Reisin, 2004). The functions of this sub-type of astrocyte is undetermined but has been suggested to be closely linked to facilitation of cognitive processes, possibly playing a role in long-distance non-synaptic signalling and integration of cortical activity (Oberheim et al., 2006).

Polarized astrocytes found in layers V and VI of the cortex are only found in humans and higher-order primates. Sometimes termed 'varicose projection astrocytes' as a result of the varicosities or 'beads' that occur down the length of the largely straight processes (approximately every 10μm), polarized astrocytes sparsely populate layers V

and VI of the cortex. In appearance, these astrocytes have between one and five straight processes measuring approximately 1mm in length that rarely branch, suggesting they may have fewer contacts with synapses, compared to protoplasmic astrocytes. These astrocytes mainly terminate in the neuropil or on blood vessels and have a more 'spiny' appearance when compared to the bulbous processes of protoplasmic astrocytes (Oberheim et al., 2006; Oberheim et al., 2009). As with interlaminar astrocytes the exact function of this sub-type is unknown, but their occurrence only in higher primates suggests that they may relate to higher cognitive abilities and long-distance communication, potentially between grey and white matter.

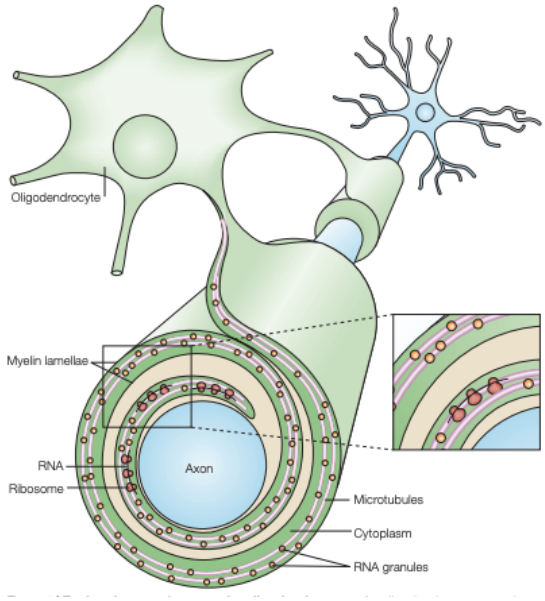
1.2.10.2. Oligodendrocytes.

Within the central nervous system oligodendrocytes are responsible for myelination of axons. Myelination allows for faster and more efficient nerve signalling by insulating axons in segments with gaps (nodes of Ranvier). Myelination of axons within the central nervous system (CNS) differs from that in the peripheral nervous system (PNS) where myelination of motor and sensory neurons is carried out by Schwann cells. Each myelinating Schwann cell insulates only one section of axon, wrapping the whole cell body around the axon numerous times with the nucleus on the outer surface (Saltzer, 2015). In contrast oligodendrocytes myelinate numerous axons of the CNS, sending out membranous extensions from the cell body that spiral around the axon (see Figure 1.9; Sherman & Brophy, 2005).

Oligodendrocytes differentiate from oligodendrocyte precursor cells (OPCs) that originate in the neuroepithilium of the ventricular/subventricular zone of the brain. The OPCs then migrate to the developing white matter until they reach the target axons. Here the OPCs exit the cell cycle and become non-migratory, differentiating into myelin forming oligodendrocytes (Simons & Trajkovic, 2006). Only axons over 0.2μm are insulated in a multi-step process; oligodendrocytes first recognise and adhere to appropriate axons. Once the oligodendrocyte plasma membrane is attached to the axon the myelin components are synthesised and transported to the adhesion site. Myelin then spirally wraps around the axon and the cytoplasm is extruded resulting in compaction of the sheath (Simons & Trajkovic, 2006). Onset of myelination requires neuronal electrical activity in combination with a number of extrinsic neuron derived signals to control timing of oligodendrocyte differentiation and identification of regions to be myelinated (Simons & Trajkovic, 2006).

Figure 1.9

Process of myelination by oligodendrocytes {Reprinted from Sherman & Brophy (2005) with permission from Springer]



Individual oligodendrocytes may contribute forty different sections of myelin across a number of different axons. This is not a sequential process, instead an individual oligodendrocyte ensheaths all target axons within a 12-18 hour period (Pfeiffer et al, 1993). The process of myelination is vulnerable in a number of ways; errors in protein manufacture or misfolding can occur within the endoplasmic reticulum. Extensive myelination over a short period of time requires high ATP metabolism, leaving oligodendrocytes vulnerable to mitochondrial injury and oxidative stress (McTigue & Tripathi, 2008) particularly as oligodendrocytes express low levels of glutathione (an anti-oxidant enzyme) (Thorburne & Juurlink, 1996). Myelin production is also vulnerable to iron deficiency due to the high level of iron required as a co-factor for many enzymes involved in the synthesis of myelin (Connor & Menzies, 1996).

Following myelin damage repair is not performed by existing oligodendrocytes. Instead mature adult OPCs switch from a quiescent to regenerative phenotype (Nait-Oumesmar et al., 1999; Raff, 1986; Sim et al., 2006), this change triggered is by activated microglia and astrocytes (Miron et al., 2013; Rhodes et al., 2006) rather than the myelin damage itself (Franklin & ffrench-Constant, 2008). Remyelinated axons can be easily identified by thinner myelin in shorter segments compared with the original axonal myelin diameter and node length (Blakemore, 1974; Franklin & ffrench-Constant, 2008; Ludwin & Maitland, 1984).

1.2.10.3. Ependymal cells.

Ependymal cells line the ventricular surface of the whole central nervous system from the lateral ventricles in the brain to the filum terminale at the base of the spine. In adults, ependymal cells in the brain are cuboid or columnar in shape, the surface facing the ventricles covered with microvilli with cilia clustered at the centre (Del Bigio, 2010). At the luminal-facing surface of ependymal cells adherens junctions are formed between cells, contributing to regulation of the blood-brain and brain-cerebrospinal barrier (Abbott et al., 2006; Alvarez & Teale, 2007). The ependymal cell cilia exhibit synchronized beating, maintaining cerebrospinal fluid (CSF) flow and facilitating migration of neuroblasts from the subventricular zone (SVZ) to the olfactory bulb for differentiation of interneurons (Luskin, 1993; Sawamoto et al., 2006). The close spatial relationship between the ependyma and the SVZ supports the hypothesized protective role of ependymal cells during development and possibly in the mature brain (Del Bigio, 2010). During development, the ependyma is particularly important in ensuring that maturing ventricles and CSF compartments remain open, with the movement of cilia clearing the wall lining particularly where the dimensions of the lumen are small (Del Bigio, 2010). Following brain maturation in humans there is loss of ependymal cells over large areas of the ventricular surface, for example the occipital horns of the lateral ventricles, these discontinuities do not seem to critically affect normal brain function and are likely a normal developmental phase. The crucial role of these cells may therefore be limited to brain development (Del Bigio, 2010).

1.2.10.4. Microglia.

The cellular origin of microglia is unlike that of many other organelles found within the brain as they originate from bone marrow infiltrates in early development, rather than from neonatal central nervous system tissue (Kandel et al., 2000). Microglia provide trophic support for neurons but function primarily as the innate immune mechanism of the central nervous system, recruiting lymphocytes and secreting cytokines and chemokines (Kandel et al., 2000). All regions of the brain express microglia in differing densities with phenotypic heterogeneity demonstrated within anatomical regions (Olah et al., 2011). Due to lack of relevant experimental data contributory factors underlying this diversity are currently speculative but seem to be related to cytoarchitecture and biochemistry (Olah et al., 2011). Research indicates significantly higher densities of microglia in white compared to grey matter, with phenotypically different populations in each (Block & Hong, 2005; Mittelbronn et al., 2001). It has also

been suggested that microglia in white matter exhibit higher basal levels of activation (Carson et al., 2007), possibly reflecting the importance of myelinated structures to effective neural function.

Under normal conditions microglia are chemically inactive, constantly surveying the environment for damage with highly branching processes. When environmental changes associated with pathogens, metabolic stress, or injury are detected microglia undergo an activation process and become motile, migrating to the site of injury, multiplying and clearing up damaged tissue via phagocytosis (Kettenmann et al., 2011). Phagocytosis is the process by which damaged or pathogenic material is engulfed by microglia and broken down, any useful material being re-cycled by the cell

In aging brains increased number and density of activated microglia are evident, particularly in the hippocampus and visual and auditory cortices (Conde & Streit, 2006; Long et al., 1998; Mosher & Wyss-Coray, 2014; Tremblay et al., 2012). In diseases of neurodegeneration (for example Alzheimer's disease) accumulations of microglia are also observed clustered around amyloid plaques, presumably as a function of the inflammatory response (Mandrekar-Colucci & Landreth, 2010). Co-localization of aggregations of plaques and tangles with populations of degenerating microglia may reflect reduced neuroprotection due to microglial senescence. Alternatively, increased production of misfolded proteins in the aging brain may cause increased numbers of activated microglia that become hyperactive and pro-inflammatory over time (Olah et al., 2011). It may also be the case that repeated exposure of microglia to reactive oxygen species over the lifespan results in conformational DNA changes affecting the capacity of microglia to respond to harmful environmental changes (Streit et al., 2008). Although the importance of microglia to the immune and inflammatory response is firmly established the exact details of microglia phenotypes, distribution, and degeneration are yet to be clearly elucidated.

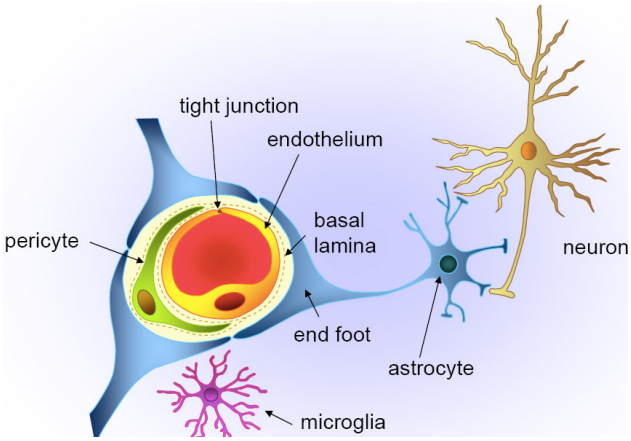
1.2.11. Blood-brain barrier (BBB)

The brain's immune-privileged status is maintained by the blood-brain barrier (BBB). The BBB is a selective barrier formed from endothelial cells that line blood vessels within the brain, as they do all blood vessels of the body (see Figure 1.10). This physical barrier, formed by tight junctions between endothelial cells, keeps blood separate from cerebrospinal fluid (CSF) and interstitial fluid (ISF). Within the brain junctions are more complex and 'tight' compared to those in the peripheral endothelium, with

intermembranous networks of strands or fibres between cells that effectively occlude the intercellular cleft (Wolburg & Lippoldt, 2002).

Figure 1.10

Structure of the blood-brain barrier [Reprinted from Abbott et al., (2010) with permission from Elsevier]



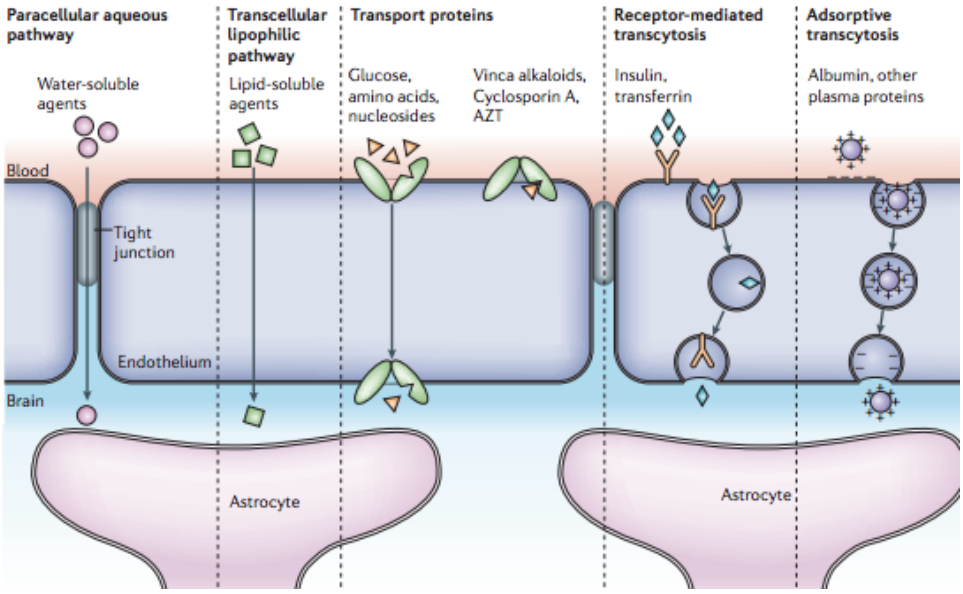
In addition to the BBB itself there are two more interfaces that make up the barrier: the blood-cerebrospinal fluid barrier (BCSFB) and the avascular arachnoid epithelium. The BCSFB is formed from epithelial cells of the choroid plexus that secrete cerebrospinal fluid into the ventricles of the brain and the spine (Cserr, 1971). The avascular arachnoid epithelium lies beneath the dura mater, completely lining the interior surface of the brain (Abbott et al., 2006; Kiernan & Rajakumar, 2013). Only small gaseous molecules (for example oxygen and carbon dioxide) and small lipophilic agents are able to diffuse freely through the membrane. Other cellular structures that compose the BBB include perivascular endfeet of certain astrocytes, microglia and pericytes (contractile cells wrapped around endothelial cells) (Abbott et al., 2006), all of which regulate brain blood flow and perfusion.

In addition to functioning as a physical barrier the BBB also operates as a transport and metabolic barrier (see Figure 1.11) allowing the influx of required nutrients and enzymes and the exclusion and efflux of toxic or harmful substances (Persidsky et al., 2006). Larger peptide and protein molecules are excluded from crossing the BBB unless they can move through the BBB by transcytosis/endocytosis via specific receptor or absorption mechanisms, the volume of this method of transport being lower in the BBB compared with peripheral tissue (Pardridge, 2003). Movement of substances through the BBB is not limited to molecular transport; the BBB also regulates movement of fluids to ensure that ISF concentrations are optimised for efficient neural function (Abbott, 2004). ISF and blood plasma are very similar in composition, however ISF has lower levels of

protein, potassium and calcium but higher magnesium levels (Abbott et al., 2010). To maintain homeostasis of the ISF, CSF and cell nutrients neurons, glia and the vasculature have a very close relationship, each neuron and glial cell being no further than 20µm from the nearest capillary (Bär, 2012).

Figure 1.11

Transport mechanisms across the blood-brain barrier[Reprinted from Abbott et al., (2006) with permission from Springer]



1.3. Cell Death

Under a variety of conditions, including developmental neuronal reorganisation, neurodegeneration, radiation treatment, and acquired and traumatic brain injury, cells of the brain die. Morphologically and mechanistically these forms of cell death (broadly categorized as apoptosis, autophagy and necrosis) differ in the effect they have on the immediate surrounding area and on the wider brain parenchyma[9], however they involve a number of the same biochemical agents.

1.3.1. Apoptosis

The term apoptosis, or programmed cell death, was first used over forty years ago to describe a form of energy-dependent cell death with characteristic morphology and physiology (Kerr et al., 1972). Briefly these features include condensation and fragmentation of the cytoplasm and nucleus, reduced cell volume and relatively preserved structure of organelles (see Figure 1.12). Apoptotic cells then form membrane bound 'blebs' that are swiftly enclosed and broken down by free-floating macrophages (Gregory

[9] Functional tissue of the brain

& Devitt, 2004). This form of cell death typically occurs within the brain during periods of synaptic pruning or to dispose of damaged or infected cells, minimally affecting surrounding healthy tissue and without generating any secondary cascade toxicity. The initiating stimulus for apoptosis can arise from either external damage activating the cellular immune response (e.g. viruses) or as a reaction to internal stress signals (e.g. DNA damage, oxidative stress, hypoxia, endoplasmic reticulum stress) activating mitochondria-initiated apoptosis (Yan & Shi, 2005).

In the extrinsic pathway apoptosis is triggered by direct activation of transmembrane death receptors on the cellular membrane by ligands of the tumour necrosis factor (TNF) superfamily, including Fas, TNF-α and TRAIL (TNF-related apoptosis-inducing ligand) (Andón & Fadeel, 2012). This in turn activates a Fas associated death domain (FADD) on the interior surface of the membrane, which in turn binds to FADD adaptor proteins. FADD adaptor proteins recruit an initiator cysteine dependent aspartate directed protease (caspase; in this case either procaspase-8 or -10), forming a death-inducing signalling complex (DISC) (Lavrik & Krammer, 2012). The large and small subunits of the procaspase subsequently cleave from the DISC to form active initiator caspase enzymes (either caspase-8 or -10). Activated initiator caspases then cleave and activate caspase-3 and -7 (effector or executioner caspases) (Yan & Shi, 2005). At this point the extrinsic pathway converges with processes in the intrinsic pathway.

The intrinsic apoptosis pathway takes a number of forms, all involving disruption of mitochondrial function. The best characterised is that critically determined by the actions of members of the Bcl-2 family of proteins, which can be divided into three sub-groups; anti-apoptotic (inhibitor) Bcl-2 proteins (including Bcl-2 and Bcl-xL), pro-apoptotic (sensitizer/activator) BH3-only proteins (including Bad, Bim and PUMA) and pro-apoptotic Bcl-2 (agonist) proteins (including Bak and Bax) (Shamas-Din et al., 2013). There are a number of models that attempt to elucidate the exact mechanisms that underlie the relationship and actions of these proteins (see Hyman & Yuan, 2012). The common feature of these models is that Bak, Bid and Bax (pro-apoptotic Bcl-2 family agonists) undergo oligomerisation (binding together) and insertion into the outer mitochondrial membrane. Insertion of a Bak/Bax/Bid aggregation results in channel formation and consequently release of cytochrome c, a vital component of the electron transport chain, from the mitochondrial intermembrane space into the cytoplasm. The lack of clarity in these models relates to the exact roles of the other two families of proteins. The presence of the BH3-only proteins (e.g Bad) leads to activation of the pro-

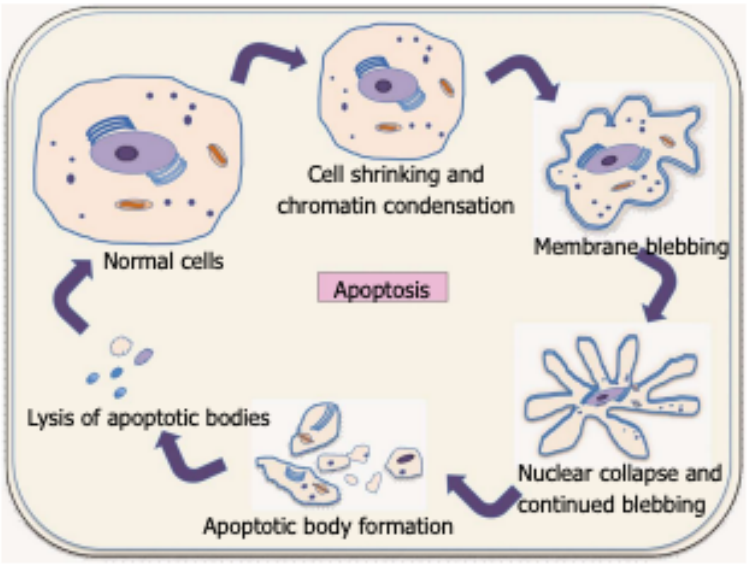
apoptotic agonists, (Bak, Bax and Bid), however it is not clear whether this is due to direct activation or indirectly as a result of sequestering of anti-apoptotic proteins (e.g. Bcl-2 and Bcl-xL) preventing Bcl-2 and Bcl-xL from inhibiting Bak, Bax and Bid through binding. The latter model operates from the standpoint that the pro-apoptotic agonists do not require activation and that apoptosis is prevented by sequestration by anti-apoptotic inhibitors (Shamas-Din et al., 2013). The balance between these proteins affects the probability of apoptosis occurring.

Following release from the mitochondrial intermembrane space, cytochrome c drives formation of an apoptosome, a large protein structure. The apoptosome then binds with apoptosis protease activation factor (Apaf-1) and procaspase-9 in the presence of ATP or dATP. This results in the activation of caspase-9 by cleavage of the large and small sub-units. This in turn activates effector caspases -3 and -7 through a cascade of further cleavages, as seen in the extrinsic apoptosis pathway (Yan & Shi, 2005). These effector caspases are then responsible for the reactions underlying the dismantling of the cell (Hyman & Yuan, 2012).

In addition to caspase-dependent cell death pathways, caspase independent forms of programmed cell death also occur. Excitotoxic injury occurs following neurotrauma as a result of glutamate overstimulation and release, this causes elevated calcium levels in the cytoplasm culminating in mitochondrial depolarization and affected electron transport (Baxter et al., 2014). Apoptosis Inducing Factor (AIF), normally confined to the mitochondria in healthy tissues, can be translocated from the mitochondria in response to overactivation of poly (ADP-ribose) polymerase-1 (PARP1; a nuclear enzyme) following DNA damage arising from failed oxidative phosphorylation (Yu et al., 2002). AIF is involved in early cell death mechanisms, facilitating partial chromatin condensation and DNA fragmentation via recruitment of endonucleaseG (EndoG) (Ye et al., 2002). This seems to occur before cytochrome c is fully released, independent of caspase involvement (Li, et al., 2001). This highlights that a number of programmed cell death pathways exist that result in cell death without associated secondary cascade toxicity.

Figure 1.12.

Diagram of the process of apoptosis. [Reprinted from Larrubia et al., (2013) under the terms of the Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/]



1.3.2. Autophagy

An alternative pathway of programmed cell death, autophagy (specifically macroautophagy), is commonly regarded as a non-selective cellular process where intracellular components, including proteins and organelles, are degraded following vacuole formation. This is a ubiquitous process, highly conserved across eukaryotic organisms[10] (recorded in yeast, plants and mammals) (Klionsky & Emr, 2000; see Figure 1.13); it occurs constantly under normal cellular conditions and is upregulated as a cellular stress response. Autophagy is primarily involved in the controlled turnover and re-use of excessive, old or abnormally formed organelles and proteins; however it also functions as a form of programmed cell death at times of cellular stress or nutrient deprivation. Under these conditions the cell will be broken down for fuel by lysosomes (Debnath et al., 2005; Klionsky & Ohsumi, 1999). These adaptive functions are critically important to maintain a balance between synthesis and degradation of cellular constituents during development and for cellular viability (through harvesting of amino acids) under stress conditions (Klionsky & Emr, 2000; Meijer & Codogno, 2004) .

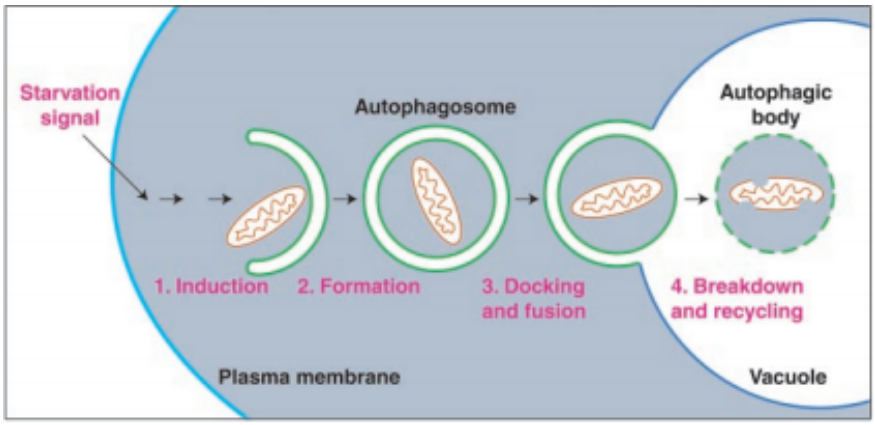
Autophagy is sensitive to modulation by a diverse range of stimuli. The kinase mammalian target of rapamycin (mTOR) seems to be a key regulator, suppressing initiation of autophagy when cellular nutrient levels are optimum (Kanazawa et al., 2004), along with ATG (AuTophaGy-related) genes (Meijer & Codogno, 2004). Following

[10] Organisms with cells that contain a nucleus

autophagy induction in mammals a membrane sac (the phagophore) expands to engulf a region of the cytosol and forms a seal. This then matures to form a double-membrane vesicle termed the autophagasome, isolating components for degradation (Baba et al., 1994; Xie et al., 2008). The material to be enclosed dictates autophagosome size and vesicles can be large enough to encompass entire organelles, regulated by a number of enzymes including GTPases (guanosine triphosphate-ases), phosphatidylinositol kinases and phosphatases (Klionsky & Emr, 2000). It is thought that organelles within the cytoplasm 'donate' membrane material to form the autophagosome, with the endoplasmic reticulum and Golgi apparatus seeming to be the most likely sources (Geng & Klionsky, 2010).

Figure 1.13

The basic process of macroautophagy. *[Reprinted from Klionsky & Emr, (2000) under the terms of the Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/]*



Mature autophagosomes then fuse with lysosomes[11], the outer membrane of the autophagosome fusing with the vacuole membrane. Each autophagosome has the capability to fuse with several lysosomes for degradation of engulfed contents. Microtubules, in combination with correct cellular acidity levels, facilitate this fusion to form a hybrid organelle termed the autolysosome (Chen & Yu, 2013). Under extended cellular starvation conditions (over four hours) lysosome numbers can become depleted as they are subsumed into the autophagosomes. Used lysosomes can then be recycled through a process of autophagic lysosome reformation, recovering lysosome populations after approximately twelve hours (Chen & Yu, 2013; Yu, et al., 2010) .

Creation of the autolysosome results in release of the autophagosome inner membrane, causing breakdown of contents. It is not clear how the vacuole membrane

[11] Specialized endosomal vacuoles containing enzymes able to break down biomolecules

avoids being digested by the lipases and hydrolases involved in degradation of the target cargo but it is proposed that the presence of glycoproteins in the membrane play a protective role (Klionsky & Emr, 2000). Once broken down the constituent amino acids and other by-products are released back into the cytoplasm for re-use (Mizushima, 2007). These products potentially may be used in ATP generation in the Krebs cycle, however this alternative form of energy conversion is relatively inefficient (Singh & Cuervo, 2011).

As autophagy is involved in developmental programmed cell death there has been research interest in the potential for autophagy to initiate cell death at other times, particularly as autophagy markers (e.g. autophagosomes and autolysosomes) have been found together with markers of apoptosis (caspase activation and mitochondrial membrane permeability) in dying cells (Debnath et al., 2005; Levine, 2005). The most likely explanation for these findings is that autophagy is induced as a response to a number of stressors reaching a threshold duration or intensity, including hypoxia (insufficient oxygen) (Mazure & Pouyssegur, 2010), excitotoxicity (Wang et al., 2008) and nutrient deprivation (Russell et al., 2014). The recycling of proteins through autophagy functions to maintain cellular function until the stress stimulus (hypoxia or starvation) is reversed and also supports the energy demands required for apoptosis. Should the stress stimulus be removed before a critical threshold of cytoplasmic contents is reached then cellular function may return to normal. Alternatively if the apoptotic pathway has been initiated and is not concluded before cellular energy is exhausted, necrotic cell death may be the outcome (Balduini et al., 2012; Debnath et al., 2005). It has therefore been argued that autophagy, apoptosis and necrosis may function on a cell death continuum, with autophagy sequentially preceding apoptosis and necrosis, (Balduini et al., 2012; Mariño et al., 2014).

In trauma situations, for example following brain injury, the picture is more complex. Autophagy is a major mechanism for the breakdown of damaged cell membranes, neuronal processes and organelles under normal conditions, however following major neuronal trauma this pathway may not be able to cope with the additional demands. Research has found increased accumulation of autophagic markers in a rodent model of TBI, compared with sham animals (Liu et al., 2008). In human TBI, individuals may initially be nutrient deprived after injury, with regions of damage to be cleared and cellular components to be recycled occurring concurrently with the requirement for autophagy to be used as a cellular survival response. As autophagy depends on the lysosome population to function efficiently it is therefore possible that following TBI the

system could become overwhelmed after a period of time, resulting in inadequate or defective autophagy. The outcome of this would be an increase in cell death turnover, either by apoptosis or necrosis (Balduini et al., 2012; Liu et al., 2008).

3.3. Necrosis

Historically necrosis has been viewed as a passive, 'accidental', form of cell death following mechanical strain during neurological insult or as a result of sudden changes in the cellular environment including hypoxic/ischaemic events, mechanical strain, or lack of essential nutrients (Galluzzi et al., 2014; Syntichaki & Tavernarakis, 2003). In contrast to apoptosis, necrosis can be characterised by lack of shrinkage of the nucleus, mitochondrial swelling, endoplasmic reticulum distension, cellular tumescence and mitochondrial permeability transition[12] (MPT), culminating in release of cellular contents directly into the intercellular space (Edinger & Thompson, 2004; Kroemer et al., 2007; Leist & Jäättelä, 2001; Syntichaki & Tavernarakis, 2003). Necrotic cell death triggers both an inflammatory and immune response as cellular contents are not fully disposed of in membrane bound blebs, as seen in apoptosis, but are instead disposed of by macrophages (Vanlangenakker et al., 2008). A number of metabolic triggers may initiate necrosis within neurons; acute energy depletion within the mitochondria leading to collapse of resting potential, depolarization, excessive glutamate accumulation and transient acidosis (Ding et al., 2000). Alternatively or concurrently endoplasmic reticulum stress caused by accumulation of misfolded proteins or increased intracellular calcium may result in necrosis (Syntichaki & Tavernarakis, 2003).

Unlike the clear pathways found in apoptosis, necrotic processes involve complex interplay between signalling events and can take a number of different forms including necroptosis, parthanatos, oxytosis, ferroptosis, ETosis, NETosis, pyronecrosis and pyroptosis (Berghe et al., 2014). A number of findings in relation to receptor-interacting protein (RIP) kinase activation and suppression and the action of tumour necrosis factor (TNF) has demonstrated that necrotic cell death may be tightly regulated, following biochemical pathways, rather than just 'accidental' cell suicide (Edinger & Thompson, 2004; Laster et al., 1988; Wilson et al., 2009). In other words, it is also a programmed cell death pathway, albeit one that induces pathogenic processes in nearby healthy cells.

As investigation of regulated necrosis (RN) is relatively recent compared to research into apoptosis, the full underpinnings of RN are yet to be elucidated, however

[12] Abrupt increase in inner mitochondrial membrane permeability

basic signalling events involving tumour necrosis factor (TNF), ATP consumption, NAD depletion and mitochondrial permeability transition have been the most documented and will be briefly covered in the following section.

The TNF-signalling pathway of RN is the most understood; research has shown that TNF is able to moderate between cell survival, apoptosis, or necrosis, depending upon cell type, activation state and the cellular environment (Wilson et al., 2009). Stimulation of TNF-receptor 1 (TNFR1) assembly by TNF results in recruitment of a number of proteins; TNFR1-associated death domain (TRADD), receptor-interacting serine/threonine-protein kinase-1(RIP1), RIP3, cellular inhibitor of apoptosis 1 (cIAP1), cIAP3, TNFR-associated factor 2 (TRAF2) and TRAF5, collectively termed complex I (Micheau & Tschopp, 2003). RIP1 in this complex effects the transition from complex I to complex II, the death-inducing signalling complex (DISC) (Cho et al., 2009; Holler et al., 2000; Micheau & Tschopp, 2003; Vandenabeele et al., 2010), which in the absence of caspase-8 activation through deletion, depletion or inhibition results in necrotic cell death (Berghe et al., 2014; Vandenabeele et al., 2010).

In addition to the TNF-signalling pathway, mitochondrial dysfunction is a factor in both apoptosis and necrosis (Kroemer et al., 2007) as these organelles are responsible for production of the greatest proportion of intracellular ATP and, as a by-product of reactions involving oxygen molecules, a major source of reactive oxygen species (ROS). What underlies the switch between apoptotic and necrotic pathways is debated; it has been suggested that the high energy required for apoptosis is the deciding factor - that once ATP stores are depleted the cell switches to necrosis (Edinger & Thompson, 2004). More recently it has been suggested that this switch is dependent upon the catalytic activation of RIP1 and RIP3 (Cho et al., 2009; He et al., 2009; Zhang et al., 2009) to activate necrosis, rather than being limited to cellular energy levels. When caspase activation does not occur (through deletion, depletion or toxicity), RIP3 interacts with a number of enzymes, enhancing glycogenolysis (breakdown of glycogen to glucose) and glutaminolysis (breakdown of glutamine), increasing overproduction of ROS (Galluzzi et al., 2009) and oxidative stress.

Cell survival is also affected by excitotoxicity during ischaemic-hypoxic events following neurotrauma. Excitotoxicity arises as a consequence of glutamate receptor (NMDA [N-methyl-D-aspartate], AMPA [α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid] and kainite) overactivation, culminating in high levels of extracellular calcium (Ca^{2+}) entering the cell and the release of endoplasmic reticulum (ER) Ca^{2+} stores (Mehta et al., 2013). Disturbed ER calcium homeostasis then proceeds to cause build-up

of misfolded proteins and ER stress (Hetz & Mollereau, 2014). These forms of cellular stress give rise to opening of the permeability transition pore complex between mitochondrial inner and outer membrane causing mitochondrial permeability transition (MPT). MPT is catastrophic for the mitochondria as the massive influx of small solutes into the organelle results in immediate loss of mitochondrial transmembrane potential, cessation of cellular energy production, and release of mitochondrial proteins that initiate cell death mechanisms (Kroemer et al., 1998). One of the most adverse effects of this release of proteins is the loss of nicotinamide adenine dinucleotide (NAD^+), a major co-factor in underlying mechanisms of mitochondrial function (Kristian et al., 2011; Oka et al., 2012). When NAD^+ is depleted from the inner mitochondrial membrane, this seems to act as an additional signal for necrosis (Berghe et al., 2014).

Research findings suggest that (i) not all of these processes are required to initiate forms of regulated cell death and (ii) that there is a certain amount of tolerance for cellular stress within the cell but once this tolerance level has been reached through a combination of mechanisms cell death can be triggered either through a TNF-related trigger or a mitochondria-related trigger (Berghe et al., 2014; Brookes et al., 2004).

1.4. Pathophysiology of Processes in TBI

1.4.1. Primary Brain Insult

Traumatic brain injuries (TBI) occur as a result of rapid acceleration and deceleration forces impacting the brain. The primary injury usually occurs in one of two ways; the individual can be in motion and collide with a stationery object (e.g. in a motor vehicle collision or a fall), or a stationery head can be impacted by a moving object (e.g. being hit over the head accidentally or as an act of violence). In addition to these classic causes TBI can arise as a result of a blast injury, the most prevalent cause of head injury in armed service personnel. Traumatic brain injury can occur in the absence of direct impact to the head due to the relatively free movement of the soft brain within the skull, and of the head itself due to extension and flexion of the neck. This results in coup (point of internal or external impact) and contrecoup (opposite point of impact) injuries as the brain moves back and forth within the skull (Whitfield, 2009), further complicated by fixed internal support structures acting as regions of strain (particularly the falx and tentorium, see Figures 1.14 and 1.15) and by torsion and tension (twisting and stretching) following lateral impact (Bigler, 2001). This forward and back motion also results in lacerations of frontal and temporal regions of the brain on bony protuberances, including

the ethmoid bone and crista galli of the cribriform plate and on the sphenoid bone, both situated at the front of the skull (Bigler, 2001; Le & Gean, 2009).

Figure 1.14

Mechanical forces involved in coup contrecoup injury. *[Reprinted from El Sayed et al., (2008) with permission from Elsevier]*

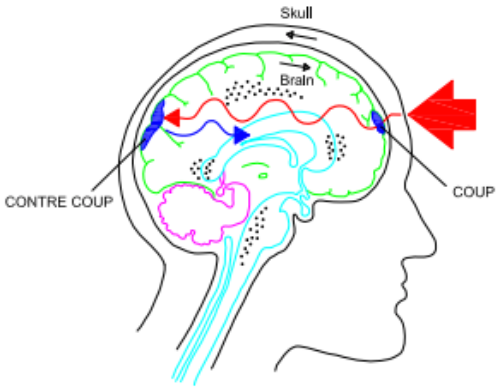
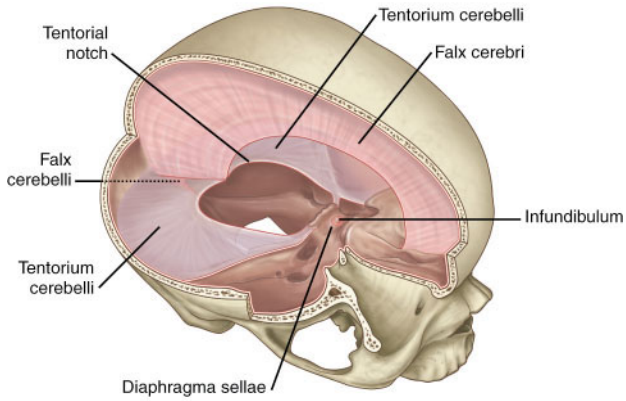


Figure 1.15

Fixed internal structures of the skull. *[Reprinted from Drake et al., (2010) with permission from Elsevier]*



The combination of these mechanisms on the brain produces a non-uniform distribution of contusions, lacerations, axonal injury, and haemorrhage (Whitfield, 2009). Due to the differing densities of brain tissue fragile white matter (containing the axons and support structures) is more easily damaged in response to an external force compared to the dense grey matter (containing the neuronal cell bodies). The outcome of this is axonal deformation and shearing at the grey-white matter junctions in the cortex (Bigler, 2001; Wagner & Zitelli, 2013), corpus callosum and in deep brain structures including the hippocampus (Nakayama et al., 2006). Similarly, shearing forces on fine interlaced blood vessels can result in widespread haemorrhaging, particularly in subdural and subarachnoid regions (Whitfield, 2009).

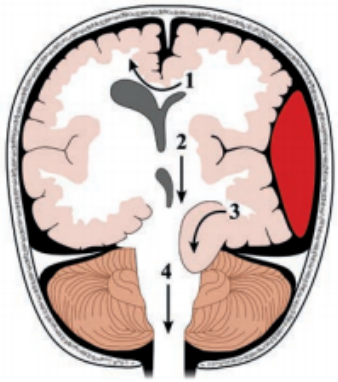
Clinical assessment of TBI severity is measured using a scale to assess level of consciousness; the most extensively utilized being the Glasgow Coma Scale (GCS; (Teasdale & Jennett, 1974). The GCS uses the best motor, verbal and eye-opening responses of the patient to give an overall score, increasing severity reflected in lowering scores. Therefore, a GCS of 13-15 reflects a minor injury, 9-12 a moderate injury and a severe injury is classed as a score of 3-8 (Whitfield, 2009). This measure is repeated at regular intervals to monitor the patient for improvement or decline. It has been argued that the GCS is too coarse a measure; that it does not reflect the heterogeneity of injury encapsulated by the 'severe' category and downplays the potential effects of 'minor' injury (Rosenfeld et al., 2012). In response to calls for a more precise classification system (Saatman et al., 2008) it has been suggested that GCS should be combined with pupillary response (GCS-P) to give a better indicator of long-term prognosis (Brennan et al., 2018; Murray et al., 2018).

The immediate consequences of TBI requiring medical monitoring and possible intervention are related to impaired cerebral blood flow, inflammation and swelling. The brain tissue is relatively soft and requires the homeostatic balance of fluids (cerebral spinal fluid and blood) to maintain structural integrity. Equally the fixed volume of brain tissue maintains ventricular size (Bigler, 2001). A consequence of fluid balance disturbance following trauma is rapid elevation of intracranial pressure (ICP). This can manifest clinically as a reduction in the level of consciousness and intracranial herniation with shifting of brain tissue from one compartment to another (as delineated by fixed brain support structures) (Finnie, 2013). Guidance suggests that cerebral perfusion pressure (the pressure gradient driving cerebral blood flow; CPP) should be maintained between 50-70 mm Hg (millimetres of mercury) in traumatic brain injury to maintain adequate cellular perfusion (Bratton et al., 2007b). ICP raised above 20 mm Hg requires intervention; increased ICP above this threshold causes herniation (see Figure 1.16) potentially crushing the brainstem or cerebellar tonsils into the foramen magnum (the hole at the base of the skull) affecting critical functions including heart rate and respiration, potentially causing death (Bratton et al., 2007a; Bratton et al., 2007b; Rosenfeld et al., 2012). Clinical observation of patients with head injuries also include physiological measures (brain tissue oximetry, brain temperature monitoring, microdialysis) and monitoring of blood serum levels of biomarker proteins to assess probability of mass lesions, haematoma or CSF volume increases that may require stabilization or neurosurgical intervention (Cecil et al., 2011). Patients requiring further investigation following this assessment often undergo computed tomography (CT)

scanning (National Institute of Clinical Excellence [NICE] Guidelines on Head Injury, 2014); CT is superior to magnetic resonance imaging (MRI) in detecting haematoma and can be carried out relatively quickly on an unstable patient. In patients presenting with mass lesions, most commonly subdural (extradural or intraparenchymal are also seen), a decompressive surgical craniectomy (DC) may be carried out (Kolias et al., 2016; Li et al., 2012). DC may also be used as part of a tiered therapeutic protocol in response to a delayed rise in ICP (Kolias et al., 2013). Decompressive craniectomy involves the removal of a large fronto-temporo-parietal bone flap to evacuate the haematoma and reduce ICP, the bone flap being replaced in a later surgery (cranioplasty) (Honeybul & Ho, 2014). The decision to carry out a DC is finely balanced, weighing up the associated complications associated with the initial surgery and the follow-up cranioplasty including haematoma, 'sinking flap syndrome', hydrodynamic disturbance, infection and death (Kurland et al., 2015) with mortality and worse clinical outcome associated with oedema and herniation with raised ICP (Badri et al., 2012).

Figure 1.16

Herniation Caused by Raised ICP. *[Reprinted from Roytowski & Figaji (2013) under the terms of the Creative Commons Attribution 4.0 International License. http://creativecommons.org/licenses/by/4.0/]*



1. Subfalcine -displacement across the falx cerebri
2. Transtentorial – displacement across the tentorium
3. Uncal (transtentorial subtype) – Displacement of uncus placing pressure on the midbrain and brain stem
4. Tonsillar – displacement of cerebellar tonsils below the foramen magnum

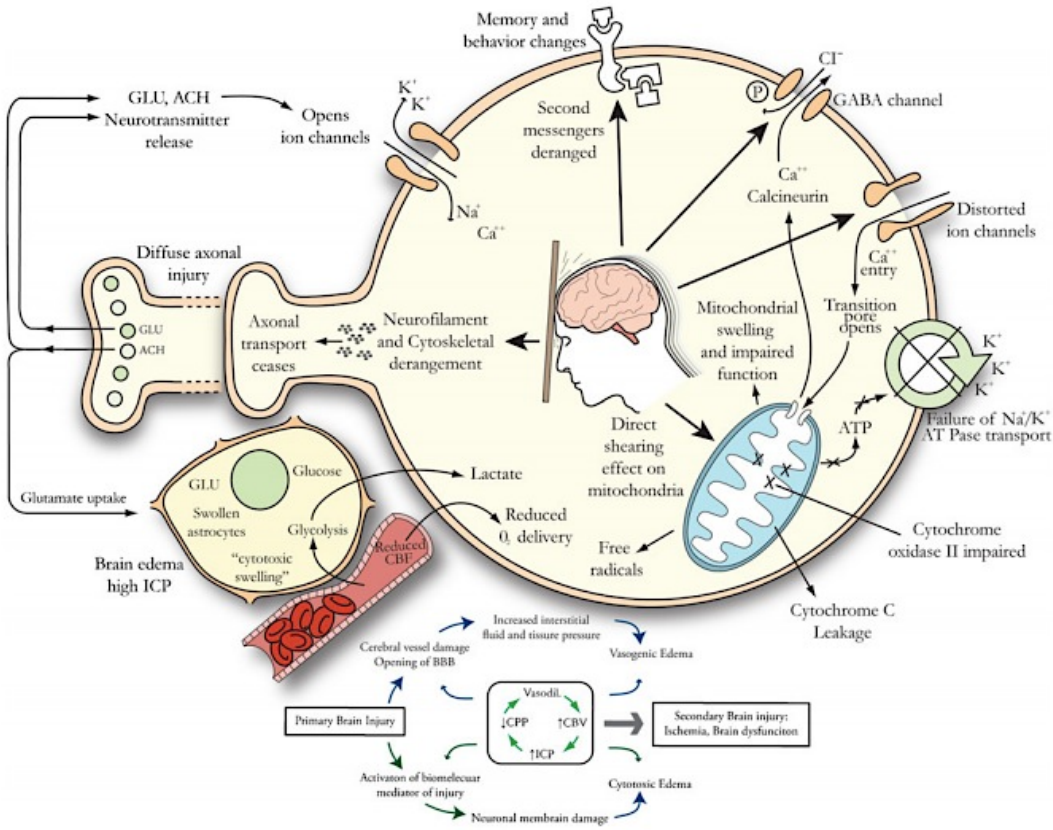
1.4.2. Secondary Brain Injury

Following the primary mechanical injury to the brain tissue there follows a cascade of metabolic, neurochemical and cellular changes that account for arguably the greater proportion of functional changes after trauma than the initial insult experienced by individuals. These changes can be categorised into two concurrent processes; metabolic crisis and excitotoxicity. Secondary cascade mechanisms give clinicians the opportunity to potentially intervene in these processes in an attempt to maximise the potential for improved outcome for the patient. In order for this clinical opportunity to be

capitalized on, the processes underlying the secondary cascade need to be fully understood (see Figure 1.17).

Figure 1.17

Secondary Biochemical Cascade Mechanisms. [Reprinted from Bigler & Maxwell (2012) with permission from Springer]



1.4.2.1. Impaired Cerebral Blood Flow.

Following traumatic brain injury autoregulation of cerebral blood flow (CBF), the ability to maintain CBF across a range of blood pressures, is compromised or abolished in most patients (Hlatky et al., 2005; Rangel-Castilla et al., 2008). This disordered autoregulation with areas of vasodilation and vasoconstriction can either appear very soon after the initial insult or develop over a number of days. It may be transitory in nature or permanent, depending upon the severity of injury (Werner & Engelhard, 2007). An important outcome of uncoupling cerebral metabolic demands and CBF is impairment in delivery of vital substances, particularly oxygen and glucose, to neural tissues, affecting both cellular energy production and maintenance of cerebral perfusion pressure (CPP), the pressure gradient driving cerebral blood flow. In terms of cellular energy production, reduced CBF adversely affects cellular membrane sodium and potassium concentrations and negatively affects mitochondrial metabolism (Finnie, 2013). As a result, mitochondrial glycolysis moves from aerobic to anaerobic respiration as ATP stores

become depleted and cellular energy synthesis degenerates. This breakdown of cellular energy function terminally depolarizes the cellular membrane, disrupting ion pumps and affecting the homeostatic balance of cellular fluids, resulting in oedema. Combined influx of calcium, sodium and potassium through the depolarized neuronal and astrocytic membranes leads to catabolic (self-digesting) processes including blood-brain barrier breakdown increasing intracellular concentrations of free fatty acids and free radicals (Floyd et al., 2005; Werner & Engelhard, 2007). This metabolic crisis can culminate in cell death when prolonged.

Ischaemia (shortage of oxygen and glucose in tissues) following impaired cerebral blood flow contributes to the initiation of excitotoxicity, a mechanism resulting from dysfunctional excessive or prolonged release of excitatory amino acid neurotransmitters, particularly glutamate (Cornelius et al., 2013; Mehta et al., 2013). Under normal conditions, over-expression of glutamate is detected by the body and removed via transport mechanisms to the blood stream (Gottlieb et al., 2003). Following TBI, however, these mechanisms are overwhelmed and excessive glutamate overly excites post-synaptic *N*-methyl-D-aspartate receptors (NMDAR), culminating in massive inflow of calcium and sodium ions (Dubinsky, 1993). Importantly calcium, a key mediator in excitotoxicity, plays an important role in a number of cell death processes (Orrenius et al., 2003). Levels of calcium involved in excitotoxic mechanisms are a cumulative result of the release from endoplasmic reticulum and mitochondrial stores as well as from voltage-gated calcium channels, overwhelming regulatory mechanisms (Mehta et al., 2013; Szydlowska & Tymianski, 2010). Prolonged elevation of intracellular calcium levels affects mitochondrial function, causing oxidative stress through over-production of reactive oxygen and nitrogen species and opening of the mitochondrial permeability transition pore, releasing pro-apoptotic factors (Nicholls, 2004). These excitatory processes, along with exhaustion of the endogenous antioxidant system also result in excessive production of reactive oxygen species (ROS). Toxic levels of ROS causes peroxidation (oxidative degradation) of cellular and vascular structures, protein oxidation, cleavage of DNA, and inhibition of the mitochondrial electron transport chain (Juurlink & Paterson, 1998; Starkov et al., 2004). These mechanisms all contribute to inflammatory processes, necrosis and delayed apoptosis (Werner & Engelhard, 2007). At the functional level oxidative stress contributes to initiation of post-traumatic epileptic seizures (Pitkänen & Immonen, 2014; Shin et al., 2011). Thus, combined actions of the secondary cascade, related to the severity of injury, worsens the recovery profile of an individual post-TBI.

1.4.2.2. Breakdown of the blood-brain barrier (BBB).

Cellular degeneration and astrocyte disruption trigger breakdown of the BBB. In addition, brain trauma widens gap junctions in the BBB and this, along with disturbances in intercellular transport mechanisms, results in vascular autoregulation failure. Mechanical disruption also causes damage to the vasculature, releasing blood products which initiates the coagulation cascade, reducing blood flow and contributing to ischaemia in the regions of damage (Chodobski et al., 2011; Prakash & Carmichael, 2015). The upregulation of pro-inflammatory cytokines (including tumour necrosis factor alpha and interleukin 1 beta) as a response to trauma have also been demonstrated to be associated with opening of the BBB (Chodobski et al., 2011; de Vries et al., 1996; Deli et al., 2005; Shlosberg et al., 2010).

Investigators have shown that BBB disruption is bi-phasic; the first stage is triggered by mechanical forces involved in the primary insult and is transient, peaking a few hours post-injury before rapidly declining. This induces the secondary biochemical cascade to stimulate prolonged BBB disruption lasting between three to seven days post-injury. This second 'phase' has the potential to be more damaging to the brain. Evidence from single photon emission computed tomography (SPECT) of TBI patients and from immunostaining of post-mortem TBI brains indicate BBB disruption occurring at least seven years post-injury (Hay et al., 2015; Korn et al., 2005). Prolonged BBB disturbance is associated with other on-going secondary biochemical cascade mechanisms including neuroinflammation and microglial activation (Shlosberg et al., 2010). BBB disruption in TBI has also been suggested to have implications for susceptibility to neurodegenerative disorders like Alzheimer's disease through initiation of gene transcription changes (Hay et al., 2015; Shlosberg et al., 2010).

Although severe disruption to the BBB has negative consequences, it should be noted that relaxing of BBB selective permeability following trauma is required to allow immune and inflammatory cells to enter the parenchyma for neuroreparative mechanisms to be initiated (Finnie, 2013). As with other brain processes these neuroreparative mechanisms can go awry and become pathogenic.

1.4.2.3. Oedema.

Oedema (swelling) of brain tissue following the ischaemic-hypoxic events of TBI, is a major contributor to elevated intracranial pressure, reduced tissue perfusion and the secondary pathophysiological cascade (Finnie, 2013). Vasogenic (open barrier) oedema occurs following breakdown of the blood-brain barrier (BBB), either mechanically or through functional breakdown of the endothelial cell layer (Finnie, 2013; Werner &

Engelhard, 2007). Breakdown of the BBB results in uncontrolled influx of ions and extravasation (leakage) of protein-rich fluids causing fluid accumulation in the extra-cellular space and a concomitant rise in intra-cranial pressure (DeWitt & Prough, 2003; Finnie, 2013). If left untreated either via medication (e.g. hypertonic saline, mannitol), cerebral spinal fluid drainage or craniectomy, raised intra-cranial pressure can result in a poor outcome or death for the individual. Oedema may result in death as increased pressure in the fixed volume of the skull causes brain tissue (specifically the brain stem) to be pushed through the foramen magnum at the base of the skull (termed 'coning') crushing the vagus nerve and precipitating multiple organ failure (Chesnut et al., 2012; Petzold & Smith, 2006). In contrast, cytotoxic oedema as a result of intracellular water accumulation in neurons, astrocytes and microglia, does not compromise the BBB (Finnie, 2013). Cytotoxic oedema results from increased permeability of the cell membrane and failure of the ATP-dependant sodium/potassium ionic pumps following cellular energy depletion. As cytotoxic oedema reflects fluid exchange between extracellular and intracellular space it does not result in brain swelling or increased ICP but does negatively affect cellular function (Donkin & Vink, 2010; Werner & Engelhard, 2007).

1.4.2.4. Neuroinflammation.

One of the major unfolding responses following brain injury is neuroinflammation, a complex coordinated interplay of mechanisms with conflicting functions. The primary role of neuroinflammation is to preserve viable neural tissue and promote reparative processes by activating the innate immune response. Conversely, prolonged neuroinflammation can aggravate the initial injury by initiating the secondary cascade and worsen individual outcomes. Cellular and molecular mechanisms underlying inflammatory processes are complex and multifactorial. They include over-production of free radicals (reactive oxygen and nitrogen species), and activation of microglia and complement fragments (Finnie, 2013; Loane & Byrnes, 2010; Werner & Engelhard, 2007) .

Inflammatory processes are triggered by activation of the complement system cascade following injury (Cederberg & Siesjö, 2010). The complement system is composed of a network of over thirty different proteins (Sarma & Ward, 2011) and in simple terms these molecules recruit the inflammatory response, increase the permeability of the BBB and upregulate synthesis of cytokines (Bellander et al., 2001; Fluiter et al., 2014). The interaction between polymorphonuclear leucocytes (PMN), platelets and endothelial cells (EC) also plays an important role in mediating

neuroinflammation. Following upregulation of adhesion molecules (e.g. P-selectin, intracellular adhesion molecules, vascular adhesion molecules) leucocytes adhere to defective and intact EC, releasing chemokines, monocytes and PMN (Werner & Engelhard, 2007). Polymorphonuclear leukocytes, monocytes and resident microglia release a number of substances toxic to brain tissue including reactive oxygen and nitrogen species (ROS and RNS), leukotrienes, prostaglandins and pro-inflammatory cytokines (Finnie, 2013). Cytokines and chemokines are peptides in control of immune and inflammatory response recruitment to the regions of damage and the modulation of leukocytes. Pro-inflammatory cytokines including IL(interleukin)-1-a and b, IL-6, TNF (tumour necrosis factor)-a and IFN(interferon)-g are secreted soon after injury, and this release initiates synthesis of anti-inflammatory cytokines, for example IL-4, IL-10, IL-13 and TGF (transforming growth factor)-b, as part of an auto-regulatory feedback loop (Finnie, 2013).

Microglia (the brain's resident macrophages) play a major role in the response to brain injury (Loane & Byrnes, 2010). Under normal circumstances microglia scan the environment for damage. When damage has been detected the activated microglia become larger and increase in number to mobilise to the site of injury (Davalos et al., 2005). Microglial processes fuse to form an area of containment between healthy and injured tissue (Kumar & Loane, 2012) producing anti-inflammatory cytokines, growth factors and prostaglandins (Finnie, 2013). Conversely, when microglia become over-activated or reactive they can give rise to detrimental neurotoxic events through the release of multiple cytotoxic substances, including pro-inflammatory cytokines and oxidative metabolites (e.g. nitrous oxide, reactive oxygen species, reactive nitrogen species; Block & Hong, 2005). Nitrous oxide released by microglia may impair mitochondrial function contributing to over-release of glutamate leading to excitotoxicity and cell death (Finnie, 2013). Upregulation of microglia affects activation of astrocytes and consequent glial scar formation (Finnie, 2013; Zhang et al., 2010).

On the other hand, astrocytes provide support for damaged neurons and guide axonal regrowth following injury. During prolonged astrogliosis, astrocytes surrounding damaged tissue contribute to the formation of an extracellular matrix composing of microfilaments and neutropenes termed glial scar tissue. This scar tissue is formed as a physical barrier to propagation of secondary cascade processes to healthy tissue (Cregg et al., 2014). The glial scar inhibits axonal regeneration and the formation of functional connections (Cafferty et al., 2007; Cregg et al., 2014; McGraw et al., 2001). This barrier seems to be related to the inhibitory environment in the region surrounding the scar rather

than to the scar acting as a direct physical barrier (Fitch & Silver, 2008). Microglia-associated processes have been demonstrated to remain activated 17 years post-TBI in some individuals, particularly in sub-cortical structures (Gentleman et al., 2004; Ramlackhansingh et al., 2011). On diffusion tensor magnetic resonance imaging the greatest microglial activation was found in regions distal to the areas of brain damage (Ramlackhansingh et al., 2011) The findings arguably suggest that astrocyte activation and subsequent glial scarring prevents prolonged microglial activation in focal regions, but not persistent activation and associated inflammatory responses in distal regions.

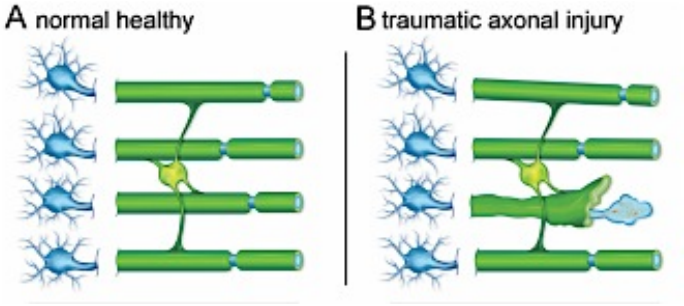
1.4.2.5. Diffuse Axonal Injury.

One of the most common neuropathological consequences for all severities of TBI is diffuse axonal injury. This has historically been difficult to capture by imaging but recent advances (for example diffusion tensor imaging) have demonstrated that even mild TBI results in white matter damage (Shenton et al., 2012). Mechanical forces acting upon axons within the cortex including extension, compression, shearing and rotational forces, result in a number of structural alterations. Complete transection of the axon (primary axotomy) usually only occurs in severe traumatic brain injuries (Bigler, 2001). The exception to this is the olfactory bulbs and extending fibres (fila olfactoria) situated beneath the frontal lobes that are vulnerable to shearing on the cribriform plate with anosmia (loss of smell) frequently reported following TBI, even following 'mild' injuries (Proskynitopoulos et al., 2016). Under normal conditions axonal structures are viscoelastic and able to cope with stretch encountered with routine head movement. During trauma, however, the rapid deformation causes axonal structures to become brittle. Microtubules (internal support structures of axons involved in axonal transport) periodically snap along their length with only a few microtubules broken in any given section of the axon (Tang-Schomer et al., 2012). This results in accumulation of essential organelles and proteins (for example amyloid precursor protein) being transported (Blennow et al., 2012; Finnie, 2013). In addition mechanical forces result in dysregulation of sodium channels causing opening of voltage gated calcium channels and associated calcium influx (Smith et al., 2013). The outcome of these physical and chemical alterations is the appearance of swellings (axonal varicosities) down sections of the axon forming a 'string of beads' (Johnson et al., 2013; Tang-Schomer et al., 2012). An alternative outcome is that a single large swelling (axonal bulb) is formed, usually indicative of complete axonal disconnection (Barkhoudarian et al., 2011; see Figure 1.18). Not all damaged axons are obliterated, some may recover. Equally axons that initially appear undamaged after TBI, with no interruption of axonal transport

mechanisms, may degenerate at a later time as a result of secondary cascade mechanisms (Johnson et al., 2013).

Figure 1.18

Axonal Injury Following Trauma.[Reprinted from Armstrong et al., (2016) under the terms of the Creative Commons Attribution 4.0 International License. http://creativecommons.org/licenses/by/4.0/]



It was previously thought that axonal injury processes were time limited, occurring only in the acute and sub-acute phases of injury. Research in individuals up to three years post-injury have however observed axonal varicosities and retraction bulbs in post-mortem brain slices (Chen et al., 2009). As varicosities either resolve or become axonal bulbs within a short period of time (two hours post-development; Smith et al., 2013) their presence at time points far removed from that of the initial injury is indicative of an on-going process. What is not clear is exactly how long after injury this delayed axonal injury can occur. It is suggested that delayed axonal injury occurs as a result of on-going neuroinflammatory processes (found by Ramlackhansingh et al., 2011 seventeen years post injury). It could therefore be posited that axonal disconnection may also co-occur at long duration after the initial injury. This adds weight to the theory that TBI is a life-long disease process rather than a single event with a fixed neuro-reparative/damaging time period in which clinical intervention can play a role (Masel & DeWitt, 2010).

1.5. Conclusion

In conclusion, almost 500,000 people sustain traumatic brain injuries each year, these injuries vary in severity and outcome. The secondary biochemical cascade following TBI affects cellular function at the level of the organelle, particularly cellular membranes, mitochondria and myelin, affecting cellular energy production and signal conduction within the neuron. Secondary cascade mechanisms significantly contribute to cognitive outcome and these deleterious changes within cells may continue for many years following the initial insult. The ongoing nature of the secondary cascade however presents an opportunity to intercede and attempt to reduce or potentially halt these

negative processes, whilst supporting neuroreparative repair mechanisms. Micronutrients (vitamins and minerals) and essential fatty acids are required for all cellular metabolic processes; catabolism (breakdown) of macronutrients (protein, carbohydrates and fats), synthesis of complex molecules to form cellular structures, and for cellular energy production within the mitochondria. There is therefore a clinical need for adequate levels of these dietary components following TBI and supplementation may meet this clinical need and a better understanding of their role in reparative processes and attenuation of secondary cascade effects.

Chapter Two: Function of Micronutrients in the Brain

2.1 Introduction

This chapter extends the literature review of Chapter One and focuses on the role of essential micronutrients (vitamins, minerals, omega-3 polyunsaturated fatty acids) within the cellular processes of the brain. This chapter will also explore research investigating the effect of deficiency and interventions on cellular processes and cognition in both normal and clinical populations.

The human diet is composed of macronutrients (proteins, carbohydrates, fats, fibre) and micronutrients (vitamins, minerals, essential fatty acids). Although macronutrients are required for energy and as building blocks for tissues, micronutrients support all essential metabolic processes within the body and are therefore crucial for normal function (Ames, 2006; Bourre, 2006a; Bourre, 2006b). The brain is a 'privileged' organ making up two percent of total body weight in adults but utilising 20% of the energy consumed and has priority for micronutrient provision, drawing from micronutrient stores elsewhere in the body if required (Bourre, 2006a). The recommended daily intake (RDI) of micronutrients is the estimated average dietary intake required to meet physiological requirements of most (97%-98%) of the population (Otten et al., 2006). Over consumption of calorie-dense, nutrient poor, and ultra-processed food is common in western diets (Monteiro, 2009; Monteiro et al., 2013). Long-term consumption of such diets results in 'hidden hunger', a term referring to deficiency in essential micronutrients (Monteiro, 2009; O'Neil et al., 2012; Zhao & Shewry, 2011). Hidden hunger is increasingly being reported in the developed world, particularly for folic acid, vitamin D, vitamin E, and iron (Biesalski, 2013); individuals may meet or surpass dietary intake to meet kilocalorie requirements, however the food may not be of sufficient nutritional quality to defend against chronic illness and disease states (e.g. heart disease, diabetes and stroke). In addition, analysis of soil and crops has demonstrated that large scale agricultural practices, driven by a desire to produce higher yields for lower cost, have resulted in a steep decline in micronutrient levels in fruits, vegetables and grains in both the United Kingdom and the United States (Davis, 2009; Mayer, 1997). This decline appears to have arisen as a result of selective plant breeding and use of chemical fertilizers on land that is continuously replanted, with little attention paid to how these practices

affect micronutrient levels (Sands et al., 2009). Considered together dietary patterns and agricultural practices may diminish the nutritional content of food in Western populations. This has potential consequences for those with poor health who require good levels of nutritional support.

Humans require 51 nutrients (including amino acids and fats), of these 19 are essential micronutrients (vitamins and minerals) that cannot be synthesized by the body. Vitamins are categorised into two groups: water-soluble (vitamin C and the eight B vitamins) and fat-soluble (vitamins A, D, E and K). Generally, although not exclusively, intake of water-soluble vitamins in excess of physiological need is excreted (Tsuji et al., 2010) whereas excess fat-soluble vitamins can be stored (Sathe & Patel, 2010). Vitamins that are not stored by the body therefore need to be consumed on a daily basis to retain adequate levels within the body. Minerals are similarly critical for physiological function; of the 19 essential micronutrients six are minerals (calcium, iodine, iron, magnesium, selenium and zinc). In addition to vitamins and minerals, omega-3 polyunsaturated fatty acids play a crucial role in health, notably brain health (Farooqui et al., 2007; Pu et al., 2013). Dietary sources of these essential micronutrients are presented in Table 2.1.

Micronutrients are necessary for physical health, an effective immune response, and for cognitive function. The result of poor nutrition on physiological health is well understood (Costarelli et al., 2013) and there is growing interest in how diet affects brain function and cognition in both normative and clinical populations (Amen et al., 2013; Kennedy 2016; Lam & Lawlis, 2017; Pillsbury et al., 2011; Tardy et al., 2020; Wahls et al., 2014).

Table 2.1
Dietary sources of micronutrients

Micronutrient	Dietary Source									
	Meat	Fish	Shellfish	Dairy and Eggs	Vegetables	Fruit	Cereals and Grains	Legumes	Nuts and Seeds	Other
Vitamin A	✓			✓	✓ Green Leafy	✓			✓	
Vitamin B_1	✓						✓			✓ Yeast
Vitamin B_2	✓	✓		✓	✓*					
Vitamin B_3	✓	✓		✓		✓ Selected	✓			
Vitamin B_5	✓			✓ Eggs	✓ Selected	✓ Selected	✓			
Vitamin B_6	✓	✓		✓	✓	✓ Selected	✓	✓	✓ Nuts	
Vitamin B_7	✓ Liver			✓ Egg Yolk	✓	✓		✓		
Vitamin B_9	✓				✓ Green Leafy	✓		✓		
Vitamin B_{12}	✓	✓	✓	✓ Eggs	✓*	✓*				✓ Seaweed
Vitamin C					✓	✓				
Vitamin D	✓ Organ	✓ Oily		✓						
Vitamin E									✓	✓ Veg. Oils
Vitamin K	✓* Liver	✓*			✓* Brassicas	✓*				
Calcium		✓		✓	✓ Green Leafy			✓		
Iron	✓		✓ Oysters	✓ Eggs		✓ Dried		✓ Dried		
Iodine		✓	✓	✓		✓				✓ Seaweed
Magnesium					✓ Green Leafy		✓	✓	✓	
Selenium	✓	✓	✓	✓ Eggs				✓	✓	
Zinc	✓		✓				✓	✓	✓	
Omega-3		✓ Oily			✓ Green Leafy				✓	✓ Algae Oil

Note: * low levels of bioavailability

2.2 Water-Soluble Vitamins

2.2.1 Vitamin C

Ascorbic acid (vitamin C) has a number of important functions including as a powerful antioxidant and being involved in immune function in the innate and adaptive immune system (Carr & Maggini, 2017; Sorice et al., 2014). As an antioxidant vitamin C, in combination with vitamin E and glutathione, directly scavenges reactive oxygen species (for example superoxides) generated during the production of adenosine triphosphate (ATP), the molecule that provides energy for cellular metabolism. Antioxidants therefore reduce oxidative stress-associated damage that would occur in their absence (Harrison et al., 2010). Levels of ascorbic acid are much higher in the brain compared with other tissue (Harrison et al., 2014). High ascorbate levels are also found in the eye (an extension of the brain) along with cells and tissues involved in the immune response including leukocytes[13] and the adrenal and pituitary glands (Agus et al., 1997; Johnston et al., 2014). The brain retains ascorbate during periods of dietary insufficiency and is the organ most resistant to depletion, however during periods of metabolic stress vitamin C is quickly utilised (Harrison & May, 2009). In a gulonolactone oxidase[14] knockout mouse model brain ascorbic acid concentrations in supplemented mice showed higher levels of vitamin C in the cerebellum, olfactory bulbs and frontal cortex compared wild-type mouse controls, indicating that these highly metabolically active regions are more susceptible to oxidative stress (Harrison et al., 2010). Research in mice reflects findings in humans that vitamin C levels in the circulating blood stream following ischaemia reperfusion injury (for example following a stroke) can be quickly depleted following increased free radical generation (Polidori et al., 2001). There is also evidence of a relationship between vitamin C levels and cellular aging and senescence in both mice and humans with levels of vitamin C found to be depleted in the pituitary gland, cortex and hippocampus (Schaus, 1957; Siqueira et al., 2011). Research in mouse models of AD has also found that elevating levels of vitamin C intake halted disease progression via reducing oxidative stress and neuroinflammation (Monacelli et al., 2017). This research emphases the importance of the antioxidant and immunomodulatory role of vitamin C in maintaining good brain health. This is particularly important following TBI as the secondary cascade impacts cellular energy production, increasing production of reactive

[13] A type of white blood cell, other white blood cell types include lymphocytes, granulocytes, and monocytes.

[14] The enzyme responsible for the manufacture of ascorbate in all mammals apart from primates.

oxygen species, and causes neuroinflammation resulting in increased utilisation of vitamin C (Polidori et al., 2001).

Research investigating any putative effect of vitamin C on cognition is limited. Studies again in AD mouse models have shown that administration of ascorbate (dosage 100-125mg/kg) can improve learning, memory and locomotor function, particularly in older animals (Harrison et al., 2009; Parle & Dhingra, 2003). These results are however not consistently repeated in studies with rats (Harrison & May, 2009), and without similar studies human populations it is not possible to determine any transferable effects. Research in human populations has investigated a possible relationship between blood plasma ascorbate levels and incidence of Alzheimer's disease, with a number of meta-analyses suggesting that lower blood plasma ascorbate levels are found in Alzheimer's patients compared with healthy age matched controls (e.g. Cao et al., 2016). Data included in these meta-analyses, however, do not consistently find a link (e.g. Charlton et al., 2004 found a link; da Silva et al., 2014 did not). Research involving supplementation with large dose vitamin C (1,000mg/day) and E (400 IU/day) in Alzheimer's disease patients found no significant change in Mini-Mental State Examination scores compared to matched controls after one year of supplementation (Arlt et al., 2012).

In summary vitamin C (ascorbate) performs a wide range of vital functions within the brain and there is evidence that ascorbate levels are reduced in dementia patients and following traumatic brain injury. There are, however, limited studies investigating the role of vitamin C in improving cognitive functions in healthy adults.

2.2.2. B Vitamins

The remaining water-soluble vitamins are referred to as the B-complex. These are grouped together due to inter-related functionality as well as the water-soluble nature of these eight micronutrients (thiamine, riboflavin, niacin, pantothenic acid, biotin, B_6, folate, B_{12}). Although these vitamins are crucial for normal cellular function, research investigating the effects on neural function and cognition of many B vitamins (except B_6, B_9, and B_{12}) is limited (Kennedy, 2016). Dietary sources of these vitamins overlap, therefore deficiency in one may indicate deficiency in another.

2.2.2.1. Vitamin B_1

The term 'B_1' refers to the vitamers[15] thiamine and thiamine pyrophosphate, collectively termed thiamine. Thiamine is present in many food sources including meat (particularly pork), yeast and cereals (Bettendorff, 2013). Thiamine diphosphate (ThDP) accounts for 80% of thiamine in the brain (Guerrini et al., 2009) and serves as a cofactor in critical metabolic pathway enzymatic reactions. Specifically, thiamine is involved in the glycolytic pathway[16], citric acid (Krebs) cycle[17], pentose phosphate pathway[18] and metabolism of branched chain amino acids as 'fuel' for the citric acid cycle (Fattal-Valevski, 2011). Sub-clinical deficiency is potentially common in the general population; symptoms are nonspecific and include fatigue, chest pain, poor appetite, memory problems and abdominal pain and as such maybe overlooked or misattributed (Fattal-Valevski, 2011).

Clinical deficiency of thiamine is seen in both the developed and underdeveloped world, however deficiency in these different environments takes different forms. In developing nations deficiency arises where the diet consists mainly of white rice and where poor access to clean drinking water causes diarrhoea. Deficiency presents as either 'wet' (affecting the cardiovascular system) or 'dry' beriberi (affecting the nervous system). Individuals with dry beriberi can present with confusion, visual disturbance and emotional lability (Bettendorff, 2013; Fattal-Valevski, 2011). In more affluent societies thiamine deficiency is most commonly seen in those with chronic alcohol consumption, although it is also seen in women with severe morning sickness (hyperemesis gravidarum; Jhala & Hazell, 2011). In chronic alcohol consumption deficiency arises as a result of poor diet (alcohol consumed instead of food) and inflammation of the gut impeding micronutrient uptake. At its most extreme this results in the development of Wernicke-Korsakoff syndrome (Martin et al., 2003), initially characterised by eye movement and gait disturbances, widespread peripheral nerve damage, and cognitive alterations (Wernicke's encephalopathy; Bettendorff, 2013; Delaffon et al., 2013). High dose thiamine supplement is used as a treatment however recovery may be incomplete, particularly with respect to cognitive deficits including apathy, confusion and reduced attention span. Repeated episodes of Wernicke's encephalopathy may lead to Korsakoff's

[15] Chemical compounds having similar molecular structures and fulfilling the same vitamin function.

[16] The catabolic process by which glucose is broken down into pyruvate (glycolysis).

[17] Chemical reactions that released stored energy in carbohydrates, fats and proteins.

[18] Primarily anabolic process parallel to glycolysis, generating NADPH, pentoses and ribose 5-phosphate.

psychosis characterised by more complex cognitive deficits including an inability to form new memories, disorientation to time and space, and confabulation (Bettendorff, 2013).

Thiamine deficiency in Wernicke's encephalopathy also results in metabolic and cellular changes that are also seen in neurodegeneration, stroke and TBI including impaired energy production, excitotoxicity, oxidative stress, neuroinflammation and cerebral oedema, along with damage to the microvasculature and breakdown of blood-brain barrier integrity (Jhala & Hazell, 2011). This is not to say that thiamine deficiency necessarily plays a role in any of these conditions, however what this research does emphasise is that adequate thiamine intake is important in individuals who have sustained damage to the brain. When looking the role of thiamine in cognition in healthy aging there is some evidence of better overall cognition in those with higher blood plasma thiamine levels. Research by Lu et al., (2015) in 636 individuals (mean age 72 years) not taking supplements and with no history of chronic gastrointestinal problems or chronic alcohol abuse found a positive correlation between thiamine diphosphate (TDP) blood plasma levels and MMSE (Mini Mental State Examination) scores. Those with high TDP levels performed significantly better on Recall, Attention and Calculation sub-scores, but not on Registration, indicating that thiamine may play a role in reducing memory decline. A systematic review evaluating research investigating the link between blood plasma thiamine levels and cognitive function in healthy aging however concluded that the evidence for this link was inconclusive to date (Koh et al., 2015). The authors stated that these findings were 'surprising' given the important role thiamine plays in neuronal function, citing the lack of research and randomized control trials as the greatest factor in being unable to come to firm conclusions. Further research is therefore needed to evaluate the potential contribution of optimal levels of thiamine to improve cognition, particularly memory.

2.2.2.2. Vitamin B_2

Unlike thiamine only small amounts of free riboflavin (vitamin B_2) are available from foods. Most riboflavin is ingested in the fully reduced vitamer flavin adenine dinucleotide (FAD) and a lesser amount in the partially reduced vitamer flavin mononucleotide (FMN) (Barile et al., 2016). Riboflavin coenzymes are not widely considered to have antioxidant properties; however, FAD may be required to reduce oxidised glutathione [19] (Ashoori & Saedisomeolia, 2014). The effect of riboflavin supplementation on reducing oxidative stress damage to tissues has limited research in

[19] Glutathione exists in oxidised and reduced states with higher levels of oxidised glutathione a marker of oxidative stress.

man and mixed results in animal models (Ashoori & Saedisomeolia, 2014; Dutta et al., 1990; Huang et al., 2010). The potential of riboflavin as a potential antioxidant is important following brain injury a key component of the secondary cascade following TBI is oxidative stress. Independent of potential involvement in the glutathione redox cycle, riboflavin may reduce antioxidant levels by directly scavenging free radicals through deactivation of hydroperoxide and via interactions with other antioxidants (Ashoori & Saedisomeolia, 2014). In addition to a potential antioxidant function riboflavin is involved in the activation of a number of other B vitamins, specifically folic acid (B_9), pyroxidine (B_6) and cobalamin (B_{12}) (Northrop-Clewes & Thurnham, 2012; Powers, 2003). Deficiency in riboflavin therefore has broader implications for cellular function as deficiency in this vitamin may indirectly affect the action of other B-group vitamins within the brain.

There has been no research investigating the effect of riboflavin deficiency on cognition in humans, despite the established involvement of riboflavin coenzymes in key metabolic functions. There has, however, been some promising findings from research investigating the potential role of riboflavin as a treatment in head injury, primarily in rodent models. Pre-treatment with riboflavin in an ischaemic stroke model in rats (where blood vessels were cauterised or occluded with thread) found that treated rats, compared to those given saline, showed reduced oedema and associated ischaemic brain injury (Betz et al., 1994). In a cortical contusion injury model of TBI in rats (unilateral) found that a combined riboflavin and magnesium intervention post injury resulted in improved sensorimotor compared with a saline control with a concomitant reduction in lesion size and oedema (Barbre & Hoane, 2006). Using a similar model of TBI Hoane et al., (2005) also found that post-injury infusion of riboflavin resulted in improved cognition (as measured by performance on a Morris water maze task), reduced oedema formation and reduced activation of glial fibrillary acidic protein+ (GFAP) astrocytes. These findings indicate better recovery from TBI in treated rats compared to saline controls. This animal data holds promise for human studies, particularly in those having sustained brain injuries or with dementia.

2.2.2.3. Vitamin B_3

Vitamin B_3 primarily acts as the precursor to nicotinamide adenine dinucleotide (NAD^+) and has three vitamers; nicotinamide, nicotinamide riboside and nicotinic acid, commonly referred to as niacin (Xu & Sauve, 2010). NAD^+ and its metabolites are involved in cellular metabolism (e.g. glycolysis and the citric acid cycle), DNA repair, cell protection, oxidative phosphorylation and cellular signalling (Chi & Sauve, 2013;

Pollak et al., 2007; Sauve, 2008). Cell stressors including DNA damage and inflammation, which are features of the secondary cascade following TBI, up-regulate NAD^+- consuming reactions in in-vitro studies (Bogan & Brenner, 2008; Hassa et al., 2006). This results in depletion of NAD^+ which has a direct impact on ATP production in direct proportion to the severity of cellular stress (Hassa et al., 2006). This reduction in NAD+ levels therefore compromises the cell's ability to produce energy, affecting all cellular processes and potentially leading to cell death. Pellagra, the condition associated with niacin deficiency, has a triumvirate of classic symptoms; dermatitis, dementia and diarrhoea. Neurologically an individual in the early stages of pellagra may present with low mood, irritability, ataxia and apathy, but in more severe cases unconsciousness and coma can occur (Hammond et al., 2013). The severity of the neurological symptoms of pellagra with potential for death emphasises the fundamental importance of niacin to cellular function and a course of high-dose supplements (50 mg two to three times daily) reverses symptoms in most individuals (Hammond et al., 2013).

Investigations into the potential role of niacin following head injury have primarily used using similar rodent models of TBI (cortical contusion injury; Haar et al., 2011; Hoane, Gilbert et al., 2006; Hoane, Kaplan & Ellis, 2006; Hoane et al., 2008) . This research has shown that niacin infusions at time points up to 72 hours post-injury have a number of beneficial effects following injury including reduction of secondary cascade processes and improvements in cognition, although dosage if infusion varies between studies. Hoane, Gilbert et al., (2006) found that treated rats given 500mg/kg nicotinamide showed reduced severity of perfusion injury and improved working memory performance on the Morris water maze compared to rats given saline. In a similar study (Hoane, Kaplan and Ellis, 2006) treated rats given the same dosage of nicotinamide showed better blood-brain barrier integrity and reduced neuronal cell loss compared to rats given saline. Research investigating whether timing of administration affecting blood plasma levels of niacin found higher levels in rats given the infusion 15 minutes post-injury, compared with rats infused 4- or 8-hours post-injury. This indicates that there may be an optimum period for administration of this vitamin, however how this translates into humans is yet to be elucidated.

Another damaging mechanism of the secondary cascade following TBI is oxidative stress. Overexpression of reactive oxygen species, as seen following traumatic brain injury, results in the overactivation of PARP1 (poly [ADP-ribose] polymerase 1), an enzyme involved in DNA repair (Cantó et al., 2015). PARP1 requires NAD^+ as a coenzyme and stores can be quickly depleted during oxidative stress, affecting DNA

repair and cellular energy production as a result (Xu & Sauve, 2010). It has also been suggested that maintenance of NAD+ levels can be neuroprotective, with axonal degeneration significantly slowed when NAD+ precursors are present. The exact mechanism behind this is unclear, but reduced NAD+ levels potentially results in energy shortage in the axon, leading to degeneration (Araki et al., 2004; Pease & Segal, 2014; Sauve, 2008). Alternatively, other research has suggested that axonal degeneration has a greater association with the accumulation of nicotinamide mononucleotide (NMN) rather than depletion of NAD+ (Di Stefano et al., 2015). Combined this evidence indicates that maintenance of adequate levels of niacin may contribute to better outcome following traumatic brain injury in animals and findings might be transferable to humans.

2.2.2.4. Vitamin B_5

The primary function of pantothenic acid (vitamin B_5) is as a precursor for coenzyme A (CoA) an enzyme involved alone or with other enzymes in hundreds of metabolic processes including synthesis of fatty acids and production of melatonin, cortisol and acetylcholine (Pietrocola et al., 2015; Spry et al., 2008). Acetyl- CoA, along with B_1 (thiamine) and B_3 (niacin), is required in the citric acid cycle, specifically in the oxidation of pyruvate. Pyruvate is a product of glycolysis, so that it can enter the citric acid cycle (the next step in cellular energy production) it needs to be oxidised, this process requiring these three B vitamins. Acetyl and acyl transfer reactions in the metabolism of fatty acids, carbohydrates, amino acids and ketones also require acetyl-CoA (Dansie et al., 2014; Rucker & Bauerly, 2013). This highlights the diversity of the involvement of CoA in metabolism of foods required as the basic building blocks of growth and repair. Metabolic reactions involving CoA derived from pantothenic acid are crucial for normal physiological function, however there is no research to date indicating a role for pantothenic acid levels in cognition.

2.2.2.5. Vitamin B_6

The term 'B_6' refers to three pyridine-based vitamers with the biologically most active form (pyridoxal 5'-phosphate; PLP) estimated to be a cofactor for over 140 enzymes, contributing to four percent of known catalytic reactions (Amadasi et al., 2007; Di Salvo, Contestabile, & Safo, 2011). B_6 is found in a wide cross-section of foods, however a study in a large general population sample (>6000 participants) in the United States found B_6 insufficiency across all age ranges, with between 16% and 32% of individuals insufficient (Morris, Picciano, Jacques, & Selhub, 2008).

A diverse number of physiological processes require B_6. These include the formation and metabolism of red blood cells (erythrocytes), conversion of the amino acid

tryptophan to niacin, and cytokine production. B_6 is also involved in homocysteine modulation and one-carbon metabolism (da Silva et al., 2013; Hellmann & Mooney, 2010; Leklem, 2001; Morris et al., 2010). Elevated homocysteine levels are associated with cardiovascular disease but have also been demonstrated to be associated with brain atrophy in Alzheimer's disease (Rajagopalan et al., 2011). One-carbon metabolism is the term for a series of interlinked metabolic pathways that also involve folate (B_9) that provides methyl groups for DNA synthesis along with polyamines, amino acids, creatine and phospholipids (Ducker & Rabinowitz, 2017). Collectively these processes underpin the building blocks required for growth and maintenance of healthy cells and tissues. Also, of significance to neural function is the involvement of PLP in the synthesis and metabolism of many neurotransmitters including serotonin (5-hydroxytryptamine), dopamine, adrenaline, noradrenaline and γ-aminobutyric acid (GABA) (Ebadi, 1978; Hellmann & Mooney, 2010; Leklem, 2001).

Another important relationship is the link between plasma PLP levels and inflammatory states, potentially through the role B_6 plays as a co-enzyme in immunomodulating metabolite reactions (Ueland et al., 2017). Research in humans has demonstrated that there is an inverse relationship between levels of PLP and the inflammatory marker C-reactive protein (CRP), indicating that B_6 intake is protective against inflammation (Morris et al., 2010). When this relationship was explored further and healthy individuals were compared with those with inflammatory conditions, and therefore higher levels of CRP, inflammatory conditions resulted in higher levels of PLP insufficiency at the same level of B_6 intake. This demonstrates that there is greater utilisation of B_6 in inflammatory conditions, compared to healthy individuals, requiring higher levels of intake to reduce inflammatory processes. Therefore, if levels of plasma B_6 are initially insufficient this may negatively impact acute and chronic inflammatory states through inefficient biochemical reactions. This may be a factor following traumatic brain injury, however there has been no research investigating this to date.

Overall vitamin B_6 plays a crucial role in healthy metabolism and mood state. In a longitudinal study (4 years) low baseline B_6 levels were shown to be associated with greater cognitive decline in an aging population (60-88 years) than with individuals with adequate B_6 (Hughes et al., 2017). Individuals were assessed using MMSE at baseline and four years later; those with low plasma PLP status (<43nmol/L) were found to have greater than expected decline in MMSE score (>0.56 points/year), calculated to be a 3.5x higher risk of accelerated cognitive decline. Collectively this evidence highlights the

central role B_6 plays in neural metabolism, immune response and biochemical cascades, with evidence that deficiency has the potential to affect cognitive functions.

2.2.2.6. Vitamin B_7

Compared with other water-soluble vitamins levels of biotin (vitamin B_7) in blood plasma are relatively small, reflecting low levels of biotin found within foods (Mock, 2014). Bioavailability of biotin, however, is very high (~100%) and is supported by continuous recycling within cells (Zempleni & Mock, 1999), therefore deficiency in humans occurs infrequently. In an early study biotin deficiency was induced in four individuals through dietary restriction in an in-patient setting for eight weeks. In the fifth week of the study neurological symptoms developed including depression, inactivity, hallucinations, seizures, lack of coordination, hearing loss, damaged vision and spasticity of lower limbs (Sydenstricker et al., 1942).

Biotin is required in biosynthesis of omega-6 fatty acids and glucose, and in many intermediary steps of the citric acid cycle (Pindolia et al., 2012; Tourbah et al., 2016). Recently evidence has indicated that biotin supplementation may have a role in treating multiple sclerosis (MS), a condition categorised by loss of myelin (Sedel et al., 2015; Sedel et al., 2016; Tourbah, 2015); as biotin-dependent reactions are involved in biosynthesis of fatty acids in oligodendrocytes, the cellular basis of myelin production (Tourbah, 2015), biotin supplementation may contribute to myelin repair mechanisms. Following demyelination loss of insulation of axons abolishes saltatory conduction; the propagation of the action potential from leaping from one node of Ranvier to another. This causes a switch to continuous conduction, increasing energy demands to maintain ion gradients. This increased energy demand indicated within the axon by increased numbers of mitochondria (Levin et al., 2014). The involvement of biotin in the synthesis of metabolites for the citric acid cycle within the mitochondria may be another explanation for measured improvement in motor and visual function seen in MS patients after high-dose biotin treatment 100-300mg/day over 2-36 months (mean 9.2 months) (Sedel et al., 2016). Biotin supplementation could therefore support axonal recovery post-traumatic brain injury in a similar way to the mechanisms in MS, particularly as biotin is not known to be toxic.

2.2.2.7. Vitamin B_9

Vitamin B_9, more commonly known as ‘folate’, refers to all forms of pteryl-monoglutamic acid including the fully oxidised synthetic form (folic acid) used in supplements and enriched foods (Czeizel et al., 2013; Patanwala et al., 2014). The key function of folate is as a component in the formation of methylenetetrahydrofolate

(methylTHF) (Selhub, 2001) involved in biosynthesis of thymidine, one of the four base pairs utilised in DNA synthesis and repair (Barua et al., 2014; Selhub, 2001). MethylTHF is then involved in a reaction with homocysteine (with B_{12} as a co-enzyme) to form the amino acid methionine (Barua et al., 2014). Methionine acts as a precursor in the formation of *S*-adenosylmethionine (SAM), involved in many reactions contributing to the formation of DNA, RNA, hormones, neurotransmitters, membrane proteins and lipids (McNeil et al., 2011; Selhub, 2001; Wallingford et al., 2013). The direct involvement of folate in DNA and RNA synthesis means that insufficient levels of folate intake, either from diet or supplements, has the potential to dysregulate gene expression causing faults in replication (Kim et al., 2009).

During the above-mentioned reactions SAM is irreversibly converted to *S*-adenosylhomocysteine (SAH). Hydrolysis of SAH results in formation of adenosine, and homocysteine (Bailey et al., 2014); as homocysteine is toxic the body attempts to neutralise it quickly. Approximately half is metabolized to methionine, requiring vitamin B_{12} as a co-factor, the other half is involved in the synthesis of cysteine (an amino acid) in reactions also requiring pyridoxal-5'-phosphate (vitamin B_6) as a co-factor (Bailey et al., 2014; Barua et al., 2014). Elevated levels of homocysteine cause oxidative stress leading to pathological and epigenetic changes, however the underlying mechanisms behind these changes remain unclear. Evidence from research has shown that folate supplementation reduces levels of homocysteine and associated oxidative stress (Kalani et al., 2014). Examination of a number of meta-analyses indicates that the reduction in homocysteine following folic acid supplementation is between 20-25% (Clarke et al., 2010; Wang et al., 2007). There is, however, a lack of agreement on whether these reductions in homocysteine are associated with reduced risk of cardiovascular disease or stroke with findings ranging between no significant effect (Clarke et al, 2010), a trend towards an effect (Lee et al., 2010) and a significant effect (Wang et al., 2007). It can therefore only be said that findings are inconclusive in terms of the efficacy of folate supplementation in cardiovascular disease, however it is clear that supplementation with this vitamin does have a positive effect on moderation of homocysteine levels, reducing oxidative stress.

Vitamin B_9 clearly has a significant role to play in normal neural function. Evidence that low levels may increase oxidative stress indicate that optimal levels of this micronutrient may be beneficial to recovery post head injury, however more data is clearly needed.

2.2.2.8. Vitamin B_{12}

Cobalamin is the name given to forms of vitamin B_{12}. B_{12} is stored within the body and therefore deficiency may not become evident until later adulthood or old age. It has been calculated that in complete absence of B_{12} in the diet it would take between three to five years to deplete stores (Briani et al., 2013). Clinical cobalamin deficiency can arise through the autoimmune condition pernicious anaemia, in which individuals are not able to absorb B_{12} as they do not produce the necessary intrinsic factor in the stomach (Briani et al., 2013). Cobalamin acts as a cofactor in a number of metabolic reactions, particularly in mitochondria where it acts as coenzymes in key intermediate steps in the citric acid cycle. Cobalamin is also involved in the metabolic reactions involved in the synthesis and maintenance of myelin (Briani et al., 2013; Brito et al., 2016; Moll & Davis, 2017). Vitamin B_{12} deficiency may therefore result in defective myelin synthesis or demyelination (particularly in the spinal cord and occasionally the brain), affecting the functioning of the nervous system (Scalabrino, 2009). In addition, cobalamin acts as a catalyst for nitric oxide synthase, producing nitric oxide for cell signalling and vasodilation (Wheatley, 2012).

Another important function of cobalamin is as a coenzyme in folate-dependant methylation of homocysteine into methionine, as described in the previous section on folate. B_{12} deficiency causes folate in the form of tetrahydrofolate (THF) to become trapped, as cobalamin is required to free THF from 5-methylTHF in an irreversible reaction. The physiological consequence is an accumulation of homocysteine and methylmalonic acid as the methylation reaction is halted, increasing oxidative stress and affecting myelin synthesis. In individuals with sufficient or high intakes of folate the B_{12} deficiency may be hidden; levels of folate may be high enough for erythrocyte maturation and DNA synthesis, avoiding overt symptoms of deficiency (Cuskelly et al., 2007).

Those with B_{12} deficiency may present with haemolytic or neurological symptoms. Neurological symptoms of B_{12} (peripheral and autonomic neuropathy, gait ataxia, optic atrophy, anosmia, impaired proprioception, mood disorders and psychosis) can occur with or without haematological changes (anaemia), with 19% to 24% of clinically deficient patients presenting with no anaemia (Carmel, 2013). If not treated with supplements neurological changes can be irreversible (Bar-Shai et al., 2011; Briani et al., 2013; Jayaram et al., 2013; McCaddon, 2013). Links have also been drawn between sub-clinically low B_{12} levels and neurodegenerative diseases of aging, particularly Alzheimer's disease, vascular dementia and Parkinson's disease (Moore et al., 2012). The link may not be causal as these diseases have an inflammatory component worsened by

raised homocysteine levels and oxidative stress associated with B_{12} (and folate) deficiency (Lucas et al., 2006; McCaddon, 2013). Cobalamin deficiency is particularly relevant in head injured populations as signal conduction in peripheral white matter has been shown to improve following cobalamin supplementation in overtly asymptomatic but deficient individuals (Brito et al., 2016) where neurological changes associated with deficiency may be present (Smith & Refsum, 2011). Further evidence for this comes from reports of frontal-dysexecutive syndrome in cobalamin deficient but otherwise healthy aging individuals, with verbal fluency, inhibition, and flexibility of thinking affected (Akdal et al., 2008; Blundo et al., 2011; Briani et al., 2013).

2.3 Fat-soluble vitamins

Unlike water-soluble vitamins that vary in methods of absorption and storage, fat-soluble vitamins are all absorbed, transported and stored in the same way as other lipids (Goncalves et al., 2015). As such absorption of fat-soluble vitamins is more efficient when ingested with other fats in a meal (Borel et al., 2013; Niramitmahapanya et al., 2011; Shearer et al., 2012; van het Hof et al., 2000).

2.3.1. Vitamin A

Retinoic acid (RA: vitamin A) plays a critical role in embryonic neurological development, particularly early in gestation with both deficiency and excess resulting in teratogenic neural tube defects (Maden, 2002; Ransom et al., 2014). RA metabolites continue to be involved in neuronal differentiation, axonal outgrowth, myelination, and remyelination in the adult brain (Huang et al., 2011; Maden, 2007). Retinoic acid receptors (RARs), retinoid X receptors (RXRs), retinoid binding proteins (RBPs) and RA enzymes are also widely distributed within the adult brain, particularly in the hippocampus, limbic system, cortex, olfactory bulb and optic tract, potentially involving retinoids in learning and memory (Maden, 2007). Results of studies in RXR-γ knockout rats found severe inhibition of oligodendrocyte differentiation *in vivo*, reducing remyelination in induced lesions in a multiple sclerosis model (Huang et al., 2011). Research in rodents has also indicated that down-regulation in RA signalling in during aging may contribute to incidence of age-related neurodegeneration (Maden, 2007). Finally, it has been reported that RAR-β contributes to slow wave sleep in mice through indirect regulation of delta waves (Maret et al., 2005; Ransom et al., 2014), which may be another way vitamin A is involved in learning and memory as these are consolidated during sleep.

In conclusion vitamin A plays a number of crucial roles in human growth, development and repair. Deficiency is rare in the UK due to the broad number of food sources; however, it is important that levels are maintained as low levels may contribute to neurodegeneration.

2.4 Vitamin D

Unlike the other water or fat-soluble vitamins vitamin D (calciferol) is not a true vitamin but a fat-soluble seco-steroid. The majority of vitamin D is formed in the skin after exposure to ultraviolet B radiation (sunlight) to form vitamin D_3. Smaller amounts, insufficient to maintain required levels, can be derived from dietary sources in the form of D_2 (Holick et al., 2011; Pittas et al., 2010).

Vitamin D is considered a neuroactive steroid as it is both synthesized and has sites of action throughout the central nervous system (Norman, 2008; Pearce & Cheetham, 2010), and is able to cross the blood-brain barrier (Harms et al., 2011). Vitamin D hormone, the bioactive form of the vitamin, is a potent modulator of the cell cycle, immune function, and of calcium homeostasis (Pearce & Cheetham, 2010; Sassi et al., 2018). Neurons express vitamin D receptors (VDRs) making them a potential target tissue for vitamin D metabolites. VDRs appear to stimulate intracellular signalling pathways (Carlberg & Campbell, 2013) and are most abundantly expressed in the hypothalamus, substantia nigra, cortex and hippocampus (Annweiler et al., 2009; Garcion et al., 2002; Oudshoorn et al., 2008). The presence of VDRs in pathways responsible for a diverse functions including physiological homeostasis, movement, learning and memory, emphasises the importance of this micronutrient.

Vitamin D deficiency is common in the UK, with 25% of the general population deficient in the summer months and 60% in the winter (Webb et al., 2010), reflecting similar patterns in other countries in the northern hemisphere (Flicker et al., 2003; Romagnoli et al., 1999; Wilkins et al., 2009). Several medications are prescribed to prevent or manage seizures following TBI (for example phenytoin, carbamazepine). These have the unwanted side effect of elevating renal metabolism of vitamin D and so individuals prescribed these medications may require additional supplementation as a precaution (Siniscalchi et al., 2016).

Research has been conducted investigating links between low plasma vitamin D levels and cognitive and physical function in a number of populations. In a study investigating the relationship between vitamin D levels and cognition across three age ranges (adolescents 12-17 years, adults 20-60 years, older adults 60-90 years) no association was found between performance on cognitive tasks administered (learning

and memory in the older adults, processing speed and attention in the other two groups) and plasma vitamin D (McGrath et al. 2007). Manzo et al., (2016) also found no association between plasma vitamin D levels and performance on the Mini Mental State Examination (MMSE), a test of everyday mental skills used to assess cognitive decline, in older adults either at baseline or after a six-month vitamin D intervention. In contrast to these studies Laughlin et al., (2017) did find a relationship between vitamin D insufficiency (<30ng/mL) and poorer performance on MMSE, Trail Making B, Category Fluency and a long-term retrieval task in those aged over 50 compared to those with sufficient levels of vitamin D. There was no relationship between insufficiency and cognitive decline at follow-up over 12 years (at four-year intervals). Buell et al., (2009) found that blood plasma levels of vitamin D >20ng/mL was associated with better performance on a number of executive function, attention and processing speed tasks compared with individuals with levels below that cut-off. No association was found for memory tasks. When taken together the evidence from this research indicates that plasma vitamin D levels are associated with performance on tasks of executive function, attention and processing speed. The relationship between plasma vitamin D levels and memory is less clear and requires further research to clarify whether age of participant and cut-off criterion for insufficiency is a factor in these differing results.

There has been a substantial amount of work investigating vitamin D alongside progesterone as a treatment following TBI in both animal models and human trials. In a rat model of TBI (electromagnetic impulse injury) progesterone treatment was combined with three levels of vitamin D (1μg/kg; 2.5μg/kg; 5μg/kg; Hua et al., 2012). After 21 days spatial memory processing and acquisition was assessed using a Morris water maze task. This found that the combination of vitamin and progesterone was more effective than progesterone alone (although progesterone only treatment did result in improved preservation of function). In patients with severe TBI (Glasgow Coma Scale ≤ 8) given either placebo, progesterone, or progesterone a vitamin D combined therapy initiated within eight hours of injury and continuing for five days (Aminmansour et al., 2012) . Measures used to assess the efficacy of treatment were the Glasgow Coma Scale (GCS) and Glasgow Outcome Scale (GOS; for the purposes of this study categorised into ‘favourable’ and ‘unfavourable’ recovery). These were completed at baseline and then repeated at one (GCS) or three (GOS) months post-injury. A significant difference in recovery was found between groups at follow-up with 25% of participants having a favourable recovery in the placebo group compared to 45% in the progesterone alone group and 60% in the combined therapy group. These findings are thought to reflect

reductions in neuroinflammatory processes following injury (Hua et al. 2012; Tang et al., 2015).

In another study a very high single dose vitamin D intervention (120,000 IU; equivalent to 3000μg; RDA 10μg) or saccharide placebo was administered to vitamin D deficient ICU patients (mean age 36.4 years) with moderate to severe TBI (GCS between 4 and 12) (Sharma et al., 2020). Following treatment there was a significant rise in blood plasma vitamin D levels in the treated patients. Treatment with this large dose of vitamin D resulted in a significant reduction in mechanical ventilation period (4.7 days treatment, 8.2 days control). There were also improved levels of consciousness in the treatment group with an increase of 3.86 units on the GCS in the treatment group, compared with a decrease of 0.19 units in individuals receiving the placebo. In addition there was a reduced neuroinflammatory response in the vitamin D treatment group compared to controls with reductions in activation of a number of cytokines (interleukin-2α, interleukin-6, tumour necrosis factor-α; TNF-α), although the difference in TNF-α activation was the only one of these variable to reach statistical significance (p = .02). These findings hold a great deal of promise for acute treatment of moderate to severe TBI. The sample size for this study was relatively small (35 participants), however, and requires replication in a larger sample.

There are many studies investigating the mechanisms by which vitamin D may affect the brain. Numerous functions of vitamin D have been elucidated in both animal and human research including the regulation of neurotrophic factors (e.g. nerve growth factor, neurotrophins), neurogenesis, calcium homeostasis, oxidative stress mechanisms, premature cellular aging, and β-amyloid clearance (Brown et al., 2003; Cekic et al., 2009; Garcion et al., 2002; Gezen-Ak et al., 2014; Llewellyn et al., 2010; Tuohimaa, 2009). This body of research emphasises the critical requirement for sufficient vitamin D levels in neuronal function, however more research is required to clarify whether supplementation has consistently positive effects on cognition following neurological damage.

3.3. Vitamin E

Vitamin E refers to a family of plant-derived lipids in two groups, tocopherols and tocotrienols, each with four isoforms (α, β, γ and δ), the structural isoform differences impacting metabolism required throughout the lifespan (Traber, 2014; Cardenas & Ghosh, 2013; Schmolz et al., 2016). High amounts of α-tocopherol, the most abundant form found in blood and tissue, are found in almonds, hazelnuts, wheatgerm oil and

sunflower oil, with γ-tocopherol found in walnuts, palm oil and soybean products (Jiang et al., 2001). Of the eight tocopherols and tocotrienols only α- and γ-tocopherol are found in human tissue, with α-tocopherol found in quantities four to ten times higher than γ-tocopherol (Behrens & Madère, 1986). All other vitamin E isoforms are metabolized more quickly and excreted from the body (Traber & Kayden, 1989a).

There is a consensus that α-tocopherol is the only vitamin E isoform that meets human requirements (Food and Nutrition Board, Institute of Medicine, Dietary Reference Intakes of vitamin C, vitamin E, selenium, and carotenoids, 2000), with the natural form *RRR*-α-tocopherol preferentially maintained in blood and plasma (Traber & Kayden, 1989a; Traber & Kayden, 1989b, Kayden & Traber, 1993). The primary function of vitamin E is as a potent antioxidant, protecting cell membranes from free-radical damage following lipid peroxidation (Cardenas & Ghosh, 2013; Dobrovolny et al., 2018)[20]. Specifically, vitamin E ensures protection of long chain polyunsaturated fatty acids in membranes, maintaining biochemical reactions reliant on membrane integrity and associated cellular signalling (Traber & Atkinson, 2007; Ulatowski & Manor, 2013). The chain of reactions involved in cellular metabolism produces antioxidant-derived radicals (Niki et al., 1993; Niki, 2014). The fate of these radicals is an important determinant of antioxidant efficacy; if the radical remains reactive it has the potential to continue oxidation and become pro-oxidant. Ascorbic acid (vitamin C) plays an important role in reduction of the α-tocopherol radical (Niki, 2014). It is therefore important that both these vitamins (C and E) are ingested in sufficient amounts to efficiently counteract free-radical production and lipid peroxidation, particularly during periods of cellular stress, for example following traumatic brain injury.

Dietary sources of vitamin E are varied however, evidence suggests up to 75% of the population are not meeting recommended intake (Troesch et al., 2012). Following prolonged low vitamin E status, for example in those with physical or genetic problems that prevent the absorption or metabolism of vitamin E, there is the potential for onset of neurological and cardiac symptoms. These symptoms include problems with balance, coordination and speech along with deterioration of heart muscle which can be fatal if not treated (Traber et al., 1994). In Vitamin E deficient individuals high-dose supplementation (up to 1000 mg/day) has been found to improve symptoms and prevent further deterioration (Traber, 2014).

[20] Tocotrienols are thought to be more effective than tocopherols, although this is a matter of debate (Müller et al., 2010; Peh et al., 2016).

Overall vitamin E has not been shown to have an obvious effect on cognition, however maintenance of adequate levels seems to slow build-up of amyloid plaques and neurofibrillary tangles in dementia in rodents and humans (Dobrovolny et al., 2018; Hensley et al., 2011). Adequate vitamin E is required in early embryogenesis to maintain levels of omega-3 and omega-6 within neurons (Lebold et al., 2014). This requirement may potentially continue throughout the lifespan, although there is limited research in this area.

3.4. Vitamin K

Phylloquinones and menaquinones found in foods are commonly referred to as vitamin K (Booth & Rajabi, 2008; Suttie, 2013). Adults require very low levels of vitamin K with relatively high levels of the vitamin in dietary intake and so deficiency is rare (Suttie, 2013). Excess consumption of vitamin K-rich foods can exacerbate the effect of blood-thinning medication like warfarin, however as this is a known effect and as such patients taking this drug receive dietary advice (Leite et al., 2016).

Vitamin K-dependent proteins (VKDPs) are involved in a number of vital processes within the body. These include bone metabolism (along with vitamin D and calcium) and inhibition of soft tissue calcification (Price, 1988; Schwalfenberg, 2017; Viegas et al., 2009) and vascular repair (Benzakour & Kanthou, 2000; Melaragno et al., 1998). Within the vascular system vitamin K is involved in regulation of blood coagulation factors VII, IX, X, prothrombin, protein C, and protein S (Suttie, 2013). Research has suggested that VKDPs within the nervous system also increase neurite outgrowth (Tsang & Kamei, 2002) and are involved in biosynthesis of sphingolipids (e.g. sphingomyelin and gangliosides). Sphingolipids are cellular membrane structural components present in high quantities in the cells of the nervous system particularly the myelin sheath and glial cells (Posse de Chaves & Sipione, 2009; Ferland, 2012). In addition, sphingolipids have also been implicated in modulating membrane receptors and ion channels, in cell proliferation, differentiation and senescence, as well in secondary messenger systems (Posse de Chaves & Sipione, 2009; Ferland, 2012; Tsaioun, 1999).

Vitamin K-dependent protein S (VKDPs) and the homologue growth arrest specific gene 6 (Gas6) have been shown to have a number of functions in the brain. The main roles of these VKDPs are in myelination, neural stem cell proliferation, differentiation and survival (Ji et al., 2014), and in modulation of microglial phenotypes in response to illness or injury (Colonna & Butovsky, 2017). As an example, oligodendrocyte generation and increased myelin production for repair has been shown to be stimulated by signalling of Gas6 in a mouse model (Goudarzi et al., 2016). Gas6

also appears to reduce damage following sub-arachnoid haemorrhage through its role in cytokine signalling (Tong et al., 2016) with the homologue protein S shown to be neuroprotective in mouse models of ischaemic/hypoxic stroke as a result of anti-thrombotic and anti-inflammatory properties (Liu et al., 2003). Further to this, protein S has been demonstrated in mice to reduce oedema and improve blood flow following brain ischaemia, lowering the inflammatory response, reducing neuronal apoptosis, and offering protection from *N*-methyl-D-aspartate receptor glutamate toxicity (Liu, et al., 2003; Zhong et al., 2010). This evidence from mice highlights the potential importance of adequate vitamin K in attenuating negative effects of ischaemic/hypoxic injury. Although vitamin K deficiency is rare due to the small quantities necessary for physiological function, vitamin K does not appear to be stored by brain tissue (Ferland, 2012) and therefore maintaining a level of intake sufficient to manage inflammation and repair of damaged tissue is essential particularly after neurological injury.

2.4. Minerals

Levels of mineral content in foods are related to levels found in the soil or the sea, these micronutrients are then taken up by plants and eaten by animals that enter the food chain. Levels in diet in different regional areas therefore fluctuate, affecting levels of sufficiency in diet. This means that sources of minerals are potentially more fragile and may therefore be candidates for supplementation to ensure sufficient intake.

4.1. Calcium

Within the body most calcium (>99%) is stored in bone; in addition to giving skeletal strength this also serves as a store to maintain intra- and extra-cellular calcium pools. The remaining calcium (<1%) is in constant exchange with these calcium pools and is involved in intra- and extra-cellular signalling, muscle contraction, nerve impulse transmission and regulation of gene expression (Bading, 2013; Berridge et al, 2000, Zhang et al., 2009).

Calcium is central to many neural functions including signal transduction, neurotransmitter release, gene expression, synaptic plasticity, memory formation, acquired cellular immunity and neurite outgrowth (Bading 2013; Bas-Orth & Bading, 2013; Berridge et al., 2000; Li et al., 2016; Papadia et al., 2005). Calcium also acts as a second messenger transmitting signals to the soma and nucleus of all cells (Clapham, 2007; Hagenston & Bading, 2011; Peacock, 2010). These enhanced synaptic events can result in long-lasting neuroprotection against excitotoxic insults and programmed cell

death (acquired neuroprotection; Bas-Orth & Bading, 2013; Papadia, et al., 2005). As calcium is a critical moderator of cellular signalling, dysregulation of calcium balance has an inevitable adverse effect on the brain and is a feature of neuropsychiatric and neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, amylotrophic lateral sclerosis, schizophrenia, epilepsy and migraine (Berridge, 2014; Bezprozvanny, 2010; Cain & Snutch, 2011).

Following primary mechanical damage in traumatic brain injury calcium homeostasis can be disturbed, contributing to cellular injury and death (Weber, 2012). ATP production is also often affected following TBI either as a result of decreased levels of glucose following alterations in cerebral blood flow or through mitochondrial damage. One down-stream effect of reduced ATP production is failure of calcium ATPase pumps into endoplasmic reticulum stores and out of the cell, again causing cytotoxic calcium accumulation (see Cross et al., 2010; Tsutsui & Stys, 2013 for reviews). When considered in combination with involvement in signal transduction, neurotransmitter release and synaptic plasticity sufficient levels of calcium may be essential to recovery post head injury.

4.2. Iodine

Iodine is a vital component of T3 (triiodothyronine) and T4 (thyroxine) thyroid hormones, consequently most iodine in the body is stored in the thyroid gland. Thyroid hormone is a required metabolite in all body tissues with thyroid hormone receptors widely distributed in the brain. Triiodothyronine and thyroxine are critical for brain maturation (most crucially between the second trimester in utero and two years of age) and are involved in neuronal migration, formation of the layered structure of the cortex, and differentiation of glial and neuronal subtypes (Ahmed et al., 2008; Ausó et al., 2004; Zoeller & Rovett, 2004). Maturation and myelination of axons is also thyroid-dependent, with hyperthyroidism (over production from disease) prematurely initiating myelination and hypothyroidism (under production from deficiency or disease) resulting in delayed or incomplete myelination due to errors in oligodendrocyte differentiation and the critical diameter for myelination not being reached (Bernal et al., 2015; Simons & Trajkovic, 2006; Walters & Morell, 1981). Thyroid hormone may also be involved in stimulation of oligodendrocyte progenitor cells in the sub-ventricular zone during re-myelination following injury (Calzà et al., 2010; Dugas et al., 2012).

Symptoms of iodine deficiency include emotional lability, confusion, dementia, cognitive deficits, and alterations in personality (Bauer et al., 2008). These symptoms are reversible following treatment except in rare cases. Findings of cognitive deficits and

depression at subclinical levels of disordered iodine/thyroid levels have been inconsistent (see Ritchie & Yeap, 2015 for review) with different findings perhaps reflecting variability in methodology and lack of control of other variables (for example comorbidities or other dietary deficiencies).

Thyroid hormone also interacts with gene regulation and signal transduction of a number of neurotransmitter systems including noradrenaline, serotonin and dopamine. The regulation of these systems is not currently well understood, however the involvement of thyroid hormone in the functioning of these neurotransmitters is another indication of the necessity of adequate iodine to regulate mood state (Bauer et al., 2008). Although iodine is only a trace element with overt deficiency not widely reported in the United Kingdom, it has been demonstrated to play a role in aspects of cognition and mood regulation and as such remains an essential micronutrient following brain injury.

4.3. Iron

Iron is most commonly linked with haemoglobin to facilitate oxygen transport in red blood cells; however, haemoglobin production also requires vitamins A, B_2 (riboflavin), B_9 (folate), and B_{12} (cobalamin) (McLean et al., 2009; von Drygalski & Adamson, 2013). In addition, iron is involved with a number of vital functions within the brain, most importantly within the mitochondria and oligodendrocytes, in nitric oxide metabolism, neurotransmitter production, dendritogenesis[21], and DNA synthesis (Lozoff, 2011). One essential cofactor in many cellular metabolism reactions are iron-sulphur (Fe/S) clusters, synthesized within and important to mitochondrial functions (Braymer & Lill, 2017). These clusters are essential components in the citric acid (Krebs) cycle and in the electron transfer chain during ATP production (Gille & Reichmann, 2011), highlighting the necessity of iron in normal cellular energy metabolism.

Oligodendrocytes are the most metabolically active cells within the brain, particularly during periods of peak myelination and to support myelin once formed. Iron stains more strongly in oligodendrocyte cell bodies than any other healthy adult brain cells, with processes particularly visible in the substantia nigra, cerebellar nuclei and striatum. Staining is not homogenous but is seen in patches or rows, although the functional significance of this is not yet clear it does indicate preferential uptake of iron by these cells (Todorich et al., 2009). Iron is also a cofactor in synthesis of a number of myelin proteins (Möller et al., 2019; Ortiz et al., 2004), therefore iron deficiency will adversely affect myelin synthesis. In addition to supporting oligodendrocytes and myelin,

[21] Formation of neural dendrites

iron functions as a cofactor for a number of enzymes involved in neurotransmitter biosynthesis including tyrosine hydroxylase involved in synthesis of catecholamines, for example dopamine, and tryptophan hydroxylase involved in synthesis of serotonin (Crichton et al., 2012; Hasagawa et al., 1999; Jáuregui-Libera, 2014; Ramsey et al., 1996; Youdim et al., 1989). Dopaminergic and serotonergic signalling within the mesolimbic pathway of the midbrain (between the ventral tegmental area, nucleus accumbens and olfactory tubercle) is also dependent upon adequate iron intake (Scott & Murray-Kolb, 2016). The role of iron to this pathway is of particular importance following TBI, as the mesolimbic pathway is susceptible to inflammatory injury during the secondary cascade (Chen et al., 2017).

Iron is normally efficiently recycling within the body, consequently the population most susceptible to iron deficiency are menstruating women. Cross-sectional research in menstruating women has found a significant effect of iron status (sufficient/deficient) on working memory and planning ability even when anaemia is not present, with no effect on other executive functions tested (inhibitory control or set shifting) (Blanton et al., 2013; Scott & Murray-Kolb, 2016). It has been postulated that this effect is a result of poorer neurotransmitter signalling and integrity of the fronto-parietal network rather than poor myelination or cellular energy metabolism (Scott & Murray-Kolb, 2016). As participants in both these studies were between the ages of 18-35, a period of peak myelination in frontal regions (Arain et al., 2013; Taylor et al., 2013) poor myelination as a contributing factor in these results should not be excluded. There is also some evidence that iron deficiency (without anaemia) affects cognition in aging populations, with lower iron levels related to lower scores on the Mini Mental State Examination (Yavuz et al., 2012), although this finding is not consistently reported (Milward et al., 2010).

Research to date indicates that iron deficiency has negative effects on cognition in infants, women in early adulthood and in aging populations. There is no evidence of iron status in early adult men, potentially as a result of the supposition that iron recycling in the body is efficient. Iron status in men is mediated by findings that inflammatory processes related to illness and injury, in addition to blood loss, could result in anaemia (Abbaspour et al., 2014; Von Drygalski & Adamson, 2012). Conceivably, it is possible that male individuals in early adulthood who have experienced brain trauma, an age group highly represented in the TBI population, may have iron deficiency and potentially associated cognitive deficits as a result.

4.4 Magnesium

There are a number of similarities between the functions of magnesium and calcium within the body. Magnesium is involved in bone formation and muscle contraction (through active transport of potassium and calcium), with the greater proportion of body magnesium (~60%) stored in bone (Gröber et al., 2015). Magnesium, however, also functions as a natural agonist for calcium, regulating calcium levels within the cell (Iseri & French, 1984). Magnesium also inhibits calcium-induced death mechanisms including mitochondrial permeability transition and apoptosis triggered by calcium overload and so is a highly protective micronutrient (Jahnen-Dechent & Ketteler, 2012; Kristal & Dubinsky, 1997).

Over 600 enzymatic reactions are magnesium dependent, including most aerobic and anaerobic energy metabolism reactions, signal transduction, synaptic plasticity, synthesis of glutathione, serotonin synthesis and neurotransmitter release (De Baaij et al., 2015; Gröber et al., 2015). Magnesium is also required in nucleic acid (DNA and RNA) synthesis and formation and maintenance of cellular proteins including those for organelle structural integrity (including mitochondria) (De Baaij, et al., 2015; Elin, 1994; Terasaki & Rubin, 1985). Equally important magnesium acts as a cofactor in hydroxylation reactions to form vitamin D hormone and in binding to its protein receptor for transport (Gröber et al., 2015).

Low magnesium levels have been associated with a number of neurological conditions including migraine, epilepsy, stroke and Alzheimer's disease (AD) (De Baaij et al., 2015; Veronese et al., 2016). In AD magnesium depletion seems to particularly affect the hippocampus, suggesting a link between magnesium levels and memory function (Durlach, 1990), however whether this association is the result of disease progression or poor dietary intake is not established. The link between magnesium levels and memory function is supported by findings in rodents where increasing levels of magnesium in the brain enhancing learning and memory in both young and aged rats in a model of Alzheimer's disease (Xu et al., 2014). Following brain injury, levels of magnesium are depleted in both humans and animals (Sen & Gulati, 2010; Vink et al., 1987). Magnesium depletion impacts many aspects of the secondary biochemical cascade including homeostatic control of NMDA receptors (resulting in substantial calcium influx into the cell), reduced cellular energy production and an increase in associated excitotoxicity (Arifin et al., 2014; Vink, 2016). A magnesium intervention given 30 minutes post induced diffuse TBI model in rodents (via controlled cortical impact) was compared on measures of sensorimotor performance, learning and stress with untreated

injured animals and sham controls (Vink et al., 2003). Animals given the magnesium intervention showed no difference in levels of stress and anxiety and no sensorimotor deficits compared with sham animals, this was in stark contrast to the untreated injured animals who showed no improvement on the sensorimotor task (rotarod test) and high levels of stress (open field test). When compared to the sham controls on the learning task (Barnes maze) the treated animals showed 62% the rate of learning, this contrasted with only 11% of the rate of learning in the untreated injured animals. These findings may be the result of magnesium suppressing cortical spreading depression and relaxation of vascular smooth muscle which increases cerebral blood flow and reduces ischaemia (Temkin et al., 2007). In humans, however, research findings have not been as positive. Continuous infusion of magnesium at either a low or high dose for five days following initiation of treatment soon after moderate to severe TBI (Temkin et al., 2007) had no overall effect on outcome at one, three or six-month follow-up when compared to a placebo group. Outcome measures in this study included 39 measures of health status (mortality, seizures), physiological measures (blood pressure, cerebral perfusion pressure, intracranial pressure), medical complications (oedema, respiratory distress), and cognitive performance (IQ, memory, executive function, motor speed, processing speed) with only blood pressure and cerebral perfusion pressure reduced in the high dose magnesium group, however this group also had a higher mortality rate when compared with the other two groups (low dose magnesium and placebo). In another study magnesium administration immediately on admission to hospital and for the following five days only showed a trend towards improving outcome (as measured by the Glasgow Outcome Scale) in severe TBI (GCS 3-8) when compared to treatment as usual (Zhao et al., 2016). The main difference between the animal and human studies was the administration method; in animals magnesium was given in a single dose, whereas in humans there was a 5 day period of infusion. It may be the case that this difference in administration resulted in the variability in findings, further research is required in human populations to investigate this further. There is therefore currently no convincing evidence that magnesium supplementation has a positive effect on cognition.

4.5. Selenium

Selenium principally forms part of the amino acid selenocysteine (SeCys) present in proteins; currently 25 selenoproteins (Se-proteins) have been identified in humans. Knowledge of the functional role of all Se-proteins is currently limited, with those involved in antioxidant defence and thyroid hormone metabolism the most fully understood (Kryukov et al., 2003; Papp et al., 2007; Roman et al., 2014; Schomburg &

Kohrle, 2008). Selenium is found in higher concentrations in grey matter and glandular regions compared to white matter within the brain (Chen & Berry, 2003). Levels of selenium in the brain are constantly maintained even following long periods of dietary deficiency, in such circumstances levels are reduced but not depleted (Savaskan et al., 2003; Schweizer et al., 2004). This indicates that maintenance of selenium levels is important for neural function and may be important following injury.

One of the most damaging processes of the secondary cascade following brain trauma is glutamate excitotoxicity and associated reactive oxygen and nitrogen species accumulation that leads to apoptotic and necrotic cell death. Se-proteins form part of the redox system[22] modulating the inflammatory cascade (Roman et al., 2014; Yeo & Kang, 2007). Findings from a number of *in vitro* in and mouse *in vivo* studies investigating the anti-oxidant mechanisms of Se-proteins (Kumari et al., 2012; Savaskan et al., 2003; Yeo & Kang, 2007) have shown that selenium supplementation soon after injury stabilizes mitochondrial membrane potential, reduces mitochondrial fragmentation and controls production of free radicals, particularly hydrogen peroxide. This indicates that even though selenium levels within the brain a homeostatically controlled increased levels are required to reduce injury. Selenium treatment also modulates other aspects of the inflammatory cascade in rodents and rodent cell lines. In vitro studies have shown that in models of glutamate-induced excitotoxicity treatment with selenium up to 8-hours after introduction of glutamate significantly reduced cell death by up to 90% compared to untreated cells (Kumari et al., 2012; Savaskan et al., 2003). This protective effect was found to be the result of reductions in production of ROS and maintenance of mitochondrial integrity. Interestingly, these protective effects still 70% effective even if the selenium was 'washed out' of cell culture after two hours (Savaskan et al., 2003). This indicates that selenium is incorporated into proteins quickly and it is the action of these proteins that offers protective effects to cells. In a different model of neuronal injury pre-treatment of neural progenitor cells with selenium resulted in survival of over 60% of cells following introduction of a cytotoxic agent (hydrogen peroxide) (Yeo & Kang, 2007). This indicates that in individuals with diets low in selenium reduced levels of this micronutrient may impact survival of neurons. Further to this a review of the literature reports that selenoproteins are also involved in the recruitment of cytokines and macrophages, and in the reduction of reactive gliosis (Roman et al., 2014).

[22] Redox = oxidation-reduction status; a regulator of a number of cellular metabolic functions.

Selenium deficiency and associated depletion of Se-proteins has been associated with a number of disease states including neurodegeneration in humans (Rayman, 2012; Roman et al., 2014; Shahar et al., 2010). Research findings in older populations, both those with a diagnosis of mild cognitive impairment or Alzheimer's disease (AD) and healthy aging populations have shown an association between levels of plasma or fingernail selenium and cognitive decline; lower levels of selenium from diet over time being associated with increased risk of cognitive decline (Berr et al., 2000; Cardoso et al., 2014). As these findings are only associative it cannot be confirmed that lower levels of selenium are causal in these diseases. Evidence support a causational link comes from a triple transgenic mouse model of AD (Zhang et al., 2017). Four-month old transgenic mice were fed on either a selenium-enriched (selenium yeast) or common (control) diet ad libitum for three months. Transgenic mice fed the enriched diet significantly improved learning and retention of spatial information compared with mice fed the common diet; they were quicker to find the platform in a Morris maze task in the learning phase and had significantly better short term recall of the position of the platform (but not improved long-term recall). On sacrifice of the mice examination of brain tissue showed better normal metabolism in the hippocampus of the mice fed on the selenium enriched diet compared with controls reduced activation of astrocytes and microglia and a reduction in tau pathology (Zhang et al., 2017). To date there has been no similar research in humans.

To conclude, selenium has the potential to be neuroprotective and neuroreparative in acute brain injury and may affect learning and memory through reduction of hippocampal and cortical damage based on animal models. Whether selenium has a positive effect on brain trauma in humans has not yet been investigated, however the antioxidant action of this mineral may have a positive effect on on-going secondary cascade mechanisms.

4.6. Zinc

Zinc is known to have wide reaching effects on physiological function in all tissues including the brain (McAllister & Dyck, 2017). Most importantly zinc is a key component of immune function, cellular signalling, protein synthesis and cell differentiation as well as being a co-factor in more than 300 enzymatic reactions (Vallee & Falchuk, 1993; McAllister & Dyck, 2017). Most zinc in the body is bound to proteins, with 10% of the human proteome consisting of zinc-binding proteins (Andreini et al., 2006). Zinc also acts as an intracellular signalling molecule that responds to stimulation by extracellular stimuli and contributes to the functioning of the innate immune response and T-cell formation (Rink & Gabriel, 2001). In the brain zinc deficiency is associated

with altered production of cytokines, including IL-1-β, Il-6, IL-8 and TNF-α, stimulating an inflammatory response and resulting in cell death associated with lysosomal dysfunction (Mariani et al., 2006; Summersgill et al., 2015). During ischaemic events excess zinc concentrations in the cell co-occur with excess calcium and glutamate accumulation promoting cell death mechanisms. Oxidative stress also results in excess cellular zinc following the release of protein bound intracellular zinc (McAllister & Dyck, 2017).

Following traumatic brain injury (TBI) patients are at risk from zinc deficiency due to elevated renal and hepatic clearance from the body into the urine in the weeks following injury (McClain et al., 1986). The level of zinc loss is proportional to injury severity, with the most severely injured patients having mean urinary zinc levels fourteen times higher than normal values (McClain et al., 1986). As zinc deficiency stimulates pro-inflammatory cytokine production zinc loss may exacerbate the secondary cascade. To investigate the effect of zinc status prior to injury on recovery research in a rodent controlled cortical impact model of TBI in which mice were fed on either a marginally zinc deficient diet, a zinc adequate diet or a zinc supplemented diet for four weeks prior to injury was conducted (Cope et al., 2012). This found that zinc-deficient animals displayed anxiety and depression-like symptoms but did exacerbate cognitive impairment on a Morris water maze task compared to the zinc-adequate diet animals. Zinc supplemented diet prior to injury resulted in performance on the Morris water maze not significantly different to mice who had a sham injury. This has implications for individuals with low dietary levels of zinc prior to injury and potentially indicates that zinc supplementation may be of benefit to those at risk of TBI, for example armed forces personnel and those involved in contact sports, however findings in animal models do not always translate to humans.

To address reduction in zinc levels following injury Young et al., (1996) supplemented TBI patients in the acute period following injury. Patients did not differ on serum zinc levels on admission; individuals who were randomly allocated to receive supplementation showed improved Glasgow Coma Scale scores compared with controls 28 days post-injury and had lower mortality (12% compared to 26%). One caveat to this research is that a larger number of those in the control group had decompressive craniotomies than in the supplemented group, indicating their injuries may have been more severe which may have affected findings. Zinc insufficiency may also play a role in mood dysregulation. Depression is common following TBI, with up to 53% of participants meeting the criteria for major depressive disorder following injury

(Bombardier et al., 2016) that is often resistant to conventional selective serotonin reuptake inhibitor treatment (Cope et al., 2012). Zinc supplementation prior to injury has been shown to reduce depressive-like symptoms in a rodent model of TBI (Cope et al., 2011). Whether zinc supplementation would reduce depressive symptoms when give post-injury is yet to be explored.

In conclusion zinc is ubiquitous within the body and plays vital functions in all aspects of physiological functioning. As an intracellular and extracellular neurotransmitter zinc has a role in both normal and pathological states, affecting inflammatory processes and cell death mechanisms. There is evidence that zinc loss occurs following injury; restoration of zinc to normal levels may have positive effects physiologically and may improve cognition as a consequence.

2.5 Omega-3 Polyunsaturated Fatty Acids

Omega-3 polyunsaturated fatty acids (PUFAs) are important contributors to neural function; as with other essential micronutrients PUFAs cannot be synthesized by the human body and must be obtained through dietary intake or supplementation (Tur et al., 2012). The two classes of PUFA (omega [n]-3, omega[n]-6) are distinct and mammals do not possess the enzyme required to convert n-6 to n-3 fatty acids (Simopoulos, 2002). The same enzymes facilitate the conversion of both n-3 and n-6 fatty acids short-chain PUFAs to long-chain PUFAs utilised by the body, resulting in competition for receptor sites. Conversion of short-chain alpha linolenic acid (ALA) to long-chain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is inefficient and this conversion rate is reduced by between 40-50% in individuals with a diet rich in n-6 polyunsaturated fatty acids (Gerster, 1998) due to enzymatic competition. To meet daily requirements and maximise health benefits of the biologically active longer chain n-3 PUFAs it has been suggested that EPA and DHA should be consumed in their preformed configurations, for example in oily fish, cod liver oil and refined algae oil (Brenna et al, 2009). Eicosanoids (signalling molecules) synthesized from EPA (n-3) and arachidonic acid (AA; n-6) have been demonstrated to have opposing effects, with AA eicosanoids being pro-inflammatory and pro-arrhythmic, and EPA eicosanoids having anti-inflammatory and anti-arrhythmic effects (Schmitz & Ecker, 2008).

Westernized diets generally have an imbalance between n-3 and n-6 PUFAs, with diets relatively rich in n-6 compared to n-3 fatty acids (Hasadsri et al., 2013; Simopoulos, 2002), particularly where dietary intake of oily fish is limited or from farmed sources. It is presumed that humans evolved eating diets with a n-6:n-3 fatty acid ratio of 1:1 (in line

with the diets of other animals) whereas typical westernized diets have a n6:n3 ratio of approximately 15-20:1 (Simopoulos, 2008). The imbalance between n-3 and n-6 PUFA intake is posited to be a contributing factor in many long-term health conditions involving an inflammatory response (Scrimgeour & Condlin, 2014). These conditions are seen less frequently in populations with traditional diets rich in oily fish with research confirming the protective effects of omega-3 (Dewailly et al., 2001; Saravanan et al., 2010). What should also be taken into consideration is that TBI induces intestinal permeability which further increases neuroinflammation through the bi-directional gut-brain axis (Kharrazian, 2015). Research in mice has found that administration of probiotics improves EPA metabolism and leads to significantly greater levels of DHA in the brain (Wall et al., 2010).

Omega-3 PUFAs (EPA, DHA) contribute to the structural make up of cell membrane phospholipid bilayers, modulate cell wall thickness and are involved in synaptogenesis, cellular signalling and mitochondrial function (Dyall & Michael-Titus, 2008; Pillsbury et al., 2011), with DHA constituting 50% of the phospholipid composition of the neuronal membrane. As part of the cellular response to the secondary cascade following TBI, EPA and DHA act as precursors to anti-inflammatory mediators termed 'protectins' and 'resolvins'. Current understanding of resolution of inflammatory processes suggests that inflammation does not simply decline and fade to a state of homeostasis, instead during the resolution phase different proactive mediators (resolvins) including those synthesized from omega-3 PUFAs are released (Bistran et al., 2011; Serhan et al., 2008; Weylandt et al., 2012). DHA is also thought to be involved in protection of cells through upregulation of anti-apoptotic proteins (e.g. Bcl-2, Bcl-xL) and downregulation of pro-apoptotic proteins (e.g Bad and Bax) (Bazan et al., 2011; Hasadsri et al., 2013). Analysis of blood plasma of mice and humans has demonstrated that levels of DHA in the brain are reduced following injury (Emmerich et al., 2016, 2017) as the result of injury reducing expression of enzymes important for the synthesis of DHA in the brain (Wu et al., 2013).

Research investigating omega-3 supplementation following TBI has shown effects on cellular function and behaviour; animal studies have demonstrated that DHA supplementation reduces glutamate cytotoxicity and calcium influx (Wang et al., 2003). In rodent studies DHA supplementation following fluid percussion injury decreased observed levels of β-amyloid precursor proteins (a marker of axonal injury), compared to untreated animals, to levels similar to that seen in uninjured animals (Bailes & Mills, 2010; Mills et al., 2011). There have been some striking findings in rodents given omega-

3 pre-treatment before injury (Pan et al., 2009; Pu et al., 2013). In an ischaemia-reperfusion model rats were pre-treated either 1 hour, 3 days or daily for 6 weeks prior to injury. All protocols resulted in dose-dependent reductions in necrotic tissue, significantly improved blood-brain barrier integrity and significantly decreased oedema compared to untreated rats (Pan et al., 2009). Similarly, protection against physiological damage and memory deficits was seen rats given an omega-3 enriched diet for two months prior to a controlled cortical impact (Pu et al., 2013). Treated rats had decreased white matter injury in the hippocampus, attenuated inflammatory response and better performance on a Morris water maze task when compared with rats fed on a low omega-3 diet for the same period. What was particularly notable in these findings from Pan et al., (2009) was the lack of statistically significant difference in the dose-dependent neuroprotection between these protocols. This indicates that regular inclusion of omega-3 fatty acids in the human diet may offer neuroprotection from some of the effects of stroke and TBI. This suggestion is supported by research in mice fed either an omega-3-deficient or omega-3-adequate diet for three generations resulting in substantial DHA depletion in the rats fed the deficient diet (Desai et al., 2014). Following controlled cortical impact DHA-deficient rats showed greater motor and memory deficits and more anxiety behaviours when compared with performance of DHA-adequate injured animals.

Findings from research with a healthy aging human population (≥55 years, MMSE score >26) have shown that DHA supplementation of 900mg/day for 24 weeks improved visuo-spatial learning, episodic memory and immediate and delayed verbal recognition memory when compared with individuals taking a placebo (Yurko-Mauro et al., 2010) suggesting that supplementation may be beneficial in reducing age-related cognitive decline. Supplementation with 1800mg EPA for 10 days following sub-arachnoid haemorrhage associated with a ruptured cerebral aneurysm has also been shown to improve functional recovery (as measured by the Glasgow Outcome Scale); 85% of patients were rated as having a 'good' outcome compared with 64% in the untreated control group (Yoneda et al., 2008). The mechanism for this improvement in outcome potentially related to reduced vasospasm and infarct area in treated patients compared with controls. A case study of a teenage boy who was involved in a motor vehicle accident sustaining a severe TBI (GCS 3 on admission to hospital) provides evidence that early and sustained omega-3 intervention maybe a very effective treatment (Lewis et al., 2013). The patient was rated level I on the Rancho Los Amigos (RLA) Cognitive Scale (no response, total assistance) and the attending surgeon's opinion was that the injury was likely fatal. By day 10 the patient was believed to be in a permanent

vegetative state and was given a tracheostomy and fitted with a percutaneous endoscopic gastrostomy; PEG) for long term care. On day 11 a high-dose omega-3 fatty acid (15ml twice daily) was introduced to the enteral feed. By day 24 the patient had been weaned off ventilation and transferred to a specialist rehabilitation centre where level of functioning had progressed to RLA III (localized response, total assistance). The patient continued taking a high dose omega-3 supplement with vitamin D_3 for over a year (1280mg/day) and by two years post-injury had progressed to RLA VIII (purposeful, appropriate response: stand-by assistance) and was working in a part-time job. No information was provided about cognitive function of this patient, which would have provided useful to give a more-rounded picture of the patient's recovery. Nevertheless, this study indicates that supplementation with omega-3 fatty acids could have a significant effect on recovery following severe traumatic brain injury, however as this an individual case study it is not possible to predict outcome for this individual if they had not received the intervention.

2.6 Summary

A large body of research has demonstrated a relationship between micronutrient deficiencies and a wide range of neurological conditions including dementia, Parkinson's disease, multiple sclerosis, autism spectrum disorder, depression, fatigue and schizophrenia (e.g. Balion et al., 2012; Bitarafan et al., 2014; Nimitphong & Holick, 2011; Oudshoorn, et al., 2008). Sub-clinical micronutrient deficiency has also been shown to risk biochemical imbalance in the processes underlying cognition (Tardy et al., 2020), and potentially has wider implications for the long-term health of the individual, the contribution of each micronutrient to neural function summarised in Table 2.2. In addition, there is growing evidence that the bidirectional gut-brain axis (GBA) and healthy gut microbiota are important in brain functions including regulation of neurotransmitters (particularly serotonin), the neuro-endocrine stress response, and memory (Carabotti et al., 2015). In turn the brain modulates many aspects of effective gut function including gastrointestinal motility and secretion, (Macfarlane & Dillon, 2007). The synthesis and absorption of micronutrients is dependent upon a healthy and competent gut, which in turn impacts cognition (Kau et al., 2011) and in TBI this process is disturbed (Kharrazian, 2015).

The initial mechanical impact of TBI results in damage to white matter pathways in all severities of injury (Armstrong et al., 2016); biotin, cobalamin, vitamins A and K, iron, iodine and omega-3 PUFAs are all required for efficient oligodendrocyte function

and for myelin synthesis and repair (Brito et al., 2016; Dyall & Michael-Titus, 2008; Huang et al., 2011; Lozoff, 2011; Posse de Chaves & Sipione, 2009; Tourbah, 2015). This initial insult initiates a secondary biochemical cascade within neuronal tissues that includes the accumulation of reactive oxygen species and associative oxidative stress, neuroinflammation, and perturbations in cellular energy production (Donkin & Vink, 2010; Finnie, 2013; Johnson, et al., 2013; Juurlink & Paterson, 1998; Starkov, et al., 2004). Sufficient anti-oxidant intake is required to counteract oxidative stress associated with over-production of reactive oxygen and nitrogen species following TBI due to compromised autoregulation of cerebral blood flow; vitamins C and E (Cardenas & Ghosh, 2013; Sorice et al., 2014) are considered the primary antioxidants, however riboflavin (B_2), vitamin K and calcium also have anti-oxidant capabilities (Ashoori & Saedisomeolia, 2014; Liu, et al., 2003; Papadia et al., 2005). In addition, folate and magnesium reduce oxidative stress (Kalani et al., 2014; Schreurs & Cipolla, 2014; Zhao et al., 2016). Oxidative stress in turn leads to chronic inflammation; vitamins D and B_6, along with selenium, zinc and omega-3 PUFAs are integral to a balanced inflammatory response to injury (McAllister & Dyck, 2017; Pearce & Cheetham, 2010; Roman et al., 2014; Ueland et al., 2016; Weylandt et al., 2012).

Table 2.2
Functional contribution of micronutrients

Micro-nutrient	Antioxidant	Substrate Synthesis	Neurotransmission	Immune Function	Mitochondrial Function	Metabolic Reactions	Gene Expression	Myelin
Vitamin A				✓			✓	✓
Vitamin B_1						✓		
Vitamin B_2	✓						✓ DNA Synthesis	
Vitamin B_3		✓ Protein	✓			✓	✓ DNA Repair	
Vitamin B_5		✓ Fatty Acids	✓ Acetylcholine			✓		
Vitamin B_6	✓		✓ Synthesis All	✓		✓		
Vitamin B_7						✓		✓
Vitamin B_9			✓ Synthesis			✓	✓ DNA Synthesis	
Vitamin B_{12}						✓		✓
Vitamin C	✓	✓ Protein	✓ Synthesis					
Vitamin D			✓ Intracellular	✓				
Vitamin E	✓							
Vitamin K			✓	✓				✓
Calcium			✓Release		✓		✓ Chromatin	
Iron			✓ Synthesis		✓	✓	✓ DNA Synthesis	✓
Iodine			✓ Transduction				✓	✓
Magnesium	✓ Indirect		✓ Synthesis		✓	✓	✓ DNA Synthesis	
Selenium	✓			✓	✓			
Zinc			✓ As Transmitter	✓				
Omega-3		✓Phospholipids		✓	✓			✓

Mitochondrial dysfunction is another key marker of the secondary biochemical cascade, impacting processes involved in cellular energy production including the pentose phosphate pathway, glycolytic pathway and citric acid cycle (Chance & Williams, 1955; Krebs & Johnson, 1937a; Krebs & Johnson, 1937b). All of the B-complex vitamins except for riboflavin (B_2) in addition to iron, magnesium and omega-3 PUFAs play key roles in maintaining the function of the mitochondria and cellular energy production and therefore sufficient intake is necessary to ensure this is maintained (Braymer & Lill, 2017; Dyall & Michael-Titus, 2008; Gröber et al., 2015; Kennedy, 2016). In addition to the direct role these micronutrients play within the brain some micronutrients have interdependent functions, for example riboflavin is involved in the activation of folic acid (B_9), pyridoxine (B_6) and cobalamin (B_{12}), magnesium is a co-factor in vitamin D conversion reactions and vitamin D facilitates the absorption of calcium from the gut (Fleet, 2017).

Following TBI a number of micronutrients can become depleted as a result of increased renal clearance and increased cellular utilisation, including vitamins C, E, D, magnesium, zinc and omega-3 PUFAs (McClain et al., 1986; Polidori, et al., 2001; Sen & Gulati, 2010; Siniscalchi et al., 2016; Wu et al., 2013). This further emphasises the necessity for good micronutrient intake following TBI. Addressing increased energy demands in acute TBI has significantly reduced morbidity and mortality rates (Cook et al., 2008), however there is a comparative dearth of research investigating nutritional status in post-acute and chronic TBI patients and no standard of nutritional care following hospital discharge. This is despite evidence that brain injured individuals make poor food choices resulting in insufficient intake of micronutrients (Duraski et al., 2014; Wahls, et al., 2014). TBI research involving multimicronutrient interventions is currently limited. In one study involving 30 retired American Football players participants were given a combination omega-3 and multimicronutrient intervention for an average of six months (range two to twelve months) (Amen et al, 2011). Participants underwent a single-photon emission computed tomography (SPECT) scan and completed the Microcog Assessment of Cognitive Functioning (MACF) which measured general cognitive functioning and proficiency, information processing speed and accuracy, attention, reasoning, memory, spatial processing and reaction time at baseline. Participants were also offered a 'pragmatic' intervention including information discussing the importance of proper nutrition and regular exercise, limiting alcohol consumption, desistance from illicit drug taking and cigarette smoking, good sleep hygiene and a weight loss programme for the 48% of participants who were obese or overweight. Follow-up SPECT scan showed

significantly increased brain perfusion focused in the pre-frontal cortex, anterior cingulate gyrus, parietal lobes and cerebellum, regions involved in executive functions, sensory processing and motor control. Repeat administration of the MACF showed participants had significant improvements on all measures except for spatial processing speed and reaction time. These findings indicated that micronutrient interventions have the potential to significantly improve cognition, however, there are a number of methodological limitations with this study. There was no control group who underwent the 'pragmatic' lifestyle intervention without multimicronutrient supplementation, therefore it is not possible to solely attribute improvements in cognition and brain perfusion to the multimicronutrients. This, along with the lack of control for the number of concussive events experienced and non-standardized trial length (2-12 months) means that the results are difficult to draw firm conclusions from. In another study a micronutrient intervention was given to a single individual who was experiencing extreme alterations in mood with episodes of explosive anger which had been diagnosed as permanent (Kaplan et al., 2016). The individual took a broad-spectrum multimicronutrient following their own research and saw improvements in their own mood state after two months with the clinician noting improvements after three months. As this was a single case study the findings need to be replicated in larger-scale research to confirm findings.

In normative groups research investigating the effects of multimicronutrient interventions on cognition have been mixed, with little consensus on benefits of supplementation (Amen et al., 2013; Buell et al., 2009; Grima et al., 2012). This is potentially as a result of the large heterogeneity in cohorts, interventions and cognitive measures. For example, some studies were in single sex cohorts (e.g. Haskell et al., 2010; Kennedy et al., 2010), others in mixed cohorts (Pipingas et al., 2014), using different interventions and test measures. As such it is difficult for comparisons to be made. A systematic review of the literature carried out by Forbes et al., (2015) found that omega-3, B group vitamin and vitamin E had no effect on cognition in healthy older adults. A meta-analysis of randomized placebo-controlled trials investigating the effect of micronutrient supplementation on cognition concluded that interventions did not result in significant improvement in verbal fluency, attention, visual search or simple reaction time tasks in healthy cognitively intact adults (Grima et al., 2012). Conversely other research has found improvements in processing speed (Haskell et al., 2010; Kennedy et al., 2010; Small et al., 2014), choice reaction time (Haskell et al., 2008), reasoning, information processing, memory and mood (Amen et al., 2013; Grima et al., 2012) compared to baseline following multivitamin supplementation in healthy adults. The varied results

from micronutrient studies is emphasised by the dissimilar findings obtained in research using the same supplement (Swisse Men's Ultivite) and a similar computerized cognitive test battery (Harris et al., 2012; Pipingas et al., 2014). Pipingas et al., (2014) found a trend towards significance on measures of selective attention and response inhibition in males (50-70 years), whereas Harris et al., (2012) observed significant improvements in recognition memory in males of a similar age (50-74 years). These dissimilar findings suggest that other factors in addition to the effects of micronutrient supplementation may contribute to cognitive performance in this type of research, however identification of these is difficult to establish. What was consistently found in these two studies was significantly raised plasma levels of B_6, B_{12}, B_9 and homocysteine after eight weeks of supplementation (Harris et al., 2012; Pipingas et al., 2014) indicating that an eight-week intervention can have a significant effect on physiological levels of micronutrients.

In conclusion vitamins, minerals and omega-3 PUFAs play pivotal roles both in normal cellular processes within the brain and in neuroreparative mechanisms following trauma. There is a lack of research investigating the effect of micronutrient and omega-3 support on cognitive outcome following traumatic brain injury and evidence for the role of micronutrient supplementation on cognition in normative groups is mixed. The following chapters will investigate the effects of micronutrients and omega-3 on cognition in both normative and traumatically brain injured populations.

Chapter Three: Normative Study Methodology and Procedure

3.1. Introduction

Vitamins, minerals and omega-3 PUFAs (micronutrients) are required by neuronal cells for biochemical processes including cellular energy production, reduction of free radicals, and maintenance of efficient signal conduction in neurons (Harrison et al., 2010; McAllister & Dyck, 2017; Tourbah, 2015). Insufficiencies in micronutrient intake may have long terms consequences neuronal health and cognition (Kennedy, 2016; Pillsbury et al., 2011). A normative study was conducted to provide a comparative baseline of cognitive performance and dietary intake in the general population to inform research in a traumatically brain injured group. Previous research investigating the effects of micronutrient supplementation on cognition has had mixed findings, from no cognitive changes seen (e.g. Forbes et al., 2015) to improved processing speed (Haskell et al., 2010; Kennedy et al., 2010; Small et al., 2014), improved immediate verbal memory and verbal fluency (Grima et al., 2012), and better selective attention and response inhibition (Pipingas et al., 2014) in healthy adults. It is therefore unclear from the literature whether single micronutrients or multivitamin/mineral supplements are beneficial for cognitive function. To try to clarify issues raised by previous research this study compared supplementation with a single micronutrient (Vitamin D) with a multivitamin/mineral supplement over an 8-week period using Vitamin C as a control in a third group (see Appendix A1 for full information on supplement composition).

3.2. Participants

Healthy participants (n = 61) were recruited from a range of socio-economic and educational backgrounds (range 21-59 years; $\bar{x}$ = 39.07 years; SD = 11.46; 75% female). Sixty-one participants were recruited with 60 completing the study; one was lost to attrition on physician's orders following medical diagnosis vitamin D deficiency. The cohort sample size compared favourably to that of other recent research (e.g. Harris et al., 2011 [N = 50]; Macpherson et al., 2012 [N = 41]; Scholey et al., 2013 [N = 25]; von Arnim et al., 2013 [N = 42]; Whyte et al., 2016 [N = 24]).

Participants were recruited via an advert placed in a local newspaper, in Sheffield Hallam University's staff newsletter and on social media. Further recruitment occurred through snowball sampling. All participants had normal or corrected to normal vision

with no reported auditory deficits and no history of head injury or diagnosis of age-related neurodegeneration. Individuals with a diagnosis of diabetes were excluded due changes in metabolism of micronutrients (Kaur & Henry, 2014). Women who were pregnant or breastfeeding were excluded due to increased requirement of certain micronutrients (e.g. folic acid, vitamin D) and potentially teratogenic effects of others within these populations (e.g. vitamin A) (El Shamy & Tamizian, 2018). Participants who had taken vitamin/mineral supplements within the previous four weeks were excluded from the study to prevent carryover effects. Minimal exclusion criteria were applied to get a representative sample of the general population.

3.3. Design

The study was a double blind 3*(2) design, with participants randomly allocated to one of three groups (multivitamin, vitamin D, control). Participants completed baseline cognitive testing before receiving their supplements. Following the eight-week micronutrient supplementation period, during which participants also completed a food diary for 14 days, participants were re-tested on the cognitive battery, completing alternative forms of measures where available. A random number generator (random.org) was used to assign participants to groups. Use of a random number generator is an approved method to ameliorate any bias related to the assignment of participants to groups in experimental research (Schultz & Grimes, 2002). Random allocation was then independently undertaken by a member of the supervisory team to ensure the study met double-blind conventions; a record of allocation kept on a spread sheet. An eight-week intervention has previously been demonstrated to be enough to influence both physiology (e.g. energy metabolism; Kennedy et al., 2016; micronutrient blood plasma levels, McKay et al., 2000; Harris et al., 2012; Pipingas et al., 2014) and cognition (Kean et al., 2015; Small et al., 2014).

3.4. Measures

3.4.1 Food Diary

Participants were instructed to complete a food diary each day for the first two weeks of the supplementation period. A 14-day food diary is considered the optimum time frame to capture normal variety in eating patterns, covering both weekdays and weekends (Falciglia et al., 2009). Research has demonstrated that self-report food diaries provide a reasonable estimate of micronutrient intake when compared with physiological markers (Brunner et al., 2001; Sauvageot et al., 2013). Participants were verbally

instructed to complete the diary in as much detail as possible and were also shown the same instructions printed on the first page of the diary with an example entry for one day's meals (see Appendix A2 for example pages). Participants were instructed to be as specific as possible about the amount of each item eaten and to give brand names if applicable as well as to give constituent ingredients of any dishes prepared. Participants were reminded that it was not necessary to alter their eating patterns in any way, as the focus of the research was to look at usual eating patterns. This protocol is ecologically valid and reliable (Day et al., 2001) and is similar to that used in previous research (Hughes et al., 2012; Zweers et al., 2018). Completion of a food diary for the 8-week intervention period was judged to be onerous for participants and may have acted as a barrier to recruitment. The use of electronic-based food diary recording was also considered; however evidence suggests that this may introduce bias into the sample of participants as those unfamiliar with technology or without access to such tools would exclude themselves from participation (Amoutzopoulos et al., 2018). Any queries related to food diary entries were checked with participants for clarity, food diary entries were then transferred into food analysis software (Netwisp version 3.0; Tinuviel Software, Llanfechell, Anglesey, UK). All participants completed the food diaries successfully.

3.4.2 Mood State Measure

Positive and Negative Affect Schedule (PANAS; Watson et al., 1988).

Negative mood state has been demonstrated to affect aspects of cognition, including emotion recognition (Schmid & Mast, 2010), memory, attention (Gable & Harmon-Jones, 2010) and executive function (Snyder, 2013). In addition, micronutrient supplementation has been demonstrated to have a positive effect on mood state in healthy adult populations (Haskell et al., 2010; Kaplan et al., 2007).

The PANAS is a twenty item self-report measure of positive and negative affect, the two dimensions providing measures of subjective level of distress/contentment and displeasure/pleasure. Participants were asked to rate their strength of experience of 20 given emotions e.g. (e.g. 'interested', 'distressed') using a Likert scale from 1 ('very slightly or not at all') to 5 ('extremely') over the previous week. Scores relating to the dispositional dimensions (positive affect, PA; negative affect, NA) were totalled to give an overall measure of positive and negative affective state. The PANAS (Watson et al., 1988) was administered at the beginning of a session in both studies to ensure responses were not affected by emotions related to completion of other measures.

Reliability (internal consistency) of the PANAS two scales (PA and NA) has been reported as r = .89 for the PA scale and r = .85 for the NA scale (Crawford & Henry, 2004).

3.4.3 Demographic Measures

Wechsler Abbreviated Scale Intelligence-II (WASI-II; Wechsler, 2011).

The WASI-II provided an estimate of general intellectual ability through administration of four subtests. Vocabulary and Similarities subtest scores combined gave a measure of crystallised verbal ability (VCI). Block Design and Matrix Reasoning subtests combined gave a measure of non-verbal fluid skill and visuomotor coordination (PRI). Combining these composite measures provided an estimate of full-scale IQ (FSIQ-4).

The Block Design subtest (measuring visual-motor coordination, abstract concept formation and reasoning) consisted of thirteen two-dimensional geometric designs of increasing complexity (Lichtenberger & Kaufman, 2009). Participants were required to reproduce presented designs using up to nine identical blocks; higher scores denoting swifter completion. The task was discontinued after two consecutive scores of 0 (for incorrect designs or correct designs completed outside the given time limit) or when all items had been completed. To ensure participants understood the task the solution to the two initial designs was modelled prior to participant completion. Following the practice participants were informed that solutions would no longer be modelled, and that time taken to complete each design would be recorded. Test-retest reliability for Block Design is reported as .88 for all adults (age range 17-90) with a split-half reliability of .91 (Wechsler, 2011).

The Vocabulary subtest measured verbal concept formation, word knowledge and degree of language learning (Lichtenberger & Kaufman, 2009). Participants were asked to provide definitions for given nouns and verbs of increasingly uncommon general English usage (first item ‘Shirt’; final item ‘Pavid’). The words were visually presented in short lists and additionally each word was read to participants. Responses were written down verbatim and scored 0, 1 or 2 dependent upon description accuracy until the discontinuation rule was reached (three consecutive scores of 0) or the task completed. If the discontinuation rule was reached part way through a word list, responses were recorded but not scored until the page was completed to ensure participants were unaware of their level of performance. Adult test-retest reliability for Vocabulary is reported as r = .94 with split half reliability of r = .92 (Wechsler, 2011).

Spatial ability, perceptual organization and conceptual knowledge of part-whole relationships were indexed with the Matrix Reasoning subtest. Participants were presented with thirty incomplete matrices and asked to select the correct item to complete the pattern from a choice of five. A score of 1 was given for each correct response, with the task discontinued after three consecutive incorrect responses. Items were presented individually until the discontinuation rule was reached or the task was completed. Adult Matrix Reasoning test-retest reliability is reported as $r = .83$ with split-half reliability of $r = .90$ (Wechsler, 2011).

For the Similarities subtest (measuring verbal concept formation and abstract reasoning; Lichtenberger & Kaufman, 2009) participants were read a pair of words and asked to describe in what way they were alike. The items began with straightforward pairings (e.g.'Green-Blue') and concluded with more conceptual pairings (e.g.'Memory-Practice'). Verbatim responses were recorded and scored 0, 1 or 2 dependent on the accuracy of the explanation given, the task discontinued after three consecutive scores of 0 or following task completion. Adult test-retest reliability is reported as $r = .89$ with split-half reliability of $r = .91$ (Wechsler, 2011).

Verbal ability subtest responses (Vocabulary and Similarities) were scored according to guidance in the WASI-II manual. In total the WASI-II (Wechsler, 2011) took between thirty and forty-five minutes to complete, dependent upon individual differences. All raw scores for the WASI-II (Wechsler, 2011) were converted to age-scaled scores and collated into scores of Verbal Comprehension, Perceptual Reasoning and Full Scale Intelligence Quotient (4 subtests). At the composite level test-retest reliability coefficients range from $r = .90$ (PRI) to $r = .95$ (VCI) with $r = .96$ for the FSIQ-4. Split half reliability for composite scores range from $r = .94$ (PRI) to $r = .95$ (VCI), with $r = .97$ for FSIQ-4 (Wechsler, 2011).

3.4.4 Processing Speed

Symbol Search - WAIS-III (Wechsler, 1997a).

The Symbol Search provided a measure of visuospatial processing speed under timed conditions (Kim & Park, 2018; Nouchi et al., 2012) and consisted of sixty items displayed as lists of two abstract figures on the left side of a page and five abstract figures on the right. Participants were asked to identify if either of the two target figures on the left were repeated in the five figures on the right of the page by putting a mark through either a 'yes' or 'no' box, a score of 1 given for each correct response. The task was explained using sample items; participants were then given a pencil and asked to complete the practice to ensure full understanding of the task. Following completion of practice

items participants were instructed to complete as many items as possible within a two-minute period.

Reliability coefficients for Symbol Span range from r = .74 to r = .82, with test-retest stability ranging from r = .74 to r = .82 across the age range 16 to 90 years (Wechsler, 1997b).

3.4.5 Memory

Digit Span (WAIS-III Wechsler, 1997a).

The Digit Span, a measure of auditory attention, working memory and mental manipulation (Clayton et al., 2016; Foxe et al., 2016) required participants to repeat back strings of digits of increasing length verbally presented by the administrator in two conditions (forwards and backwards). The 'forward' condition consisted of eight pairs of digit strings ranging from 2 to 9 digits; the 'backward' condition having seven pairs of digit strings ranging from 2 to 8 digits. Digit string pairs in each condition increased by one until participants incorrectly recalled both digit strings of a pair or the end of the task was reached. Correct repetition of each presented digit string scored 1 mark. In total, the Digit Span task took approximately five minutes to complete, depending on individual differences.

Reliability coefficients for the Digit Span range from r = .84 to r = .93 for age range 16-90 years. Test-retest stability for Digit Span ranges from r = .83 to r = .85 across the age range 16 to 90 years (Wechsler, 1997b).

Wechsler Memory Scale-IV (Wechsler, 2009a).

Five subtests of the WMS-IV (Wechsler, 2009) were administered to measure auditory memory, visual memory, and visual working memory without prolonged testing.

Logical Memory I and II.

Logical memory measured immediate and delayed narrative (auditory) memory through recall of two short stories. Following hearing the story being read participants were asked to immediately repeat back as much as they could remember, as close as possible to the language used. This process was then repeated for a second story. Participants were informed that they would be asked again about the stories after a 25-minute delay. A mark of 1 was given for each individual element of the story correctly recalled up to a maximum score of 25 for each of the two stories.

Reliability coefficients for the Logical Memory immediate condition range from r = .80 to r = .87 for age range 16-90 years, for Logical Memory delayed this ranged from r = .80 to r = .90 for the same age range (Wechsler et al., 2009b).

Visual Reproduction I and II.

The Visual Reproduction task measured immediate and delayed visuo-spatial memory. Participants were presented with abstract diagrams of increasing complexity (three single designs, two paired designs) for ten seconds, the stimulus was then removed, and participants were asked to draw the design to their best recollection (immediate recall). On completion of all five items in the task the response booklet was removed, and participants were informed they would be asked about the designs again after a 25-minute delay. Following the delay participants were asked to again draw the designs; they did not need to reproduce the designs in the order of presentation but were told they should attempt to draw the correct number of designs, in correct pairings where required. Items were scored using the same criteria in both conditions; a score of 1 given for each correctly recalled element of each diagram up to a maximum score of 45. If participants expressed concern about poor drawing skills, they were reassured that this was not assessed as part of the task.

Reliability coefficients for the Visual Reproduction immediate condition range from r = .88 to r = .96 for age range 16-90 years, for Visual Reproduction delayed this ranged from r = .96 to r =.98 for the same age range (Wechsler et al., 2009b).

Symbol Span.

For the Symbol Span task, measuring visual working memory (Pauls et al., 2013), participants were presented with increasing numbers of abstract figures for five seconds. Following exposure participants had to identify the correct symbols from a number of distractors, recalling the order of symbols from left to right. To ensure participants understood the requirements of the task a practice item composed of two symbols was administered. The task began with one target item, the cognitive load building incrementally stepwise with increasing numbers of items. A score of 2 given for completely correct responses, 1 was given or the correct figures in the wrong order and 0 for incorrect or incomplete responses. The task was discontinued following four consecutive imperfect scores (1 or 0) or when all items had been administered.

Reliability coefficients for Symbol Span range from r = .81 to r = .92 across ages 16-90 years (Wechsler et al., 2009b).

Doors and People (Baddeley et al., 1994).

The Doors and People Test provided a quickly administered measure of learning and memory. The overall score was broken down into measures of visual and verbal memory recognition, recall and forgetting through the administration of four subtests (MacPherson et al., 2016).

For the ‘Doors’ task participants were asked to identify a previously presented photograph of a door from three distractors. A practice trial of two items was given to check understanding of task instructions. Following the practice participants were shown twelve doors individually for three seconds with a verbal label, for example ‘This is a front door'. Participants were then shown a page with four doors (one target, three distractors) and asked to identify the door previously presented; order of presentation was not the same as the learning phase. This was repeated with a second set of doors with distractors more similar to the target. A score of 1 was given for each correctly identified door, up to a maximum score of 24.

To assess verbal memory participants were asked to learn the names of four people (People Task), with a maximum of three learning trials. Each of the names were presented for three seconds with a photograph of an individual and an occupation, for example “This is Jim Green, he’s a doctor”. After presentation of all four names the stimuli were removed and participants were asked to recall the names with a prompt, for example “Can you give me the doctor’s name?”. If participants did not recall all names correctly the stimuli were presented again. If participants were unable to recall all four names after the second trial the process was repeated for a final time. Following this, participants were asked about the names again following a ten-minute delay. Marks were given for each correctly recalled element of the names up to a maximum score of 36. In the delayed condition participants were again asked to recall the four names (maximum score of 12).

The Shapes test was administered to assess visual memory. Participants studied each of four individually presented shapes for three seconds and drew them. Once participants had seen and copied all four shapes the stimuli and participant copies were hidden from view and participants were asked to draw the shapes again from memory. If participants did not correctly recall all shapes, they were shown the stimuli again one at a time but were not permitted to copy them. Once the stimuli had been presented for a second time, participants had another opportunity to recall them. If participants did not correctly reproduce the shapes on this trial the process was repeated for a third time. Participants were asked to draw the shapes again following a ten minute delay. Scores were given for each correctly recalled element of the shape up to a maximum total score of 36 across all three trials. Following a delay, participants were asked to try to draw the four shapes again, scoring for this delayed recall task was identical to that for the immediate condition up to a maximum score of 12.

The auditory memory 'Names' recognition task procedure was similar to that of the Doors task; participants were shown 12 names individually and then asked to correctly identify the names from one target and three distractors. As with the Doors subtest this task had a two-item practice and a second condition of twelve items of increased difficulty with distractors more similar to the target. Presentation orders in the identification phases were different to that in the demonstration phases. Participants were given a score of 1 for each correct name identified up to a maximum score of 24 for both trials.

Overall the Doors and People took approximately thirty minutes to complete. There is limited data on test-retest reliability, but inter-rater reliability is reported as good, r = .98, (Baddeley et al., 1994).

3.4.6 Executive Function

As higher order thinking is often impaired following traumatic brain injury (Caeyenberghs et al., 2014; Draper & Ponsford, 2008; Edwards & Wood, 2016; Hartikainen et al., 2010) broad assessment of executive function in relation to micronutrient supplementation was undertaken in the normative study to provide a comparative baseline.

Trail Making Test (Delis-Kaplan Executive Function System: Delis et al., 2001).

Isolation of visuo-motor set shifting by controlling for component skills (letter sequencing, number sequencing, visual scanning, motor speed) was achieved using the Trail Making tasks (Yochim et al., 2007). These five tasks also assess sequencing, visual attention and flexibility of thinking via sequentially 'connecting the dots'; numbers (1, 2, 3 through to 16), letters (A, B, C through to P) and switching between the two (1, A, 2, B through to 16, P). This test also included visual search (crossing out the number 3 from distractors; condition 1) and motor speed (joining circles together; condition 5) tasks to rule out deficits in these domains affecting performance. Each of the tasks had a practice element to ensure participants fully understood instructions and scores were age-scaled to the speed of completion of each subtest.

Test-retest reliability for the Trail Making Test ranges across conditions from r = .38 (switching) to r = .77 (motor speed), with internal consistency in the range r = .69 - r = .81 across a 16-89 years age range.

Verbal Fluency (Delis-Kaplan Executive Function System: Delis et al., 2001).

This task assesses semantic and phonemic lexical access speed in generation of words beginning with specific letters (phonemic fluency) or belonging to specific categories (semantic fluency) and the ability to switch semantic sets in six 60-second subtests (Swanson, 2005). Responses were recorded in quartiles of sixty seconds (0-15, 16-30, 31-45, 46-60) and note was taken of any repetition or incorrect set errors. Each sub-test had an alternate form.

For phonemic fluency participants were given the letters 'F', 'A', and 'S' or 'B', 'H' and 'R' to generate responses. In the semantic fluency condition participants were given the categories 'Animals' and 'Boys' Names' or 'Items of Clothing' and 'Girls' Names'. In the final condition participants were instructed to switch responses between two semantic categories; 'Fruits' and 'Furniture' or 'Vegetables' and 'Musical Instruments'. Encouragement and reassurance were given to participants who felt that they were performing poorly.

Test-retest reliability for the Verbal Fluency Test ranges across conditions from r = .36 (category switching) to r = .80 (letter fluency), with internal consistency across conditions in the range α = .43 to α = .90 across the age range 16 – 89 years.

Design Fluency (Delis-Kaplan Executive Function System: Delis et al., 2001).

Fluency of design generation observing set rules, inhibition of previously drawn responses and cognitive flexibility across three conditions were assessed using the design fluency tasks (Pålsson et al., 2013; Swanson, 2005). Participants were asked to create as many different designs in identical boxes containing five dots using four straight lines in sixty seconds. Following practice trials and any corrections in rule understanding participants completed each condition; filled in dots, empty dots with filled dots as the distractor, and switching between the two dot forms. Responses were monitored and if participants made three consecutive incorrect designs (designs that contravened rules) they were alerted that these designs were incorrect. A score of 1 was given for each novel design produced in each condition.

Test-retest reliability for the Design Fluency Test ranges across conditions from r = .32 (design switching) to r = .58 (filled dots), with internal consistency across conditions in the range α = .72 to α = .86 across the 16-89 age range.

Tower Task (Delis-Kaplan Executive Function System: Delis et al., 2001).

The Tower Task measured spatial planning ability, rule learning, inhibition of impulsive and perseverative responses and the ability to establish and maintain an instructional set (Swanson, 2005). Participants were presented with a frame with three pegs and five discs of increasing size with a hole in the centre. Participants were told that they were going to make towers on the frame using the fewest number of moves possible and following a number or rules; they were to move only one disc at a time, use only one hand, and to never to place a larger disc on top of a smaller disc. Discs were placed in a starting configuration and the test booklet turned to display the target configuration and the stopwatch started. The task continued until either the participant had three consecutive item failures, or all nine configurations were worked through. Scores were based on accuracy of response (number of moves made), time to first move, completion time, and an overall achievement score (reflecting time to completion and number of moves used). Scores for all measures were age-scaled. Completion of this task took approximately twenty minutes, dependent upon individual differences.

Test-retest reliability for the Tower Test is reported as $r = 0.44$ in the technical manual, with internal consistency ranging between $\alpha = .56$ and $\alpha = .78$ in age ranges 16-89 (Delis et al., 2001).

3.4.7 Implicit and Explicit Learning

Implicit learning refers to the tacit acquisition of complex, abstract knowledge in response to unnoticed or unattended stimuli (Reber, 1989) and is different to explicit learning where knowledge is consciously attained. A task of implicit learning was included in the test battery, supported by evidence that implicit learning can be affected by micronutrient supplementation as measured using a serial reaction time task (Tupe & Chiplonkar, 2009).

Serial Reaction Time Task (Barker, 2012; Seger, 1997)

The task was programmed in Psyscope (Cohen et al., 1993) and presented on a Macintosh Powerbook 5300. Presentation of the task followed that of previous studies (Barker et al., 2004; Barker et al., 2006; Morton & Barker, 2010); participants were asked to press a key on the keyboard corresponding to the position of one of four target locations (1cm circles) on the screen mapped to the V, B, N and M keys on the keyboard. Participants were also informed that the dot on the screen would not disappear until the correct key had been pressed. The random blocks were programmed so that a circle did not appear in the same location in succession nor followed the pattern 1234 or 4321 at

any time. This was to ensure that the random blocks were as indistinguishable from pattern blocks as possible. The task consisted of ten blocks of fifty trials, the first trial forming a practice session. The learning phase consisted of one random block followed by six sequence (learning) blocks. The test phase consisted of three blocks (random, test, random) that followed the learning phase without participant's awareness. Each test block provided 50 reaction time values divided into five repeats of ten trials. A median reaction time was calculated for each of these blocks of ten; these were then combined to give three mean values (one sequence, two random). The two random block values were then combined to give a single mean. To get the implicit learning score for each participant the sequence block mean was subtracted from the combined random block mean.

Following task completion participants completed an explicit knowledge questionnaire consisting of four questions (Seger, 1997). On the first part of the questionnaire participants were asked to rate how certain they were of the presence of a pattern on a seven-point Likert scale from *'I did not even suspect a pattern'* to *'I was completely certain there was a pattern'* and additionally to describe any pattern they noticed. On the second part of the questionnaire (on the reverse of the paper) participants are asked how sure they were that the sequence consisted of a) ten positions (correct) and b) 12 or more positions (foil), again using a seven-point Likert Scale from *'I think it is very unlikely that is the pattern'* to *'I think it is very likely that is the pattern'*. Explicit learning score was calculated followed the template originally described by Seger (1997) with participant's score comprising of their ratings from question 1 and question 3 in combination with double the score from question 2 (description of the sequence). Ability to rate the pattern sequence was on a 6 point scale (0-5).

3.4.8 Social Cognition

Social cognition, the ability to process the emotional content of facial expressions and spoken communication, is important for successful interactions with others and often affected following traumatic brain injury (Cassel et al., 2019). Research involving supplementation of the diets of prison populations with micronutrients found that those taking the intervention had significantly improved interpersonal relationships and a reduction in anti-social behaviour (Gesch et al., 2002) when compared to controls, demonstrating that micronutrient interventions have the ability to improve social cognition.

Reading the Mind in the Eyes - Revised (RME-R; Baron-Cohen et al., 2001).

The RME-R is considered an advanced theory of mind task, requiring participants to identify the complex mental state presented in black and white photographs of the eye

area of an individual (Gregory et al., 2002). To familiarise participants with the task a practice example was given. Following this, participants were given a response sheet and a folder containing 36 black and white photographs showing only the eye area of a face. They were asked to select which of the four given descriptors at the corners of the photograph best fit the expression they could see, marking down their response on the sheet in whatever way they felt comfortable (circling or placing a tick or cross). Foil words were designed to have, where possible, the same emotional valence as the target word. If participants were unsure of word meaning they were able to refer to the accompanying glossary. Participants were told to work through the photographs at their own pace, the task taking between five to ten minutes to complete.

Movie for the Assessment of Social Cognition (MASC; Dziobek, 2006).

To provide a well-rounded picture of individual's social cognition skills participants were also administered the MASC. This task assessed theory of mind, empathy and ability to detect sarcasm and faux pas, using a fifteen-minute film showing four individuals (two men and two women) at a dinner party. Slides with written instructions displayed on the screen instructing participants that they were to see a short fifteen-minute film. This film would be stopped at several intervals to ask questions about what the characters in the film were thinking or feeling. Participants were then shown images of the four protagonists in the film for familiarisation. The film was stopped at fifty-one predetermined points the for a multiple-choice question related to the interaction they had just seen. Six of these questions were controls measure level of attention participants to the task. The task took approximately thirty minutes.

Test-retest reliability for the MASC is $r = .97$ and has internal consistency of $\alpha = .84$ (Dziobek et al., 2006).

3.5. Rationale for supplement selection

3.5.1 Multivitamin

The multi-micronutrient supplement used in this study was selected to ensure participants would have supplement intake that met recommended daily amounts. Micronutrients have direct actions on normal adult neuronal functioning (e.g Harms, et al., 2011; Bourre, 2006a; Choi and Koh, 1998; Jahanshad et al., 2013). As examples the B-complex of vitamins, including thiamine, niacin and pyroxidine, are involved in neurotransmitter biosynthesis, maintenance of the myelin sheath and neuronal cell metabolism (Molina et al., 2012; Parletta et al., 2013) and calcium is vital for maintenance of the mitochondrial matrix, neuronal gene expression and cellular calcium homeostasis

(Catterall, 2011). Sub-clinical deficiency in micronutrients carries the risk of chemical imbalance in neuronal processes affecting cognition and may also have wider implications on the long-term health of the individual.

3.5.2 Vitamin D

Vitamin D deficiency is very common in the normal UK population (25% in the summer, 60% in the winter; Webb et al., 2010) and has two vitamers, D_2 (ergocalciferol) and D_3 (cholecalciferol). Participants were given D_3 as this form has greater affinity with vitamin D receptors and is more bioactive compared with D_2 as it mimics the vitamin D precursor formed in the skin after exposure to UVB light (Houghton & Veith, 2006). Research findings of investigations into the relationship between vitamin D levels and cognition have been inconsistent (Buell et al., 2009; McGrath et al., 2007) and have been focused on older populations. As such vitamin D_3 at the current RDI level (10µg/day) was selected as the mono-nutrient supplement to investigate any effect of supplementation on cognition in a broader demographic group.

3.5.3 Vitamin C (control group)

A control group was included to account for practice effects. Although there are suggestions that vitamin C intake may be neuroprotective for cognitive decline in dementia due to its antioxidant properties (Crichton et al., 2013), studies indicating a relationship between vitamin C intake and cognitive measures have been at supplementation doses of 500mg/day or above (e.g. Arlt et al., 2012). A supplement of less than half this amount (200mg) was therefore selected to function as a control.

Supplements were prepared in identical dark blue opaque bottles. The bottle colour served two purposes; prevented degradation of the supplements by sunlight and obscuring the contents to preserve the double blind.

3.6. Hypotheses

Based on previous research findings it was hypothesised that there would be an improvement in performance following the multivitamin and vitamin D intervention, with no change in performance following the vitamin C intervention. It was hypothesised that there would be a difference in the level of improvement seen in the multivitamin and vitamin D groups, but there was no hypothesis related to which domains the improvements would be seen. It was expected that the profile of micronutrient intake would be altered by the interventions, with those in the multivitamin group having

significantly greater intake levels of all micronutrients, compared with the other groups, apart from vitamin D and vitamin C. Vitamin D and vitamin C intake levels were expected to be higher in the respective intervention groups, compared with the multivitamin group.

3.7. Procedure

Written informed consent was obtained from participants. Participants were also informed they were free to ask any questions at any time during the study. Testing with the cognitive battery took place over two sessions each lasting approximately two hours, participants taking rest breaks as required. Test measures were counterbalanced between and within participants across the study to prevent order effects. Following completion of baseline testing participants were given instructions on how to complete the food diary and their allocation of supplement with the instruction to take one tablet per day with food. Following the eight-week supplementation period all cognitive test measures were repeated, using alternate forms where available. All participant materials can be found in Appendix A.3.

Participants were consulted regarding the method of contact (email, text, voice call) for reminders about taking tablets and completing food diaries. Participants were contacted twice weekly throughout their involvement in the study, maintaining contact to improve participant retention.

3.8. Ethics

This study was conducted at the Psychology Department, Sheffield Hallam University, according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects approved by the Sheffield Hallam University Faculty of Development and Society Research Ethics Committee (192014). Written informed consent was obtained from all participants.

The following chapter provides results of the study in a normative cohort.

Chapter 4 – Normative Results and Summary

4.1. Introduction

This chapter presents the findings from the micronutrient intervention study with a control group. A normative cohort from the general population was assigned to one of three conditions (Multivitamin, Vitamin D, Vitamin C) in a double-blind randomised control trial. The Vitamin C condition was originally designated a quasi-control as there were no placebo matches for the multivitamin or vitamin D tablets at this stage of the research. Previous research investigating putative effects of micronutrient interventions on cognition having been equivocal (e.g. Buell et al., 2009; Grima et al., 2012; Small et al., 2014; see Chapter Two).

In brief sixty participants were randomly allocated to one of the three conditions in a double-blind protocol. Participants completed baseline testing before taking their tablet allocation for eight weeks and filling in a food diary for the first 14 days of this period. At the end of this eight-week period participants completed follow-up testing on the same battery of counterbalanced measures (full details of the study methodology and procedure can be found in Chapter Three). Cognitive domains assessed included mood state, full scale IQ, processing speed, memory, executive function, and social cognition.

4.2. Results of demographic analyses and descriptive statistics

Raw data from cognitive measures was scored and age-scale adjusted with reference to corresponding test administration manuals (see Appendix B1 for baseline and post-intervention descriptive statistics). One participant lost to follow-up was removed from the data set prior to analyses. Test scores were z-transformed to assess potential outliers; analyses of z-scores (N=60) indicated three outliers (±3.29 standard deviations from the mean) at baseline and seven outliers at follow-up. Outliers were all transformed to scores ±3.29 standard deviations (SD) from the mean in line with Tabachnick and Fidell (2014).

Analyses of descriptive data at baseline (see Appendix B2) showed no significant difference between groups on measures of IQ ($F_{(2, 57)} = 0.60$, $p = 0.553$, $\eta_2 = 0.02$), or age ($F_{(2, 57)} = 0.69$, $p = 0.505$, $\eta_2 = 0.02$) indicating that participants were demographically matched and that putative differences between the groups following the intervention

could not be attributable to baseline demographic group differences. A MANOVA was conducted to investigate potential differences between groups on cognitive performance at baseline with supplement group as the independent variable and score on test measures as the dependent variables (see Table 4.1 for list of measures, Appendix B3 for output). Results of this analysis showed no significant difference between groups on any measure ($F_{(27,54)} = 1.15$, $p = 0.296$, $\eta_2 = 0.49$).

Table 4.1

List of measures included in the MANOVA

Cognitive Function	Measure
Memory	Digit Span (WAIS-III)
	Logical Memory Immediate & Delayed (WMS-IV)
	Visual Reproduction Immediate & Delayed (WMS-IV)
	Symbol Span (WMS-IV)
	Doors and People Overall Score
Executive Function	Trail Making (D-KEFS)
	Visual Scanning
	Number Sequencing
	Letter Sequencing
	Number/Letter Switching
	Motor Speed
	Design Fluency Overall Score (D-KEFS)
	Verbal Fluency (D-KEFS)
	Phonemic Fluency
	Semantic Fluency
	Semantic Switching
	Tower (D-KEFS)
	Total Score
	Mean 1st Move Time
	Time per Move
	Move Accuracy
	Symbol Search (WAIS-III)
Serial Reaction Time Test	Explicit Learning
	Implicit Learning
Mood State	Positive and Negative Affect Schedule
Social Cognition	Reading the Mind in the Eyes
	Movie for the Assessment of Social Cognition

4.3. Analyses of food diary data

All participants completed a consecutive fourteen-day food diary at the beginning of the intervention period. This length of food diary was longer than that used in many studies (usually 3 or 7 days; Hughes et al., 2012; Whyte et al., 2016; Zweers et al., 2018)

and is considered the optimum length for capturing normal variety in eating patterns (Falciglia et al., 2009). Self-report food diaries have also been shown to provide a good estimation of micronutrient intake, when compared with reliability of physiological biomarkers (Brunner et al., 2001; Sauvageot et al., 2013). Participants were asked to give as much detail as possible in their entries and to note down what was eaten as close as possible to the time of ingestion to aid reporting accuracy (Kirkpatrick et al., 2014). Participants were not asked to weigh or measure constituent items in meals. Any queries in food diary entries were clarified with the participant prior to being input into nutritional analysis software (Netwisp version 3.0; Tinuviel Software, Llanfechell, Anglesey, UK). Input of food diary data was completed as accurately as possible with new food items created within the database where necessary, for example for plant-based milk substitutes. Following input, the software calculated a mean intake value for each micronutrient for each participant; these data were then input into SPSS v23 (IBM Corp., 2015) for statistical analyses.

Micronutrients of interest were 18 of the 19 'essential' micronutrients (see Table 2); information on vitamin K intake was not provided by the nutritional analysis software however there are usually relatively high levels of vitamin K in most diets (found in meat, fish, fruit, vegetables) and healthy adults only require small amounts (Suttie, 2013). As recommended daily intakes vary micronutrients were analysed separately.

Table 4.2

List of Vitamins and Minerals included in Analyses

Vitamins	Minerals
A, C, D, E, thiamine, riboflavin, niacin, pantothenic acid, B_6, biotin, folic acid, B_{12}	Calcium, iodine, iron, potassium, selenium, zinc

Daily dietary intake of micronutrients were compared to recommended dietary reference intake levels issued by the United States Food and Nutrition Board of the Institute of Medicine (Bendich, 2001; Del Valle et al., 2011; Institute of Medicine (US), 1997; Institute of Medicine (US), 1998; Monsen, 2000; Trumbo et al., 2001). The US IoM levels were selected for comparison as these are the guidelines used as the basis for World Health Organisation recommendations (2004). The comparison of dietary intake with recommended levels was calculated for each of the three groups (Vitamin D, Multivitamin, and Vitamin C) as a baseline. In addition, total micronutrient intake for each group was calculated from the sum of dietary intake plus micronutrient supplementation following the intervention and again compared with recommended daily

intake levels. Difference scores for dietary intake alone and dietary intake plus supplementation were converted to a percentage to account for differences in scale (μg/mg) so that a direct comparison could be made between different micronutrients.

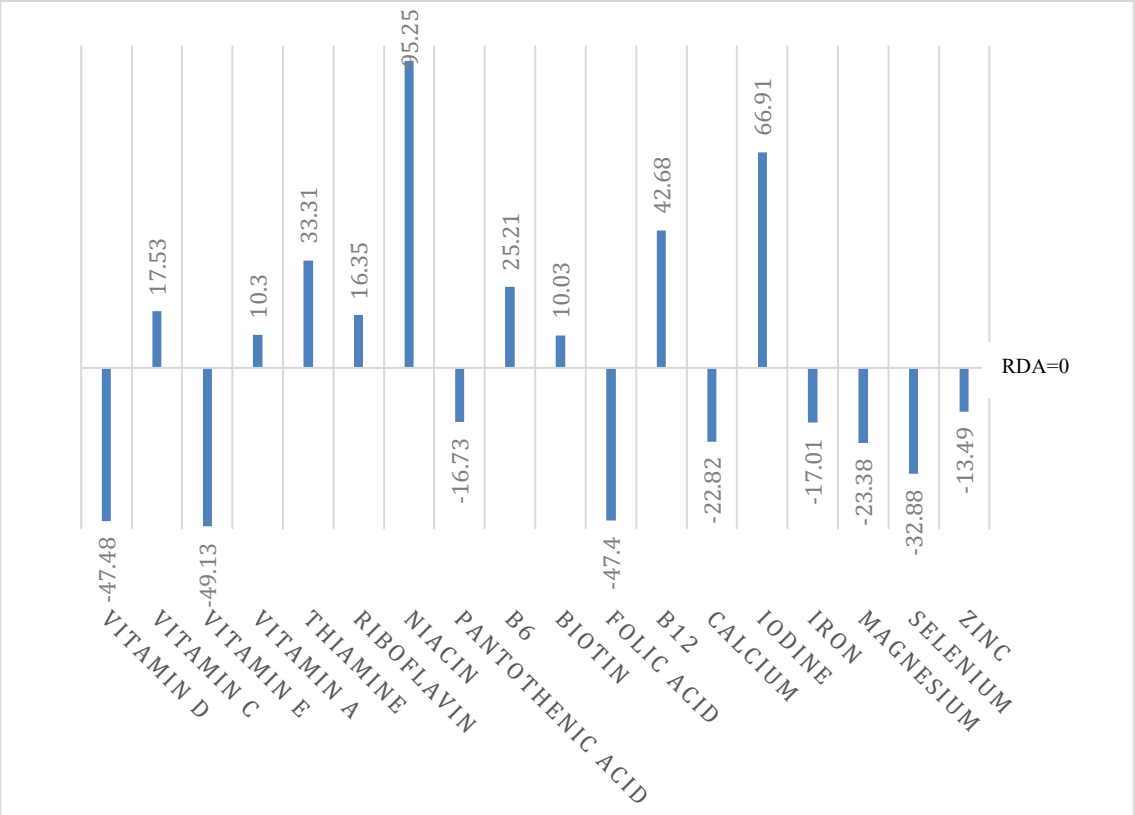
There was no significant difference between groups at baseline ($F_{(38, 80)} = 0.90$, $p = 0.632$, $\eta_2 = 0.30$) using MANOVA with average daily micronutrient intake taken from food diaries as the independent variable and group as the dependent variable (see Appendix B4). The groups could therefore not be distinguished based on micronutrient intake at baseline. Absence of statistical difference in dietary micronutrient intake meant that any changes in cognitive task performance was more likely to be attributed to supplement group rather than being a result of differing dietary micronutrient levels across groups. Analyses of micronutrient intake from diet was therefore analysed for the whole cohort.

4.3.1 Summary of whole cohort nutritional status at baseline

Results of analyses showed that participants had insufficient dietary intake to reach RDI levels in nine of the sixteen micronutrients at baseline. Those micronutrients below RDA included two fat-soluble vitamins (D and E), two B vitamins (pantothenic acid and folic acid) and all minerals excepting iodine (calcium, iron, magnesium, selenium and zinc). Levels of vitamin D, vitamin E and folic acid were the most deficient across the cohort when compared to RDA values with intake being almost 50% short of recommended amounts (see Figure 4.1 and Appendix B5). Most of the B vitamins along with vitamins C and A had dietary intake above recommended daily amounts. Intake of iodine was significantly higher than recommended daily levels.

Figure 4.3

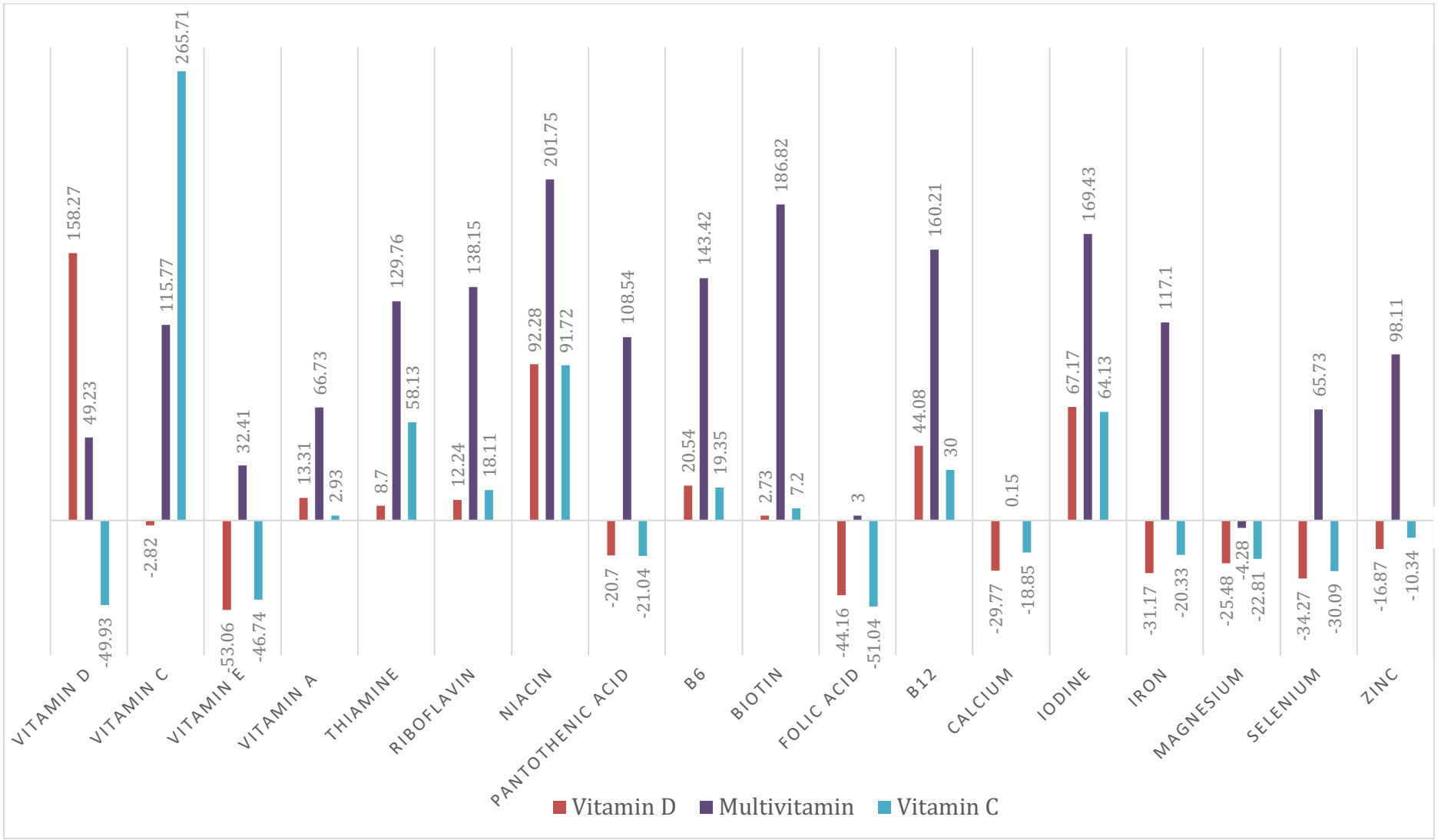
Dietary intake of micronutrients as a percentage above and below RDA for the Whole Cohort (N = 60)



Results of repeat MANOVA following supplementation showed a significant effect of group on overall micronutrient intake (dietary intake plus supplementation), $F_{(36, 82)} = 73.28$, $p < 0.001$, $\eta_2 = 0.97$. Between group ANOVAs were all significant at the <.001 level indicating that there was a significant difference in intake between all conditions. *Post-hoc t*-tests showed that the Multivitamin group had micronutrient levels that were significantly greater than the other two groups except for vitamins C and D. This was as expected due to the broad composition of the supplement. The Multivitamin group had significantly higher levels of vitamin C intake when compared to the Vitamin D group ($t_{(38)} = 6.16$, $p < .001$), however the Vitamin C group had significantly higher intake of vitamin C than both the Multivitamin ($t_{(38)} = 6.88$, $p < .001$) and Vitamin D ($t_{(58)} = 17.03$, $p < .001$) groups as might be expected. Finally, the Vitamin D group had significantly higher vitamin D intake than either the Multivitamin ($t_{(38)} = 8.64$, $p < .001$) and Vitamin C groups ($t_{(38)} = 21.92$, $p < .001$). See Figure 4.2 below for comparison of levels of intake following the supplementation period.

Figure 4.2

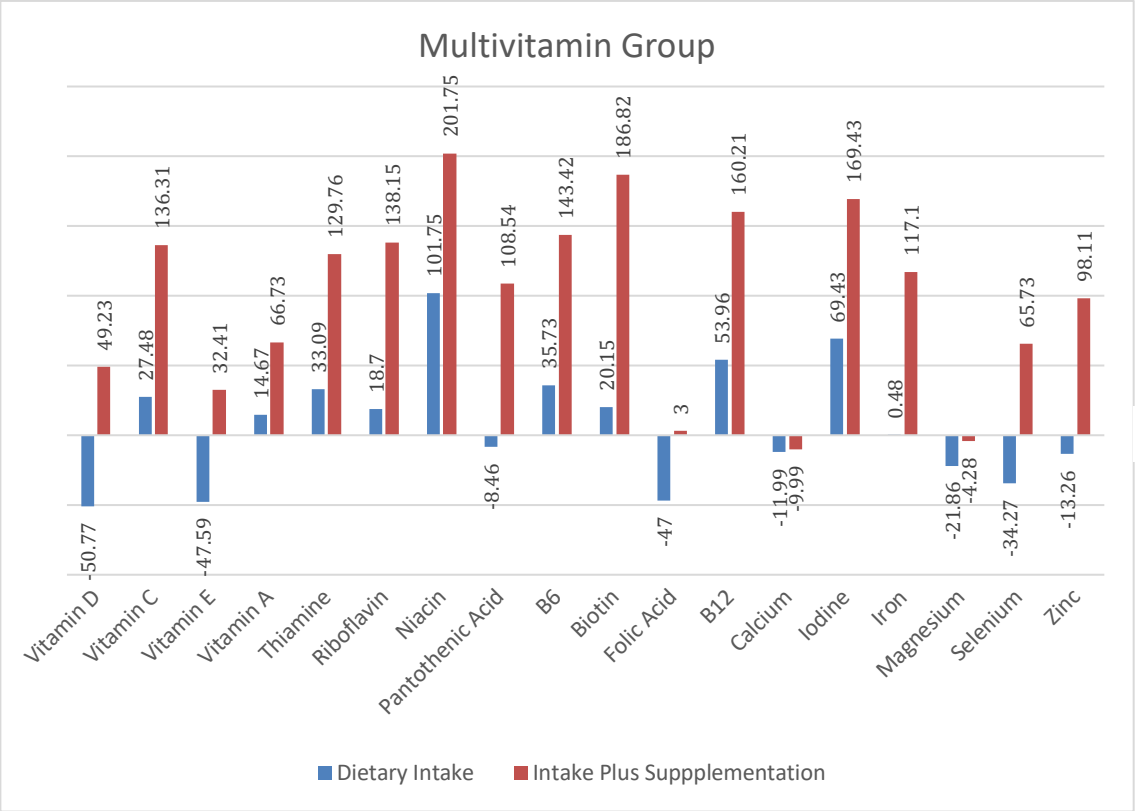
Intake of micronutrients dietary intake plus supplements) as a percentage below and above RDA for each group.



The addition of the multivitamin therefore completely changed the micronutrient profile of the Multivitamin group who no longer showed micronutrient deficiency for most micronutrients (see Figure 4.3 comparing intake pre- and post-supplementation).

Figure 4.3

Intake of micronutrients in the multivitamin group pre- and post-Intervention (n = 20)



The micronutrient profile of the Vitamin D and Vitamin C groups however remained essentially the same as baseline levels, with the exception of vitamin D and vitamin C intake respectively (see Figure 4.4 and 4.5 for micronutrient intake levels of the vitamin D and Vitamin C groups from diet alone and following supplementation).

Figure 4.4

Intake of micronutrients in the vitamin D group pre- and post-intervention (n = 20)

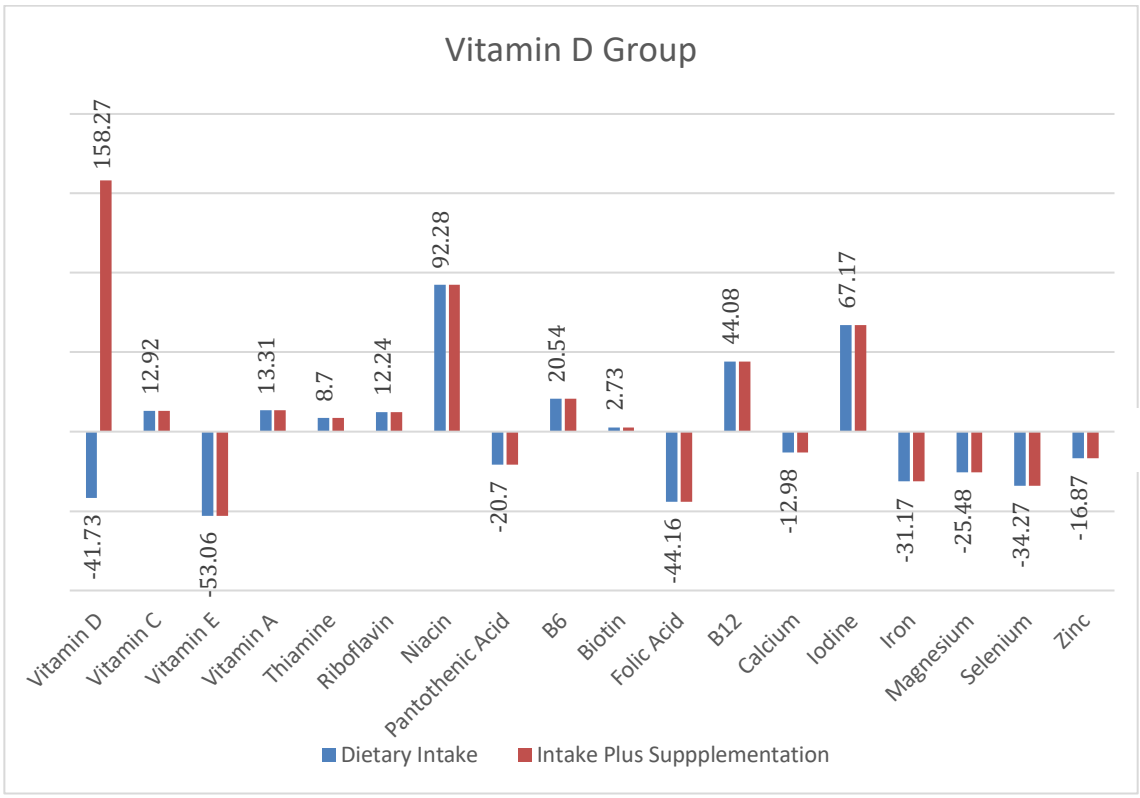
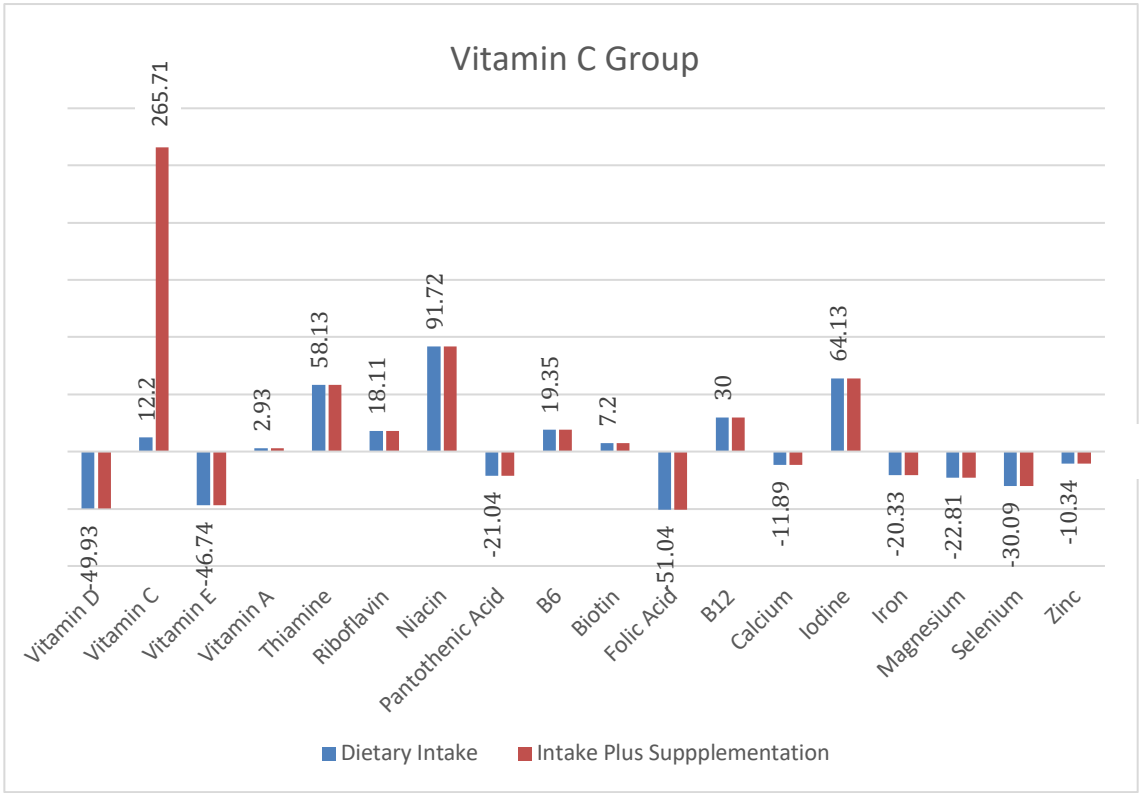


Figure 4.5

Intake of micronutrients in the vitamin C Group pre- and post-intervention (n = 20)



4.4. Summary of cognitive task performance findings

Time 2 cognitive data were analysed separately for each group as total intake of micronutrients following the intervention period were nutritionally distinct whereas at Time 1 they were no different. Comparison of each group's cognitive test performance from baseline to follow-up was conducted using paired *t*-tests (see Tables 4.3, 4.4, 4.5; Appendix B6). A corrected α of .010 (two-tailed) was applied to account for multiple comparisons (Tabachnick & Fidell, 2014). As sample size affects *p* values, effect size (a measure independent of sample size) is also reported in the form of Cohen's *d* (Cohen, 1988; 0.2 = small, 0.5 = medium, 0.8 = large). To ensure that any skew in the data did not have an effect on findings, both non-parametric Wilcoxon signed rank and parametric paired *t*-tests were conducted. Results from these analyses were consistent and did not produce divergent results (see Appendix B7), parametric paired *t*-tests have therefore been reported in the following sections.

4.4.1 Multivitamin group

Tables 4.3 and 4.4 show the results of cognitive task performance analyses in the Multivitamin group. There was significant improvement on Perceptual Reasoning subtests (Block Design and Matrix Reasoning) of the WASI-II (Table 4.3). This improvement in perceptual reasoning was also reflected in a marginally significant change in overall Full-Scale IQ (reflecting enhanced perceptual reasoning scores).

On tasks of memory (Table 4.4), functions assessed using the WMS-IV, findings showed significant improvements on delayed recall of visually and verbally presented information (with a large effect size) and on visuo-spatial working memory tasks (Symbol Span). Immediate recall of verbally presented information was approaching significance. On the Doors and People overall score, a measure of learning and memory, there was a significant improvement from baseline (Time 1) to follow-up (Time 2).

Table 4.3

Multivitamin Group paired t -tests comparing pre- to post-intervention cognitive performance showing means, standard deviations, t-statistics, p values (two-tailed), effect sizes and confidence intervals for IQ and memory scores

Measure/Function	Time 1 mean (SD)	Time 2 mean (SD)	*t* (19)	*p*	*d*	95% CI LL	95% CI UL
IQ:							
WASI-II Verbal Comp.	105.70 (9.78)	106.70 (8.06)	0.70	.490	0.07	-3.97	1.97
WASI-II Percept. Reasoning	113.55 (14.39)	118.95 (13.21)	3.65	**.002**	0.39	-8.49	-2.31
WASI-II FSIQ-4	110.40(12.07)	114.05(10.42)	2.64	.016	0.32	-6.54	-0.76
Memory:							
WAIS-III Digit Span	10.15 (2.96)	10.60 (2.35)	1.12	.275	0.17	-1.29	0.39
WMS Verbal Mem. Imm.	10.80(2.59)	12.50(2.59)	2.76	.012	0.66	-2.99	-0.41
WMS Verbal Mem. Delayed	11.00(2.63)	13.30(2.43)	3.63	**.002**	**0.91**	-3.62	-0.98
WMS Visual Repro. Imm.	12.25 (2.34)	12.00 (2.17)	0.79	.437	0.11	-0.41	0.91
WMS Visual Repro. Delayed	10.95 (2.35)	14.30(2.43)	5.95	**<.001**	**1.40**	-4.53	-2.17
WMS Symbol Span	11.80(3.58)	13.65(3.13)	3.00	**.007**	0.55	-3.14	-0.56
Doors & People Overall	12.05(2.63)	13.70(2.56)	3.73	**.001**	0.64	-2.58	-0.72

Note: significant *p* values and large effect sizes (Cohen's $d > .8$) in **bold**

Results of task performance in the Multivitamin group on D-KEFS (Delis et al., 2001) subtests can be seen in Table 4.4. There was a significant improvement in the novel visual strategy generation task involving a distractor (Design Fluency Empty) shown by a significant improvement in the Design Fluency Total Score. The Multivitamin group also had significantly improved scores on the Tower test Mean 1st Move Time, a measure of task initiation and motor planning, but this did not result in an improvement on other metrics of this task. Visuo-motor processing speed (Symbol Search) additionally showed significant improvement from Time 1 to Time 2.

The Multivitamin group showed significantly increased explicit awareness of the pattern sequence on the Serial Reaction Time test with a large effect size. This group also demonstrated a significantly reduced reaction time on implicit response to the pattern showing improved procedural learning from Time 1 to Time 2. There was no significant change in mood state as measured by the PANAS from baseline to follow-up. Measures of social cognition (Movie for the Assessment of Social Cognition and Reading the Mind in the Eyes) also showed no significant improvement.

Table 4.4

Multivitamin group paired t -tests comparing pre- to post-intervention cognitive performance showing means, standard deviations, t-statistics, p values (two-tailed), effect sizes and confidence intervals, executive function, learning, affect, and social cognition.

Measure/Function	Time 1 mean (SD)	Time 2 mean (SD)	*t* (19)	*p*	*d*	95% CI LL	95% CI UL
Executive Function:							
DKEFS Trail Making Visual Scanning	12.65 (1.27)	12.15 (1.46)	1.65	.116	0.37	-0.14	1.14
DKEFS Trail Making Number Sequencing	11.80 (2.33)	12.20 (1.70)	0.90	.379	0.20	-1.33	0.53
DKEFS Trail Making Letter Sequencing	12.65 (1.87)	12.45 (2.03)	0.64	.530	0.10	-0.45	0.85
DKEFS Trail Making Number/Letter Switching	11.75 (1.92)	12.10 (1.83)	1.20	.246	0.19	0.96	0.26
DKEFS Trail Making Motor Speed	11.55 (1.88)	12.05 (1.47)	1.49	.154	0.30	-1.20	0.20
DKEFS Design Fluency Filled	7.35 (1.57)	7.65 (1.79)	1.06	.301	0.18	-0.89	0.29
DKEFS Design Fluency Empty	6.85 (1.23)	7.95 (1.85)	3.32	**.004**	0.70	-1.79	-0.41
DKEFS Design Fluency Switching	10.05 (1.96)	11.20 (2.33)	1.98	.063	0.53	-2.37	0.07
DKEFS Design Fluency Total Correct	7.90 (1.55)	9.45 (2.31)	3.81	**.001**	0.23	-2.40	-0.70
DKEFS Verbal Fluency Phonemic Fluency	11.90 (3.67)	12.25 (3.63)	0.63	.538	0.10	-1.52	0.82
DKEFS Verbal Fluency Semantic Fluency	12.80 (3.86)	13.05 (4.28)	1.06	.302	0.06	-2.82	0.92
DKEFS Verbal Fluency Semantic Switching	12.85 (3.22)	13.05 (3.33)	0.39	.700	0.06	-1.27	0.87
DKEFS Tower Total Score	12.30 (2.56)	12.50 (1.85)	0.35	.731	0.13	-1.40	1.00
DKEFS Tower Mean 1st Move Time	10.95(2.37)	11.95(1.50)	3.01	**.007**	0.52	-1.70	-0.30
DKEFS Tower Time per Move	11.00 (1.72)	11.35 (1.73)	1.20	.246	0.20	-0.96	0.26
DKEFS Tower Move Accuracy	10.50 (1.73)	10.35 (1.31)	0.34	.735	0.10	-0.76	1.06
WAIS-III Symbol Search Correct	12.05(2.67)	13.40(2.37)	3.18	**.005**	0.53	-2.24	-0.46
Learning:							
SRT Explicit Learning	11.15 (5.33)	15.85(5.27)	3.73	**.001**	**0.89**	-7.33	-2.07
SRT Implicit Learning	102.46 (73.65)	64.74 (63.25)	3.63	**.002**	0.55	-59.47	-15.97
Affect:							
PANAS Positive Affect	36.30 (6.14)	35.00 (6.74)	1.10	.096	0.34	-0.41	4.61
PANAS Negative Affect	17.45 (6.38)	17.80 (6.72)	0.11	.914	0.02	-3.03	2.73
Social Cognition:							
Reading the Mind in the Eyes	27.20 (3.97)	27.90 (2.43)	1.02	.320	0.22	-2.13	0.73
Movie for the Assessment of Social Cognition	36.00 (3.55)	37.50 (3.69)	2.64	.016	0.41	-2.69	-0.31

Note: significant *p* values and large effect sizes (Cohen's *d* >.8) in **bold**

4.4.2 Vitamin D group

Analyses of the Vitamin D group's task performance showed a significant improvement on the Perceptual Reasoning subtest of the WASI-II, reflected in a significant improvement in Full Scale IQ, similar to that seen in the Multivitamin group (Table 4.5). On tests of memory the Vitamin D group showed significant improvements on immediate and delayed recall of verbally presented material, and on delayed recall of visually presented material with a moderate to large effect. There was also a significant improvement seen on overall Doors and People score, a task measuring learning and long-term memory.

Table 4.5

Vitamin D Group paired t -tests comparing pre- to post-intervention cognitive performance showing means, standard deviations, t-statistics, p values, effect sizes and confidence intervals for IQ and memory measures.

Measure/Function	Time 1 mean (SD)	Time 2 mean (SD)	*t* (19)	*p*	*d*	95% CI LL	95% CI UL
IQ:							
WASI-II Verbal Comp.	106.70 (7.33)	108.75 (7.75)	2.22	.039	0.27	-3.99	-0.11
WASI-II Percept. Reasoning	117.10 (14.18)	122.20 (15.63)	4.75	**<.001**	0.34	-7.35	-2.85
WASI-II FSIQ-4	113.15 (10.41)	116.50 (11.11)	3.96	**.001**	0.31	-5.12	-1.58
Memory:							
WAIS-III Digit Span	10.85 (3.03)	11.75 (3.18)	2.39	.027	0.29	-1.69	-0.11
WMS Verbal Mem. Imm.	11.60 (2.28)	12.95 (2.56)	3.50	**.002**	0.56	-2.16	-0.54
WMS Verbal Mem. Delayed	11.35 (3.13)	13.20 (3.19)	5.07	**<.001**	0.59	-2.61	-1.09
WMS Visual Repro. Imm.	12.40 (2.74)	12.85 (2.16)	0.88	.389	0.18	-1.52	0.62
WMS Visual Repro. Delayed	11.55 (3.65)	14.35 (2.98)	5.43	**<.001**	**0.84**	-3.88	-1.72
WMS Symbol Span	11.75 (3.04)	12.80 (3.05)	2.28	.035	0.34	-2.02	-0.08
Doors & People Overall	13.35 (3.27)	13.80 (2.57)	3.07	**.006**	0.15	-2.44	-0.46

Note: significant *p* values and large effect sizes (Cohen's *d* > .8) in **bold**

Some other significant changes were seen in the Vitamin D group (see Table 4.6): the number sequencing group of the Trail Making task on the DKEFS (moderate effect size), Symbol Search from the WAIS-III (small effect), and social cognition measured by the Movie for the Assessment of Social Cognition (moderate effect) showing significant improvements from T1. There were fewer improvements on cognitive measures in the Vitamin D group, compared with the Multivitamin group. As there were no other changes to intake apart from the inclusion of the vitamin D supplement in this group one explanation for this difference in findings may relate to the effect of this single nutrient and the interactions with other nutrients in the diet compared to the effect of a broad-spectrum supplement.

Table 4.6

Vitamin D group paired t -tests comparing pre- to post-intervention cognitive performance showing means, standard deviations, t-statistics, p values, effect sizes and confidence intervals for executive function, learning, affect, and social cognition

Measure/Function	Time 1 mean (SD)	Time 2 mean (SD)	*t* (19)	*p*	*d*	95% CI LL	95% CI UL
Executive Function:							
DKEFS Trail Making Visual Scanning	12.60 (1.60)	12.00 (1.49)	1.80	.088	0.39	-0.87	0.07
DKEFS Trail Making Number Sequencing	11.40 (2.19)	12.80 (1.64)	3.07	**.006**	0.72	-2.35	-0.45
DKEFS Trail Making Letter Sequencing	12.45 (1.64)	12.75 (1.77)	0.90	.379	0.18	-1.00	0.40
DKEFS Trail Making Number/Letter Switch	12.05 (1.39)	12.40 (1.10)	1.79	.090	0.28	-0.76	0.06
DKEFS Trail Making Motor Speed	11.75 (2.40)	12.45 (0.89)	1.34	.197	0.39	-1.80	0.40
DKEFS Design Fluency Filled	7.55 (1.50)	8.00 (1.92)	1.44	.165	0.26	-1.10	0.20
DKEFS Design Fluency Empty	7.15 (2.08)	7.80 (2.09)	1.72	.103	0.31	-1.44	0.14
DKEFS Design Fluency Switching	10.00 (3.03)	10.65 (3.10)	1.63	.120	0.21	-1.49	0.19
DKEFS Design Fluency Total Correct	8.25 (2.51)	9.05 (2.80)	2.43	.025	0.30	-1.49	-0.11
DKEFS Verbal Fluency Phonemic Fluency	13.10 (2.55)	13.75 (2.61)	1.19	.247	0.25	-1.79	0.49
DKEFS Verbal Fluency Semantic Fluency	14.40 (3.07)	16.45 (3.56)	2.42	.025	0.62	-3.82	-0.28
DKEFS Verbal Fluency Semantic Switching	14.85 (3.18)	14.20 (3.09)	0.92	.370	0.06	-0.83	2.13
DKEFS Tower Total Score	12.50 (2.74)	13.45 (2.24)	1.53	.143	0.38	-2.25	0.35
DKEFS Tower Mean 1st Move Time	11.50 (1.366)	11.90 (1.75)	0.97	.345	0.26	-1.26	0.46
DKEFS Tower Time per Move	11.15 (1.14)	11.60 (1.39)	0.97	.345	0.35	-0.92	0.02
DKEFS Tower Move Accuracy	11.00 (1.30)	10.70 (1.81)	0.69	.500	0.19	-0.61	1.21
WAIS-III Symbol Search Correct	12.75 (3.52)	13.95 (3.14)	3.27	**.004**	0.36	-1.97	-0.43
Learning:							
SRT Explicit Learning	11.05 (4.47)	12.35 (5.27)	0.99	.333	0.26	-4.04	1.44
SRT Implicit Learning	79.52 (38.90)	84.84 (65.61)	0.36	.720	0.10	-36.00	25.35
Affect:							
PANAS Positive Affect	33.60 (7.35)	32.65 (7.81)	0.62	.541	0.13	-2.25	4.15
PANAS Negative Affect	19.50 (6.42)	16.70 (6.52)	1.55	.137	0.43	-0.98	6.58
Social Cognition:							
Reading the Mind in the Eyes	27.95 (2.50)	29.25 (2.83)	2.24	.370	0.48	-2.52	-0.08
Movie for the Assessment of Social Cognition	36.10 (2.86)	38.10 (2.61)	4.11	**.001**	0.72	-3.02	-0.98

Note: significant *p* values and large effect sizes (Cohen's *d* > .8) in **bold**

4.4.3 Vitamin C group

Unlike the improvements seen in the Multivitamin and Vitamin D groups there was no significant improvement seen on any measures of the WASI-II in the Vitamin C group. The Vitamin C group did, however, show the same pattern of improvement as the Multivitamin and Vitamin D groups on the memory tasks; there were significant improvements with large effect sizes on both immediate and delayed recall of verbally presented stories and significant improvements on delayed recall of visually presented stimuli (Visual Reproduction) and on the overall Doors and People score measuring learning and long term memory (Table 4.7).

Table 4.7

Vitamin C group paired t -tests comparing pre- to post-intervention cognitive performance showing means, standard deviations, t-statistics, p values, effect sizes and confidence intervals for IQ and memory measures.

Measure/Function	Time 1 mean (SD)	Time 2 mean (SD)	*t* (19)	*p*	*d*	95% CI LL	95% CI UL
IQ:							
WASI-II Verbal Comp.	109.00 (11.08)	109.50 (9.89)	0.41	.690	0.05	-3.08	2.08
WASI-II Percept. Reasoning	116.45 (12.71)	119.45 (12.50)	2.54	.020	0.24	-5.48	-0.52
WASI-II FSIQ-4	114.15 (11.16)	116.15 (10.32)	2.07	.052	0.19	-4.02	0.20
Memory:							
WAIS-III Digit Span	11.50 (2.21)	11.45 (2.96)	0.21	.905	1.52	-0.82	0.92
WMS Verbal Mem. Imm.	11.75 (2.53)	13.65 (1.84)	3.91	**.001**	**0.88**	-2.92	-0.88
WMS Verbal Mem. Delayed	11.45 (2.61)	14.20 (2.26)	6.82	**<.001**	**1.13**	-3.59	-1.91
WMS Visual Repro. Imm.	12.30 (2.87)	13.50 (2.16)	2.37	.028	0.48	-2.26	-0.14
WMS Visual Repro. Delayed	13.05 (3.25)	15.45 (2.82)	3.29	**.004**	**0.79**	-3.93	-0.87
WMS Symbol Span	12.25 (2.95)	13.75 (2.79)	2.45	.024	0.52	-2.78	-0.22
Doors & People Overall	12.65 (2.35)	14.45 (2.16)	3.89	**.001**	0.80	-2.77	-0.83

Note: significant *p* values and large effect sizes (Cohen's *d* > .8) in **bold**

On measures from the D-KEFS (Table 4.8) the Vitamin C group showed significant improvements on the Design Fluency group with no distractor (Filled Dots) and this was reflected in significantly improved Total Correct score. The Vitamin C group also showed significantly faster speed of move-making (Time Per Move) on the Tower task indicating shorter thinking time between moves at Time 2 compared to Time 1. This increased speed of move making did not translate to improved overall score or move accuracy, indicating greater confidence without improved insight into how to solve the problem on this measure. There was also a significant improvement on the Symbol Search, a visuo-spatial processing speed task, in the Vitamin C group between Time 1 and Time 2. All improvements on executive function tasks showed a moderate effect of supplementation on performance.

Table 4.8

Vitamin C group paired t -tests comparing pre- to post-intervention cognitive performance showing means, standard deviations, t-statistics, p values, effect sizes and confidence intervals for executive function, learning, affect, and social cognition

Measure/Function	Time 1 mean (SD)	Time 2 mean (SD)	*t* (19)	*p*	*d*	95% CI LL	95% CI UL
Executive Function:							
DKEFS Trail Making Visual Scanning	12.45 (1.43)	13.00 (1.49)	1.68	.110	0.38	-1.24	0.14
DKEFS Trail Making Number Sequencing	11.95 (1.54)	12.60 (1.43)	1.53	.142	0.44	-1.54	0.24
DKEFS Trail Making Letter Sequencing	12.60 (1.64)	12.85 (1.60)	0.59	.561	0.15	-1.13	0.63
DKEFS Trail Making Number/Letter Switch	12.45 (1.28)	12.95 (1.23)	2.52	.021	0.40	-0.92	-0.08
DKEFS Trail Making Motor Speed	12.20 (1.20)	12.10 (1.02)	0.42	.681	0.09	-0.40	0.60
DKEFS Design Fluency Filled	7.15 (1.27)	8.05 (1.47)	3.11	**.006**	0.66	-1.50	-0.29
DKEFS Design Fluency Empty	7.40 (1.60)	8.00 (1.41)	1.88	.076	0.40	-1.27	0.07
DKEFS Design Fluency Switching	10.65 (1.50)	11.35 (2.23)	1.52	.144	0.41	-1.66	0.26
DKEFS Design Fluency Total Correct	8.35 (1.39)	9.35 (1.57)	3.16	**.005**	0.67	-1.66	-0.34
DKEFS Verbal Fluency Phonemic Fluency	12.65 (3.47)	13.05 (3.47)	0.86	.402	0.12	-1.38	0.58
DKEFS Verbal Fluency Semantic Fluency	15.25 (2.69)	16.15 (2.80)	1.51	.149	0.33	-2.15	0.35
DKEFS Verbal Fluency Semantic Switching	14.75 (2.99)	15.30 (2.72)	0.81	.428	0.19	-1.97	0.87
DKEFS Tower Total Score	12.75 (2.17)	12.50 (1.85)	0.48	.635	0.12	-0.83	1.33
DKEFS Tower Mean 1st Move Time	11.70 (2.11)	12.35 (1.95)	2.37	.028	0.32	-1.22	-0.08
DKEFS Tower Time per Move	10.90 (1.33)	11.95 (1.39)	4.47	**<.001**	0.77	-1.54	-0.56
DKEFS Tower Move Accuracy	10.40 (1.60)	10.55 (1.47)	0.38	.711	0.10	-0.99	0.69
WAIS-III Symbol Search Correct	13.60 (2.04)	14.95 (2.33)	3.18	**.008**	0.62	-2.30	-0.40
Learning:							
SRT Explicit Learning	9.80 (3.32)	12.80 (5.70)	3.45	**.003**	0.66	-4.82	-1.18
SRT Implicit Learning	89.22 (41.08)	95.09 (44.87)	0.48	.638	0.14	-31.50	19.77
Affect:							
PANAS Positive Affect	35.50 (5.49)	33.40 (6.72)	1.75	.096	0.34	-0.41	4.61
PANAS Negative Affect	17.65 (6.38)	17.80 (6.72)	0.11	.914	0.02	-3.03	2.73
Social Cognition:							
Reading the Mind in the Eyes	27.65 (3.39)	27.75 (3.48)	0.18	.859	0.03	-1.27	1.07
Movie for the Assessment of Social Cognition	36.75 (2.69)	39.05 (2.68)	4.27	**<.001**	**0.86**	-3.43	-1.17

Note: significant *p* values and large effect sizes (Cohen's *d* > .8) in **bold**

Table 4.8 shows improved explicit awareness of the presented pattern on the Serial Reaction Time task in the Vitamin C group, however there was no improvement in implicit awareness unlike the Multivitamin group. The Vitamin C group also showed significantly improved correct interpretation of the emotion state of the characters in the Movie for the Assessment of Social Cognition, with a large effect size.

4.5. Conclusion and Discussion

This study provided normative data on nutrient intake and putative effects on cognitive performance. The finding that the cohort was deficient in the majority of micronutrients (all the minerals plus two fat-soluble vitamins and two B-vitamins) at baseline was unexpected. Prior to commencement of the study it was thought that individual participants may be deficient in a variety of different micronutrients, but that this would not be evident at a group level. The percentage under recommended daily intakes in a large number of micronutrients at the cohort level however raises concern in a sample of the 'healthy' general population eating their usual diet. These findings require attention as it has previously been suggested that micronutrient insufficiency has long-term consequences for general health (Ames 2006, 2010), particularly in terms of inflammatory diseases and cancers. As such these findings emphasise the need for better public awareness of the nutritional content of foods to ensure that individuals meet the daily micronutrient levels essential for good physiological function (Alkerwi et al., 2015; Beattie et al., 2014). Findings also support previous findings of 'hidden hunger' (deficiency in essential micronutrients) in western populations. Hidden hunger has been attributed to increased consumption of nutrient poor and over-processed foods and reduction in micronutrient content in fresh foods due to farming practices (Davis, 2009; Mayer, 1997; Monteiro, 2009; Monteiro et al., 2013). Biesalski (2013) reported that deficiency was most prevalent in folic acid, vitamin D, vitamin E, and iron; we found the same deficiencies in this study in addition to deficiency in pantothenic acid, calcium, magnesium, selenium and zinc.

Supplementation in the Multivitamin group changed the nutritional profile of this group and brought overall micronutrient intake up to RDI levels except for calcium and magnesium levels (9.99% and 4.28% below RDI respectively). The Vitamin D and Vitamin C groups only had selected nutritional improvements, as expected; despite this limited change improvements were seen in some cognitive functions over the time course of the study. This raises the potential that supplementation with single micronutrients may

play a beneficial role in cognition, however further research is required to clarify this further and establish the reliability of these findings. Specifically, what cannot be discounted are the interaction effects of a single micronutrient intervention on uptake and metabolism of other micronutrients, for example vitamin C improving iron absorption.

Administration of test order was randomized between and within participants throughout the study. Following the intervention better performance was seen in all groups on a number of tasks, specifically immediate and delayed verbal memory (Logical Memory), delayed visual recall (Visual Reproduction), overall score on Doors and People (visual and verbal learning and memory), visuomotor processing speed (Symbol Search) and social cognition (Movie for the Assessment of Social Cognition). The vitamin D group alone showed improvement in number sequencing on the Trail Making task, although a similar effect was not seen for letter sequencing. Both the Vitamin D and Multivitamin groups showed improved performance on the Perceptual Reasoning sub-tests of the WASI-II, improvements that were reflected in higher overall IQ score. The Multivitamin and Vitamin C groups showed significant improvements on tasks of motor planning, visual strategy generation and explicit awareness of a pattern, however the Multivitamin group alone showed improvements on visual spatial working memory on the Symbol Span task and implicit awareness of the presented pattern on the SRT task.

Improved cognition in the Vitamin C group was perhaps the most unexpected finding from this research. Research conducted prior to this study (e.g. Arlt et al., 2012) has suggested that this level of vitamin C supplementation would be unlikely to improve cognition. Research investigating the relationship between fruit and vegetable consumption and cognitive decline in aging populations (e.g. Gale et al., 1996) has posited that vitamin C deficiency is a determinant of cognitive decline. More recently research has found a link between plasma ascorbate levels and performance on a range of cognitive tasks with similar findings to our research, with participants with adequate ascorbate plasma levels performing better than individuals that had levels of plasma ascorbate indicative of deficiency (Travica et al., 2019; Travica et al., 2020). Considering previous research and the findings of this study it is therefore reasonable to suggest that in participants with lower levels of fruit and vegetables in their diet (as ascertained from food diary entries) increasing intake of vitamin C via supplementation, even at low levels, may improve cognition. The mechanism for this could potentially be through the role of ascorbate (vitamin C) in underlying cellular processes within the brain (Harrison & May, 2009); further research is needed to investigate vitamin C status and cognition across all ages. Vitamin C is involved in transport of lipids for catabolism (breakdown and energy

release) in the mitochondria (Harrison & May, 2009) improving cellular energy production, along with enhancing iron absorption and metabolism (Lane & Richardson, 2014). Iron is required by oligodendrocytes to maintain myelin integrity (Crichton et al., 2012) and the cohort in this study did not meet RDA amounts of iron from diet alone. It is therefore plausible that increased vitamin C intake from supplementation in the Multivitamin and Vitamin C groups resulted in more efficient uptake and metabolism of iron present in diet. This may have contributed to cognitive improvements via efficient cellular energy production and improved neuronal transmission.

The Vitamin D group showed an unexpected pattern of changes from baseline to follow-up. Most research investigating the role of vitamin D in cognition has been in older adults, as with vitamin C research. Cross-sectional research in older adults (65-99 years) found an association between plasma vitamin D levels and attention, processing speed and executive function (as measured by Trails A and B, matrix reasoning and block design). Supplementation with either a low dose (400 IU) or high dose (4000IU) vitamin D showed improved visual memory (as measured by the Pattern Recognition Memory task) in the high dose group (Buell et al., 2009). In the current study we found little improvement in executive function but improvements in both visual and verbal memory in participants taking vitamin D. A recent intervention study in a large healthy population (442 participants) over four months found no significant difference in performance between adults (40-70 years) receiving vitamin D and those taking a placebo on a verbal recall task, digit symbol coding (a measure of processing speed) or on psychomotor speed (Jorde et al., 2019). Again, the findings from our research differ from these and indicates that further research is required to investigate the effect of vitamin D on cognition.

The Multivitamin group showed the greatest number of cognitive task improvements of the three groups, with improvements seen in the same measures as the other groups in addition to improvements seen in working memory and implicit learning. Previous research has demonstrated that poor micronutrient intake can have a negative effect on cognition in throughout development and in older age (Ames, 2006; Nyaradi et al., 2013; Spencer et al., 2017). The evidence from this study suggests that the negative effect of micronutrient insufficiency on cognition may extend across the lifespan, however larger scale research is required to investigate this. Cognitive improvements seen in those taking supplements may indicate a move towards optimal levels of function in these participants from a previously ‘dulled’ level of performance. The long-term effects of micronutrient insufficiency or deficiency through the lifespan on later cognitive function is not yet known. Further longitudinal research is required in this area to

investigate this further. One potential weakness in this study is the lack of physiological measures of micronutrient status. The rationale for not including physiological markers is that physiological markers are invasive and introduce several different variables that must be controlled for including time of blood draw, time of gustation, wet lab time, and establishing the most reliable physiological markers. In addition, the prospect of a number of blood draws may have dissuaded people from participating in the research.

The cognitive functions measured in this study are also those most affected following a traumatic brain injury (Ponsford et al., 2012); executive function deficits would not be expected in a normative sample but are typically a key deficit following traumatic brain injury. As such it is important to investigate whether supplementation could improve these cognitive functions (e.g. inhibition, set shifting, strategy generation) following head injury.

This study has demonstrated that a relatively short period of supplementation can improve the cognitive profile of individuals, particularly in those taking a broad-spectrum multivitamin and mineral supplement. This study in another form is published (Denniss et al., 2019). Based on these findings the same intervention period for supplementation can be employed in a TBI sample with a similar cognitive test battery, taking into consideration limitations of this group (for example fatigue). The methodology for research conducted in a traumatically brain injured population will be presented in the following chapter.

Chapter Five: Traumatic Brain Injury Study Methodology and Procedure

5.1. Introduction

Data from the normative study (presented in Chapters Three and Four) demonstrated that a subset of the general population had diets insufficient in a number of micronutrients. Supplementation of this cohort over an eight-week period resulted in cognitive improvements. This evidence provides 'proof of concept' to undertake research in a traumatically brain injured population. In addition to the evidence from the normative study previous research has highlighted undernutrition in some individuals hospitalized following traumatic brain injuries (Chapple, 2016; Pelizzo et al., 2017) as a result of fasting for surgeries, problems with feeding and swallowing, or poor tolerance for foods. After discharge dysexecutive syndrome is a contributing factor in dietary changes post-TBI (Crenn et al., 2014) as individuals with executive deficits have difficulty shopping, planning meals and preparing food (Godbout et al., 2005). This leads to potentially choosing 'convenience' food options with poor micronutrient content (Duraski et al., 2014; Wahls et al., 2014), particularly a problem for those living alone. These factors, in combination with metabolic changes post-TBI, suggest that micronutrient intake in a brain-injured group may be worse than in the general population. This study investigated the potential for micronutrient supplementation in supporting cellular metabolism and neuronal repair mechanisms after brain injury, measured through test-retest on a cognitive battery.

5.2. Participants

Clinical participants (n = 30) were recruited from a range of socio-economic and educational backgrounds ($\bar{x}$ = 41.83 years, SD = 16.03, range 19 – 70 years; male 70%). The bias towards male participants in this study reflects the difference in incidence in the wider population (Ma et al., 2019; Munivenkatappa et al., 2016). Time since injury was a mean of 12.7 months (SD = 7.10; range 3-27 months) and 86% of participants were living with family members and as such received support with the preparation of food. Two participants withdrew from the study prior to first follow-up and were not included in further analyses. Collaborating clinicians identified potential participants from patients attending outpatient neurological or neurorehabilitation services at participating trusts

(Sheffield Health and Social Care NHS Foundation Trust, Sheffield Teaching Hospitals NHS Foundation Trust, Rotherham, Doncaster and South Humber NHS Foundation Trust, and North Derbyshire Health and Social Care NHS Foundation Trust). Individuals expressing an interest were then contacted and sent the Participant Information document to allow them to make an informed decision on whether to take part. An additional two participants were recruited into the study following self-referral after finding the research on clinicaltrials.gov (NCT03032302) (see Appendix C1 for Consort diagram and Chapter 6 for participant demography).

Inclusion criteria were that participants had sustained their first and only traumatic brain injury 3 to 24 months prior to enrolment into the study, resulting in mild to moderate cognitive deficits. One participant exceeded the time since injury criteria (27 months post-injury) due to an error in documentation. This individual remained in the study as they met all other criteria. By three months post-injury the majority of mild-moderate TBI patients medical needs have stabilised and are no longer subject to frequent change. There is debate about the length of time post-TBI where the greatest opportunity for cognitive improvement occurs, with previous research varying between eight months and two years (Brooks, 1986; León Carrión & Machuca Murga, 2001; Machuca Murga et al, 2006), the more inclusive criteria being adopted for the purposes of this research.

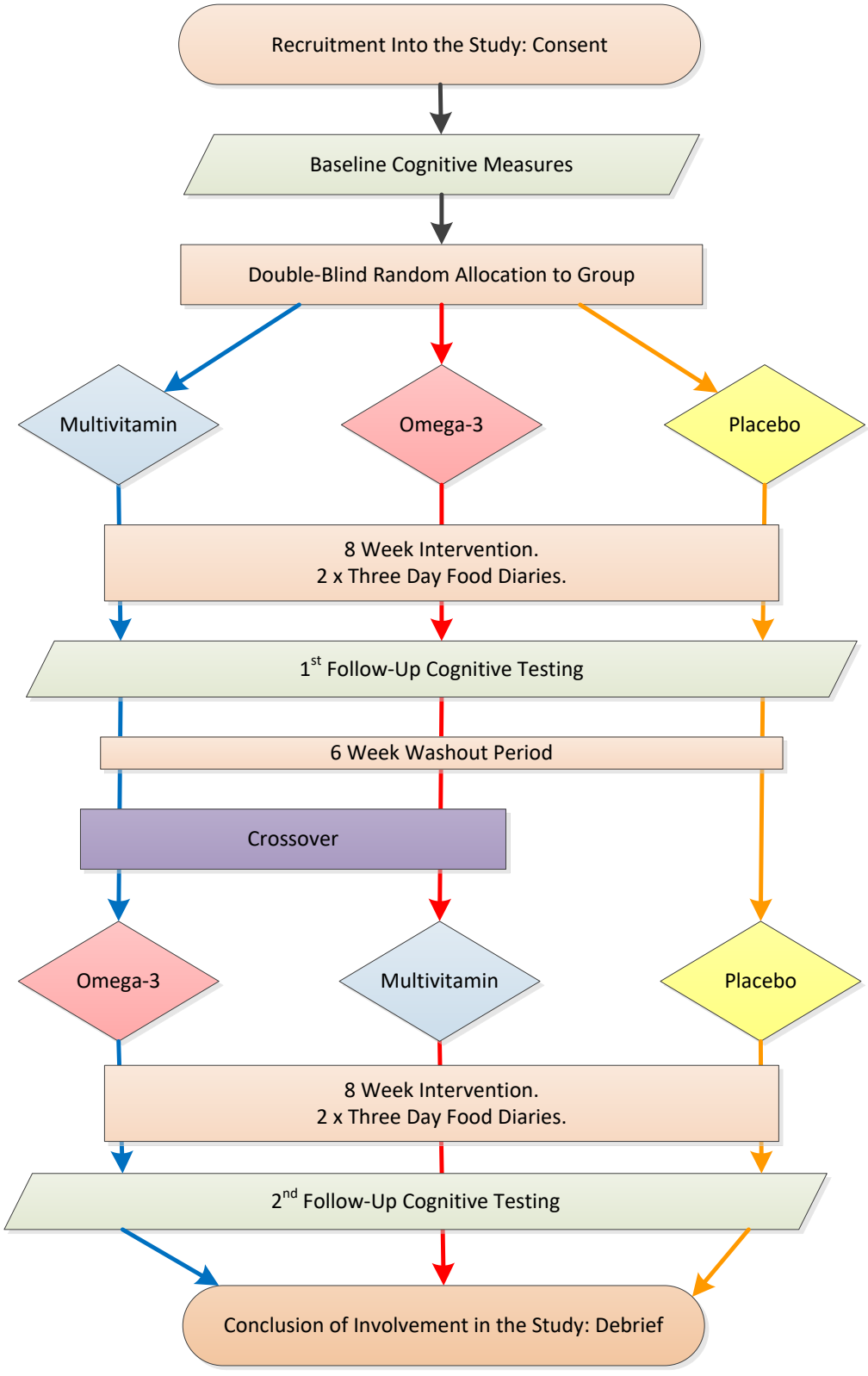
Participants were excluded if they had hemianopia or were hemiplegic and if their first language was not English due to the requirements of the cognitive test battery. Individuals were also excluded if they had a drug or alcohol problem, as measured by the SMAST (Short Michigan Alcohol Screening Test; Selzer et al., 1975) and DAST (Drug Abuse Screening Test; Skinner, 1982) as long-term drug or alcohol dependency is linked with changes in cognition (Bernardin et al., 2014; Broyd et al., 2016; Lucantonio et al., 2012). Collaborating trusts did not refer individuals with known drug or alcohol problems and no individuals were excluded when screened by the researcher. Those with a diagnosis of type 1 diabetes were excluded as metabolism of micronutrients is altered in this condition (Kaur & Henry, 2014). One individual was excluded from participation on screening. Women who were pregnant or breastfeeding were excluded due to increased requirement of certain micronutrients (e.g. folic acid, vitamin D) and potentially teratogenic effects of others within these populations (e.g. vitamin A) (El Shamy & Tamizian, 2018) in line with NHS ethical committee advice. One individual was excluded from participation as they were both breastfeeding and taking supplements. Participants were excluded if they were currently taking multivitamin/mineral or omega-3 supplements as additional supplementation would put participants at risk of toxicity of

some micronutrients. Four individuals were excluded based on this criterion. All participants had normal or corrected to normal vision with no reported auditory deficits.

A flow diagram of the study design including wash-out period and crossover is presented in Figure 5.1.

Figure 5.1

Clinical participant study design



5.3. Design

The study was conducted using a double-blind crossover study design with a parallel placebo group. Participants were randomly allocated to one of the three interventions for the first 8-week intervention period; within the crossover arm of the study participants received either the multivitamin/mineral supplement or the omega-3 polyunsaturated fatty acid supplement first, taking the other supplement for another 8-weeks after a six week wash-out. Participants allocated to the placebo intervention, running in parallel, took the placebo in both the first and second intervention periods. An eight-week intervention was again used following the findings of the normative study demonstrating that this length of time was sufficient to show significant changes to some cognitive functions and in line with previous research (Kean et al., 2015; Small et al., 2014). A six-week washout period where participants did not take any intervention was used to prevent carryover effects from one intervention to the other based on recommendations from other research (Drouault-Holowaczi et al., 2009; Fernández-Castillejo et al., 2016; Torbergsen & Collins, 2000; Wong et al., 2018). Participants taking the placebo also had this wash-out period to maintain the double-blind.

A crossover design was selected as this provides greater statistical power than the equivalent parallel design; it has been reported that a parallel design requires between 4 and 10 times the number of participants than the corresponding cross-over design (Garcia et al., 2004). This is because a crossover design allows the random variance to be split, therefore the sample size is a function of the within participant variance in a crossover design rather than a function of the overall variance in a parallel design. Previous literature suggesting that a sample size of between 10 and 12 is sufficient for a pilot study (Julious, 2005). The use of a cross-over design is of additional advantage in this study; participants with a traumatic brain injury are naturally heterogeneous in terms of injury severity, specific location of injury, and time since injury. In a cross-over design participants act as their own control, making participant matching unnecessary.

5.4. Materials

5.4.1 Supplements

See Appendix C2 for full details of composition of all interventions.

5.4.1.1 Multivitamin.

As reviewed in Chapter Two micronutrients have direct actions on diverse aspects of normal adult neuronal functioning (e.g Harms et al., 2011; Bourre, 2006a; Choi and Koh, 1998; Jahanshad et al., 2013) and conversely metabolic changes following traumatic

brain injury have an adverse effect on micronutrient levels in the body (Henry et al., 2011; McClain et al., 1986; Polidori et al., 2001; Sen & Gulati, 2010; Siniscalchi et al., 2016; Wu et al., 2013). In addition, the results of the normative study (Chapter Four) indicated that the multivitamin/mineral formulation had the strongest effect on cognition following an eight-week supplementation period and micronutrient intake levels were lower than RDI for many vitamins and minerals in the general population (Denniss et al., 2019). This combined evidence led to the selection of a supplement containing levels of micronutrients greater than the RDI; Swisse Women's 50+ Ultivite fit this profile.

5.4.1.2.Omega-3.

As this study involved those with traumatic brain injuries an omega-3 (EPA and DHA) supplement was introduced as the alternate to the multi-micronutrient. This was based on evidence that EPA and DHA act as precursors to anti-inflammatory mediators that stimulate the resolution phase of the inflammatory response (Serhan et al., 2008; Weylandt et al., 2012), normalise mitochondrial function and reduce oxidative stress (Wu et al., 2014) following traumatic brain injury. To aid with compliance in the head injured population a one-a-day omega-3 fish oil capsule with high levels of available EPA and DHA was selected (Piping Rock Triple Strength Omega-3 Fish Oil).

5.4.1.3 Placebo (sucrose).

The inclusion of a placebo group acted as an overall control and meant that spontaneous recovery post-injury could be accounted for. An extensive search was conducted to find matched placebos for the active supplements; however, the costs were prohibitive and therefore sucrose capsules were sourced. Participants in the placebo group would not see either of the active supplements during this study and therefore would have no awareness of the dissimilar appearance of the placebo in relation to the active supplements. Following completion of the study participants taking the placebo were offered the supplements to ensure parity of treatment.

Intervention packs were prepared for participants prior to recruitment. Assembling of interventions into blister packs was undertaken by the lead researcher. Blister packs were used to assist participants with compliance; each transparent blister contained one tablet or capsule with the days of the week labelled down the side of the cardboard backing, each board containing four weeks' intervention. Enough tablets for 10 weeks were then placed in a plain brown envelope; the inclusion of extra tablets ensuring that participants would have enough of the intervention to cover for unforeseen circumstances. Once all envelopes were prepared random allocation of participants to

interventions was then independently undertaken by a member of the supervisory team. This was conducted using a random number generator (random.org) using the same procedure as that used for the normative study to ensure the study met double-blind conventions and to reduce bias (Schultz & Grimes, 2002). A record of allocations was retained by the supervisor on their personal computer. To finish preparation the supervisor sealed all envelopes and labelled them for each participant (e.g. 'Participant 1, Pack 1; Participant 1, Pack 2) ensuring that all participants received the correct intervention at each time point. To assess compliance participants were asked to keep the intervention boards within the envelope and return them at the end of follow-up sessions for each intervention period. Returned envelopes were then placed in a secure cupboard and compliance was assessed by counting remaining tablets after each participant completed their involvement in the study.

5.4.2 Food Diary

As in the normative study participants were asked to complete food diaries during their involvement in the study. In this study participants were asked to complete two 3-day food diaries for each of the eight-week intervention periods; one period across a weekend (Friday, Saturday, Sunday), one during the week (Tuesday, Wednesday, Thursday) to give an overview of dietary intake. One diary was completed around week 3 of the intervention period, the other around week 6. Participants were asked if it was a convenient time to complete the diary. If participants expressed that the requested period would not be reflective of normal intake (illness or a special occasion) then another period was selected. All participants adhered to the food diary protocol completing diaries on all requested days. The shorter lengths of the food diaries (2 x 3 days) utilised in this study compared to the normative study (14 days) were still able to give a good overview of micronutrient intake without being too onerous, 3-day food diaries considered sufficient to give a good summary of dietary intake (Yang et al., 2010). Participants were contacted via their preferred method the day prior to commencement of the food diary to ask them to complete the food diary for the following three days. Participants were then given daily reminders to complete their record for that day. This reminder was given around midday so that if participants had forgotten to fill in their food diary for that morning it was close enough to that time of day for recall.

5.4.3 Test Measures

The test battery was formulated to assess cognitive domains previously demonstrated to be affected by micronutrient supplementation and also related to functional deficits seen in individuals following traumatic brain injury (TBI), based on

findings from the normative study. The same cognitive domains as studied in the normative group were assessed, however some changes were made to the tests used. The Logical Memory sub-tests from the WMS-IV was exchanged for the Verbal Paired Associates as the learning phase of the Verbal Paired Associates would support retention. Similarly, the Visual Reproduction sub-tests of the WMS-IV were exchanged for the Rey-Osterreith Complex Figure test; the 'Copy' element of the task supported retention and provided evidence for any visual or motor deficits that may affect performance. The Design Fluency and Tower tasks from the D-KEFS were not included in this battery as these were tasks many participants in the normative study found very challenging and may have caused high levels of frustration in the TBI participants. The Movie for the Assessment of Social Cognition was also not included in the test battery due to the length of administration of this measure as a primary consideration in compiling the battery was post-TBI fatigue, a common and debilitating condition in this population (Lequerica et al., 2017). The battery for this study was therefore smaller compared to the battery used in the normative group. In addition, participants were able to take self-determined rest breaks when needed and had the option to decline to complete a measure if it proved to be problematic (for example with relation to visual problems).

5.4.3.1 Screening measures.

There is evidence that drug or alcohol use is a contributing factor in sustaining traumatic brain injuries in some individuals, either following a history of misuse or associated with presence at a social occasion. In addition, it has been shown that alcohol and drug misuse have a negative effect on many aspects of cognition including memory, processing speed, and executive function (Bechara & Martin, 2002; Bernardin et al., 2014; Maurage et al., 2014), potentially acting as a confound on results. As a result of this evidence participants for the clinical study were screened using the Short Michigan Alcohol Screening Test (SMAST; Selzer et al., 1975) and Drug Abuse Screening Test (DAST-10; Skinner,1982). Those who scored more than a moderate score (see full description of measures) were excluded from the study.

Short Michigan Alcohol Screening Test (SMAST; Selzer et al., 1975).

The SMAST is a short (13 question) self-report questionnaire designed to assess common signs and symptoms of alcohol abuse. Each question required a 'yes' or 'no' answer and included items related to attitudes of others to the individual's drinking habits (e.g 'Does your wife, husband, a parent, or other near relative ever worry or complain about your drinking?'), self-perception of levels of alcohol consumption (e.g. 'Do you ever feel guilty about your drinking?'), and consequences of drinking behaviours

(hospital admittance, police involvement, e.g. 'Have you ever been in a hospital because of drinking?). Internal consistency reliability is estimated from meta-analysis to be between $r = .78$ and $r = .84$ (Shields et al., 2007), with little difference between the longer and short forms. Individuals obtaining scores ≥3 were excluded from participating in the research (Bombardier et al., 2002). No participants were excluded based on this criterion.

Drug Abuse Screening Test-10 (DAST-10; Skinner, 1982).

The DAST was used as a brief self-report measure (10 items) to assess drug use in potential participants. As with the SMAST, each question required a 'yes' or 'no' response and included items covering the same aspects of drug taking behaviours. Example items include 'Have you had "blackouts" or "flashbacks" as a result of drug use?', 'Does your spouse (or parents) ever complain about your involvement with drugs?' and 'Have you had medical problems as a result of your drug use (e.g., memory loss, hepatitis, convulsions, bleeding, etc.)?'. Test-retest reliability of the DAST-10 has been found to be $r = .71$ with internal consistency between r = .86 and $r = .94$ and concurrent validity with the long form (DAST-28) $r = .97$ (Cocco & Carey, 1998). Individuals who scored ≥3 were excluded from participating in the research (McCauley et al., 2013). No participants were excluded based on this criterion.

5.4.3.2 Demographic Measures.

Wechsler Abbreviated Scale Intelligence-II (WASI-II; Wechsler, 2011).

At baseline the four sub-tests of the WASI-II was administered to gain a measure of current IQ (see Chapter 3 for full details of the measure) as part of demographic information collected from participants.

Test of Pre-Morbid Functioning (TOPF; Wechsler, 2011).

The TOPF was used to estimate intellectual ability prior to the traumatic brain injury in participants. This is a brief (approximately 10 minutes) reading test composed of seventy words with irregular and low frequency grapheme to phoneme translations that was only administered at baseline. Participants were presented with a list of 70 words and were asked to simply read them out loud, a score of 1 given for each correctly pronounced word. Using a reading test as an estimate of pre-morbid function is predicated on the theory that reading vocabulary is an effective predictor of intellectual functioning. This is less susceptible to brain injury or neurodegenerative decline, compared to other measures of cognition (Yuspeh et al., 2010).

Internal consistency for this measure, as measured by Cronbach's alpha, is $r = 0.95$ and test-retest stability ranges from $r = .89$ to $r = .95$ across all age groups.

5.4.3.3 Affect Measure.

Positive and Negative Affect Schedule (PANAS; Watson et al., 1988).

Individuals who sustain traumatic brain injuries have high incidence of anxiety and depression (Bombardier et al., 2016), therefore measurement of mood state was of interest in this study and the PANAS was used in the same form as in the normative study. Participants were asked to complete the PANAS at the start of each set of test sessions to ensure that emotion related to task completion did not affect responses.

Reliability (internal consistency) of the PANAS two scales (PA and NA) is good; r = .89 for the PA scale and r = .85 for the NA scale (Crawford & Henry, 2004).

5.4.3.4 Processing Speed.

Symbol Search - WAIS-IV (Wechsler et al., 2008).

The Symbol Search task provided a measure of visuospatial information processing speed under timed conditions (Lezak et al., 2012). The task consisted of sixty stimuli displayed as lists of two abstract figures on the left side of a page and five abstract figures on the right. The WAIS-IV version of the Symbol Search was substituted for the WAIS-III version for the clinical study, as it is co-normed with the WMS-IV (Holdnack et al., 2011). Participants were asked to identify if either of the two target figures on the left were repeated in the five figures on the right of the page by either striking through the matching target figure or striking through the 'no' box, if they didn't see a match. This is an improvement on the WAIS-III version of the task as it required participants to identify the matching figure, rather than simply checking a box to say there was a match, allowing for the detection of errors in identification of the repeated figure. In addition, the WAIS-IV version of the task increased the size of the figures, improving visual discrimination. Participants were given two minutes to complete as many items as possible; a score of 1 was given for each correct response. Processing speed impairments are one of the core deficits seen following traumatic brain injury, even in those with mild-moderate injuries (Kashluba et al., 2008). Reliability coefficients for Symbol Search are good and range from r = .73 to r = .86, with test-retest stability of r = .81 across the age range 16 to 90 years (Wechsler et al., 2008).

5.4.3.5 Memory.

A range of memory deficits may affect individuals following TBI including episodic memory (Wammes et al., 2017), verbal memory (Vanderploeg et al., 2014), visual memory (Carlozzi et al., 2013), and working memory problems (Sánchez-Carrión et al., 2008). Findings that micronutrient supplementation can have a positive effect on memory decline in dementing populations (e.g. Mi et al., 2013) confirms the potential for

memory improvements following supplementation, which may be beneficial in individuals following TBI. The current study assessed performance on different memory tests (see below) following supplementation.

Digit Span –WAIS-IV (Wechsler et al., 2008).

The WAIS-IV version of the Digit Span was administered in this patient study. In addition to the forwards and backwards span conditions in the WAIS-III used in the normative study, the WAIS-IV version of the task incorporated a Digit Span Sequencing task requiring participants recall of digits in ascending order after listening to them presented in random order. This version of the task therefore gave an additional measure of working memory, with the cognitive demand of the Backwards and Sequencing tasks higher than the Forwards condition (Coalson et al., 2010; Young et al., 2012). Working memory tasks involve recruitment of executive control to focus attention and limit interference (Conway et al., 2003). In total, the Digit Span task took approximately ten minutes to complete, depending on individual differences. Reliability coefficients for Digit Span are good and range from $r = .89$ to $r = .94$, with test-retest stability of $r = .83$ across the age range 16 to 90 years.

'Doors' from Doors and People (Baddeley, Emslie, & Nimmo-Smith, 1994).

Individuals with traumatic brain injuries have been shown to be impaired on tasks of visual recognition (MacPherson et al., 2008; 2016), with performance below that of controls up to ten years post injury (Draper & Ponsford, 2008). The Doors task from the Doors and People measure was therefore administered in the clinical study as a measure of visual recognition memory in the same way as in the normative study.

Rey-Osterrieth Complex Figure Test (Rey, 1941; Osterrieth, 1944).

Primarily a measure of visual reproduction memory (immediate and delayed) the RCFT also assesses visuo-spatial skills and episodic memory (Neselius et al., 2013) along with planning, organisation, and problem-solving (Schwarz et al., 2009), indicating that it has an executive component which may be impaired in individuals following TBI. During the task participants are shown a two-dimensional complex figure for two minutes and are asked to copy the figure. The inclusion of an initial 'copy' condition after the two-minute observation provides a baseline score for identification of any visual perception or motor deficits that may impact task performance unrelated to memory impairment. Participants are then asked to reproduce the same figure from memory in two conditions: immediately (after three minutes) and after a delay (thirty minutes). Scoring is based on the correct reproduction of 18 features; a score of 2 was given for features placed properly, 1 for features placed poorly or those that were distorted, incomplete but

recognizable, and 0.5 for features distorted, incomplete but recognizable placed poorly. This gave a score out of 36 for each of the three conditions.

Test-retest reliability for the measure is excellent (r = .98; Loring et al., 1990).

Verbal Paired Associates (VPA) I, II, and Recognition Task (WMS-IV) (Wechsler, 2009).

Word list learning tasks measure auditory learning (immediate and delayed) with less emphasis on associative context, compared with prose learning tasks (Lezak et al., 2012). The VPA provides a measure of immediate (VPA I) and delayed (VPA II) verbal memory, shown to be impaired in TBI patients (Ariza et al., 2006; Jacobs & Donders, 2008) with deficits seen in encoding, consolidation and retrieval (Vanderploeg et al., 2014). In the learning phase fourteen pairs of words are presented, ten of which are deemed 'difficult'. After attending to the full list participants are given one word of the pair and asked to provide the counterpart from the original list. Four presentations of the same list (in differing order) are given to facilitate learning. This learning phase takes between ten and fifteen minutes. Following a 30-minute delay, participants are again asked for the second word in the pair to establish whether word-pair learning was retained. Finally, participants are read 40 word-pairs and asked to state if each pair was one previously presented (recognition task).

Reliability coefficients of the Verbal Paired Associates tasks in a traumatically brain injured population are very good; r = .95 for VPA I and r = .92 for VPA II (Wechsler et al., 2009).

5.4.3.6 Executive Function.

Higher order thinking can be impaired following traumatic brain injury (Caeyenberghs et al., 2014; Draper & Ponsford, 2008; Edwards & Wood, 2016; Hartikainen et al., 2010) so executive function tasks were included in the test battery as below.

Trail Making Test (Delis-Kaplan Executive Function System (Delis et al., 2001).

This task was administered in the same way as in the normative study (see Chapter 3 for details). Depending on individual differences in severity of cognitive deficit this task took between five and ten minutes.

Verbal Fluency (Delis-Kaplan Executive Function System (Delis et al., 2001).

With the patient group the same procedure as in the normative group was followed, using alternate forms (two versions) across the three test periods. As this is a time-constrained task it took the same length of time (approximately 10 minutes) as in the normative group.

Colour-Word Interference Test (CWIT; Delis et al., 2001).

Based on the procedure described by Stroop (1935) the CWIT is a task of verbal response inhibition, attention and cognitive flexibility, composed of four timed conditions. The first two conditions, a basic colour naming task (condition 1) and a word reading task (condition 2) provides measures of performance on the key components of the more complex later tasks. Condition 3 follows the original Stroop procedure in which participants are required to inhibit the competing automatic response (reading the word) to give the correct response (giving the colour ink the word is written in). The CWIT includes a further condition requiring participants to switch between giving the same response to that required in the previous condition (naming the colour ink the word is written in) unless the word is presented in a box. If the word is in a box then the participant is required to simply read the word, creating a switching-inhibition condition. In total, the task takes approximately fifteen minutes to administer. For all conditions, there is a practice element; if participants are unable to complete the practice element, or require four or more corrections, the condition is discontinued. If participants are unable to complete the practice element of condition 3 then condition 4 is also not administered. The CWIT is shown to be sensitive to TBI (Skandsen et al., 2010), meta-analyses of studies with TBI patients showing slower response times when compared to controls as a result of impaired inhibitory control (Dimoska-Di Marco et al., 2011). This task took between six and twelve minutes to complete, dependent on participant deficits.

Test-retest reliability of the task ranges between r = .62 to r = .76 with internal consistency moderate to high across all conditions (r = .75 to r = .86).

5.4.3.7 Implicit and Explicit Learning.

Serial Reaction Time Task (SRT; Seger 1997).

Individuals with traumatic brain injuries have been shown to be impaired on serial reaction time measures of implicit learning (e.g. Barker et al., 2006; Morton & Barker, 2010), therefore the same serial reaction time task (Barker, 2012; Seger, 1997) used in the normative group was administered to the clinical sample using the same procedure (see Chapter 3). It is thought these tacit functions contribute to explicit learning memory and attention by guiding attention without recourse to conscious attentional processes

5.4.3.8 Activities of Daily Living.

Nottingham Extended Activities of Daily Living (Nouri & Lincoln, 1987).

This is a brief self-report questionnaire (approximately ten minutes) that assesses level of day-to-day functioning across four subcategories; mobility, domestic, kitchen and leisure. Participants are asked to indicate which activities they have done over the

previous few weeks; either not at all, with help, on their own with difficulty, or on their own. Activities include crossing roads (mobility), taking hot drinks from one room to another (kitchen), completing their own shopping (domestic) and going out socially (leisure). This measure was originally designed for individuals following stroke but has been used with other neurological groups including TBI (Bovend'Eerdt et al., 2010).

Kappa coefficients measuring the test-retest agreement of the questionnaire with a two-week interval showed good to excellent agreement (κ = .62 to κ = 1.00) for all questions except for two of the 'domestic' questions related to washing small items of clothing and doing housework (κ = .29 - κ = .53). The authors suggested this discrepancy may be due to confusion about the question or another person (for example a spouse) completing the measure on one occasion (Nouri & Lincoln, 1987) as questionnaires were completed by post. As the NEADL was completed in the presence of the researcher for this study there was consistency in presentation and instruction between participants.

5.5. Procedure

Participants were randomly allocated to one of three groups (see Figure 5.1); two groups took both the multivitamin supplement and omega-3 fish oil supplement for separate time periods in a crossover study design. Either multivitamin first or omega-3 first. The third group, placebo, ran in parallel to the active crossover groups. Cognitive test measures were administered at three time points (baseline, first follow-up after 8 weeks and second follow-up after 22 weeks). Participants completed two short (three day) food diaries during each supplementation period to assess dietary micronutrient intake. Supplement blister packs were prepared by the researcher and then randomised by a member of the supervisory team (who also kept the record of allocation) resulting in double blind supplement assignment. The two supplements were different in appearance; however, participants were naive to the appearance of the tablets having been simply informed in the participant information that different formulations were being investigated. All participant materials can be found in Appendix C.3.

Participants were consulted regarding the method of contact (email, text, voice call) for reminders about taking tablets and completing food diaries. Most participants wished to be contacted via text message with some requesting daily reminders. Some participants already had strategies in place to remind themselves to complete tasks (for example mobile phone or smart watch notifications) and utilised these to adhere to the tablet-taking regime. All participants in the study received daily reminders to complete food diaries (when requested to fill them in) and were contacted twice each week to

ensure they were adhering to the tablet regime and were not experiencing any problems. Most participants completed both sets of food diaries successfully; one participant failed to provide either food diary (they had completed the diaries on a computer and failed to send through the files despite numerous reminders over a twelve month period), another participant misplaced the food diary for the second supplementation period when moving house.

5.5.1 Addendum procedure following Covid-19 pandemic outbreak

To ensure safety of researchers and participants all face to face research was halted on the 17th March 2020 due to the outbreak of the COVID-19 virus. At this time there were two participants still to complete the second follow-up sessions of the study. After careful consideration and communications with these two participants it was decided that most of the test battery could be administered via videoconferencing if some task booklets were posted to participants. The test measures that could not be administered in this way were the Doors and People, Reading the Mind in the Eyes (both required a large number of visual stimuli) and the Serial Reaction Time Task (required specific software). A meta-analysis of test performance task carried out via videoconferencing found a strong correlation between scores on measures conducted via videoconferencing and on-site, particularly for tasks with a verbal component (Brearly et al., 2017).

An addendum to the participant information and a consent form detailing these procedural changes was drawn up and received ethical approval by Sheffield Hallam University. All documents and materials were posted to participants with a stamped addressed envelope to enable responses to be returned without incurring costs to themselves. During test sessions participants were given the same instructions to complete tasks as in previous face to face sessions with the addition of instructions to photograph and email response booklets following completion to account for potential loss in the postal system.

5.6 Hypotheses

Based on previous research findings and findings from the normative study it was hypothesised that an improvement in performance would be seen following the multivitamin/mineral intervention. It was also hypothesised that there would be an improvement in performance following the omega-3 intervention. As these two interventions have not been directly compared in previous research there were no hypotheses formulated with regard to which of these two interventions would result in

the greatest improvement in performance nor whether improvements seen would be in the same or different cognitive domains. No overall improvement in performance was expected in the placebo group, except for the possibility of natural recovery from brain trauma. It was anticipated that the profile of micronutrient intake would be altered by the interventions, with those taking the multivitamin/mineral intervention having significantly greater intake levels of all micronutrients, compared with those not taking this intervention. It was also anticipated the those taking the omega-3 intervention would have significantly greater levels of omega-3 than participants not taking those intervention.

5.7. Ethics

This study was conducted at the Psychology Department, Sheffield Hallam University, according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects approved by the Sheffield Hallam University Faculty of Development and Society Research Ethics Committee (333DEN) and the NHS North-East and Yorkshire Research Ethics Committee (17/YH/0146). The study was also registered at ClinicalTrials.gov (NCT03032302). Written informed consent was obtained from all participants and storage of personal information adhered to GDPR guidelines.

The following chapter will describe demographic participant information (age, gender, time since injury). There will also be detail of how participants head injuries were sustained including information on both brain trauma and other physical injuries.

Chapter Six: Demography of Participants

This chapter gives details of participants' trauma history along with cognitive difficulties experienced. Other details provided by participants regarding their recovery trajectory is also included. See Appendix D for demographic analyses outputs.

6.1 Demographic Information

Table 6.1

Means and standard deviations of age, time since injury and IQ measures of the whole cohort

Measure	Minimum	Maximum	Mean (SD)
Age on Recruitment (years)	19	70	41.83 (16.03)
Time Since Injury (months)	3	27	12.7 (7.10)
Test of Premorbid Intelligence	87	121	104.31 (9.41)
Wechsler Abbreviated Scale of Intelligence	76	116	101.37 (11.46)

Footnote: Both IQ scores ranged between borderline to high average.

Table 4.2

Demographic measures - frequency and percentages

Factor	Level	Frequency	Percentage
Gender	Male	21	70
	Female	9	30
Living Arrangement	Alone	4	13.3
	With Family	26	86.7
Level of Education	GCSE or Equivalent	2	6.7
	A-Level or Equivalent Training	15	50.0
	Undergraduate Degree or Equivalent	11	36.6
	Masters degree	1	3.3
	PhD	1	3.3
Cause of Injury	Trip or Fall	12	40
	Occupant in Motor Vehicle	6	20
	Hit by Motor Vehicle	4	13.3
	Cycling Accident	3	10
	Accident at Work	2	6.7
	Horse Riding Accident	1	3.3
	Assault	1	3.3
	Sporting Injury	1	3.3

6.2. Participant Details

Participant 1

DW was 70 when recruited into the study 12 months post-injury. DW was found unconscious on the pavement; medical professionals assumed that DW had slipped on ice when walking and had banged his head, resulting in loss of consciousness, although no detail of site of injury or neuropathology were available to the clinician who referred DW to the study. Following injury DW was hospitalised for one month and was then referred to a neurorehabilitation unit where he stayed for another month before discharge. DW had no recollection of his time in hospital, only gaining conscious awareness of time and place when admitted to the rehabilitation ward. This length of anterograde post-traumatic amnesia is suggestive of a moderate TBI (Malec et al., 2007). Following injury DW had problems with prospective memory (remembering what he had to do) and activities of daily living, however at time of involvement in the study DW lived fully independently. DW expressed that he was now able to go about his daily activities as normal, with a sister-in-law helping with cleaning the house. DW was chatty and engaged with tasks and spoke often about his wife who died six months prior to his head injury and was clearly trying to adjust to the life changes resulting from both events.

Participant 2

JC was 24 when recruited into the study five months post-injury. JC sustained a head injury on holiday in Amsterdam, tripping on a pavement and hitting his head on two separate metal bins. JC reported no loss of consciousness (LOC) or post-traumatic amnesia (PTA), which was confirmed by his girlfriend who was with him at the time, indicative of a mild TBI. JC reports that he did have a CT scan in Amsterdam; however, this was not made available to medical staff in the UK. On his return to the UK JC suffered recurrent severe post-traumatic headaches, the severity of the pain waking him from sleep. Repeated visits to the GP (atypical for this individual) were followed by referral for a CT scan that showed no evidence of contusions or lacerations. JC however continued to experience severe fatigue and cognitive problems at his workplace particularly concentration and problems with noise levels. JC was finally referred to neurorehabilitation services who recommended a reduction in work hours. Over the period of his involvement in the study JC slowly increased his hours at work and at the time of study completion had just returned to full-time working hours. JC did have ‘bad times’ at work where he became overwhelmed and had periods where he had to take a

few days off work. JC stated that these 'bad times' were becoming less frequent and was confident that he would be able to maintain his full-time hours.

Participant 3

JG was 22 when recruited into the study three months post-injury, sustaining a head injury following a trip and fall at home. JG did not go to the hospital at the time of injury but woke the following day to numbness in half of his face. JG visited his GP who noted that JG's pupils were unequal and not reactive to light and referred JG to hospital. As JG self-referred themselves to the study further medical information was not provided, however the lack of loss of consciousness is indicative of a mild head injury. On recruitment into the study (three months post-injury). JG expressed that he was having problems with coping with university work specifically experiencing fatigue, poor concentration, and difficulty in reading and comprehension of written material. JG had negotiated extended completion times for coursework but felt that there was poor understanding of his head injury. JG's problems at university lessened over the time course of the study but did not dissipate. During testing JG showed some impulsive behaviours and had to be reminded that it was as important to be accurate as it was to be quick.

Participant 4

DW was 48 when on recruited into the study seven months post-injury. DW was on a cycling holiday with friends when a sheep wandered across the path. DW was cycling at approximately 25mph (taken from friends' cycling speed at the time) and was reported to have hit the sheep and then was propelled over the top of the animal. Bystanders reported that DW experienced loss of consciousness but the length of this was not recorded. The length of post-traumatic amnesia was recorded as five days. DW was airlifted to hospital following the accident and investigation showed fracture of the left occipital condyle (a basilar skull fracture indicative of high impact blunt trauma) and left transverse foramen at C1 and C1-C5 (cervical spine), and the vertebral body at T6 (thoracic spine). The combination of loss of consciousness, post-traumatic amnesia with cervical and skull fracture is indicative of moderate head injury (Malec et al., 2007). These injuries were accompanied by a left clavicle fracture and deep laceration above the right eye with other facial contusions (25 stitches in total). There was no record of CT scan in medical notes accessed as the injury occurred away from home. DW reported that the primary focus of the medical team was his c-spine fractures; it was only on advice of friends that DW asked for a GP referral to rehabilitation services for cognitive difficulties

(memory deficits, word finding difficulties and low mood) and visual disturbance. DW returned to work part-time prior to the first follow-up appointment (six months post-injury). This was successful and at second follow-up DW reported that work was going well. DW performed well on the tasks but showed perseveration on verbal fluency measures, which lessened but did not resolve over the time he was involved in the study.

Participant 5

SG was 50 when recruited into the study seven months post-injury. SG sustained a head injury following a motorcycling accident on a private racetrack with emergency medical care present. Loss of consciousness length is unknown as SG was placed in an induced coma. Post-traumatic amnesia lasted two weeks following withdrawal of sedation. CT scan revealed subdural and subarachnoid haematoma (brain region unspecified in notes obtained) with diffuse axonal injury. SG additionally sustained a fracture to the left clavicle and L1 transverse process (the 'wing' of the first lumbar vertebrae). On recruitment into the study SG stated that he was experiencing problems with memory and planning of immediate and prospective tasks (e.g. not able to cook a meal). At second follow-up SG commented that he had cooked a meal for his wife and was looking for a suitable occupation to correspond better with his changed cognitive status, having been a consultant in the biochemical industry prior to injury. SG had also started driving again but was not able to drive long distances due to fatigue. SG was very engaged with the study and found completion of the test measures helpful in monitoring his recovery.

Participant 6

LH was 32 when recruited into the study 24 months post-injury. LH had experienced an unprovoked attack by 12 strangers whilst visiting a nearby city and sustained a left orbital fracture and bi-lateral brain contusions with PTA of 30 days indicative of a moderate head injury (Malec et al., 2007). LH expressed problems with maintaining concentration, completing tasks with a distractor (for example problems cooking a meal if the telephone rang and disturbed his focus), fatigue, headaches, and problems with social interactions. LH expressed that the lack of understanding of other people about his changes in cognition, particularly in social situations, was difficult for him to cope with and this was compounded by agoraphobia resulting from his attack. LH used reminders on his mobile phone and post-it notes around his flat to take tablet medication, including those for the study, and to help him remember to complete tasks (for example check that the cooker was switched off). LH stated that he did not find the

cognitive measures for the study too difficult to complete but felt they did not reflect his cognitive problems, for example he was able to complete the memory tests quite well but was not able to remember to do planned tasks.

Participant 7

GK was 20 on recruitment into the study six months post-injury and was living with his parents. GK sustained a moderate to severe head injury following a road traffic accident when he hit a tree with his car at approximately 80 miles an hour. CT scan showed multiple regions of minor haemorrhage at the grey/white matter interface with a small (2mm) left parietal subdural haematoma and possible small right parietal subdural haematoma. GK's basal cisterns within the subarachnoid space were slightly effaced and the surfaces of sulci were not clearly visible, indicative of cerebral swelling and raised intracranial pressure. GK reported low mood and memory problems and showed high levels of apathy/lack of engagement during his involvement in the study. GK's parents ensured that the supplementation intervention was adhered to and that food diaries were completed; all communications with GK were through his dad as GK said that he did not pay attention to his phone.

Participant 8

SM was 49 when recruited into the study 23 months post-injury. SM had had a cycling accident in a familiar location but poor visibility due to bright sunlight and deep shadow resulted in SM missing the presence of a large branch across his path. SM lost consciousness and was in cardiac arrest when resuscitated by a passer-by who also contacted the air ambulance. Scans showed that SM had sustained a severe TBI with subdural haemorrhages overlaying both frontal lobes extending superiorly and measuring up to 4mm in maximal depth with some extension into the adjacent subarachnoid space. In addition, there was a 2mm focus haemorrhage in the left temporal lobe. Local sulcal effacement was also present. SM also suffered occipital fracture to right posterior fossa with a large displaced depressed fracture fragment. Fracture extended to foramen magnum and exteriorly through right carotid canal, right mastoid sinus and medially to involve the right sphenoid sinus. No detail on LOC was provided as SM was placed in an induced coma. There was no available information in accessed records on the length of PTA. SM was taking anti-seizure medication during involvement in the study, although this did not completely manage his seizures. On recruitment to the study SM was living with his partner and felt that he was doing 'alright' and had returned to work in his self-employed profession as a graphic designer six months post-injury. SM felt that he was

managing with daily life apart from having difficulty remembering to complete activities without reminders on his mobile phone. SM was very 'chatty' and distractible during sessions, consistent with frontal lobe injuries. Prior to second follow-up SM had experienced two seizures on consecutive days; he stated that these seizures had left him feeling empty and 'joyless'.

Participant 9

SE was 58 on recruitment into the study 20 months post-injury. SE had experienced a polytrauma following a motorcycling accident. Injuries included loss of the right arm at the shoulder and problems with left knee mobility as well as her head injury. CT scan following the accident showed right frontal traumatic haematoma and left frontal contrecoup injury. At the time of enrolment in the study SE was living with her adult children and was adapting to her limited mobility and loss of limb. SE was aware of memory problems but felt her physical limitations, particularly instability walking due to the knee injury, was the greatest impediment to achieving greater independence. SE was embarrassed about her missing arm and was aware of people looking at her when she was out, she was also concerned that if she fell over she would not be able to protect her body and her head with only one arm. SE had been unable to return to work following the injury at the time of her involvement in the study. SE fully engaged with all tasks and she was able to complete all measures with some slight help from myself (e.g. holding pieces of paper in place).

Participant 10

CW was 55 on recruitment into the study 24 months post-injury. CW was hit by a truck as a pedestrian on the pavement, with the force of impact taken to the right side of her body. The polytrauma CW experienced including liver lacerations, fractured ribs on the right side with associated punctured lung, multiple fractures to the right arm with nerve damage as a result of the complexity of the fracture, and a single fracture to left arm. A CT scan at the time of injury found no obvious brain haemorrhage and medical attention was focused on the obvious body injuries, which were severe. While an inpatient the potential for cognitive problems was not discussed with CW. Staged return to work one-year post-injury was unsuccessful as CW was unable to cope with the combination of high noise level and difficulty in maintaining several pieces of information in mind. A physiotherapist in the community later suggested that CW spoke to a psychologist about the trauma of the accident, leading to contact with cognitive rehabilitation services, which CW found beneficial particularly in terms of understanding the cognitive problems she

was experiencing. At recruitment into the study 23 months post-injury CW was living at home with her young adult children and was not working. CW was engaged with the tasks and expressed no problems with remembering to take the tablets and complete the food diary.

Participant 11

LT was 30 on recruitment into the study 12 months post-injury. LT sustained a moderate head injury as a back-seat passenger in a high-speed motor vehicle accident. Polytrauma as part of the accident included ligament damage to her left arm, oblique diplopia and pulseless electrical activity arrest secondary to pulmonary embolism eight days following injury. Due to injury severity LT was placed in an induced coma with tracheotomy. Head CT showed left frontal lobe subarachnoid haemorrhage. Corrective surgery for the diplopia occurred the week following recruitment into the study, 12 months post-injury. Following the first follow-up sessions LT began a phased return to work. Return to work was successful and by second follow-up LT was steadily increasing her hours with no reported difficulties with the workload. LT was able to complete all tasks at all stages of the study and wore corrective spectacles for her diplopia prior to surgery.

Participant 12

DG was 30 when recruited into the study 27 months post-injury, living with his partner and two small children. DG fell approximately 20 feet from an open window while on holiday in Malta, therefore some medical records were inaccessible. DG sustained a right fronto-parietal open fracture and associated subarachnoid haemorrhage with PTA of one month, indicative of a moderate head injury. DG had a craniotomy two weeks post-injury with cranioplasty four months later. DG returned to work one-year post-injury. DG stated he was able to cope with what was required at work. He did however express that he had difficulty concentrating when trying to learn new skills. He admitted that this might result from an element of self-defeat or self-sabotage when faced with tasks he found difficult. This DG commented that this was was a change following his head injury as prior to his accident he did not have such negative thoughts when faced with challenges. DG said that he found involvement in the study helpful to demonstrate what he was able to do.

Participant 13

JW was 21 when recruited into the study 14 months post-injury. JW was found collapsed in a nearby city during a night out following a suspected hit and run incident; a large subdural haematoma was relieved by decompressive craniotomy and JW spent several months on a neurorehabilitation ward. At the time of the study JW was living with his mother and had regular visits from a support worker. During the study JW showed a lack of awareness of cognitive deficits that included memory and executive functions; at the time of injury JW was attending university in London and expressed a desire to re-start his studies closer to home. Rehabilitation services were working with JW on the possibility of achieving this goal. JW was very chatty and engaged with the study but was easily distracted, at one point breaking off from the session to show his art folder to me and discuss the contents at length.

Participant 14

JA was 22 when recruited into the study 13 months after sustaining a mild to moderate head injury at work following a fall. JA had a short period of LOC (length not recorded) and CT scan showed a left fronto-temporal bone fracture with extradural haematoma and right temporal lobe contusion. JA returned to work four weeks following injury, however this was more related to expectations of the workplace rather than readiness of JA. JA reported some memory and word finding difficulties and was being seen by rehabilitation services at the time of enrolment. JA withdrew prior to first follow-up stating that he found taking the supplements for the research too onerous.

Participant 15

SS was 41 at recruitment into the study seven months post-injury and was successfully managing living alone with his young children. SS was the driver in a road traffic accident when another car pulled into him while he was waiting at a junction. Medical notes describe that SS was confused after injury although no brain changes were detected on CT scan. Medically SS had injury to his nose and a sprained shoulder. On recruitment into the study SS stated that he was experiencing memory problems post-injury but that he was using a number of strategies to compensate (keeping lists) and had successfully returned to work as a sports instructor. SS felt he was successfully able to manage his duties at work. SS engaged with the study and completed all test measures efficiently without chattiness, the same efficiency evident in his food diary and compliance with the intervention.

Participant 16

FW was 55 when recruited into the study 24 months post-injury and was living with her partner. FW was a front seat passenger in a motor vehicle accident where a larger vehicle impacted the passenger side of the car. FW went to A&E and was diagnosed with concussion and post-concussion syndrome but was not given a CT scan. FW lost most of the vision in her left eye, later diagnosed by an ophthalmologist as a traumatic shearing injury. FW's visual problems resulted in disorientation and nausea in busy environments, when observing a scene requiring swift head motion, travelling downstairs or on escalators and in dimly lit places. In addition, FW had severe tinnitus with slight hearing loss in the left ear. Cognitively FW reported suffering from fatigue, insomnia, anosmia (loss of smell) and changes in taste perception (reporting that food tasted 'stronger'), anxiety, 'brain fog', and impaired memory function. One week prior to second follow up FW experienced a dizzy spell while out with her daughter and fell and hit her head on a metal post; FW reported that this had worsened her symptoms. FW had also moved to a new house ten days prior to second follow-up, fatigue from this move potentially leading to the dizzy spell. Visual problems meant that FW was not able to complete the SRT task but completed all other measures.

Participant 17

VB was 19 at recruitment to the study four months post-injury and was living with a cousin while at university. VB was visiting a local shopping centre with friends when she 'felt funny' and fainted. This fall resulted in a left parietal skull fracture with associated right subdural haematoma visible on CT scan. VC reported problems with concentration and memory and had problems sleeping due to headaches and tinnitus. VC withdrew from the study prior to first follow-up with no reason given.

Participant 18

BY was 69 when recruited into the study 16 months post-injury. BY was crossing the road at a pedestrian crossing with the traffic lights on red; he was part way over the crossing when a car hit him. BY sustained a broken femur and broken collarbone with loss of consciousness although CT scan was normal. BY stated that he was more lachrymose following the injury and although he felt there had been no other changes to his cognition his wife stated that BY's memory was noticeably worse. BY had been able to successfully return to his part-time occupation following injury and found this to be a positive part of his life. BY fully engaged with the study and was very interested in the process.

Participant 19

PM was 61 when recruited into the study six months post-injury; PM was at a casino when he felt dizzy and then fell, hitting his head. GCS was 15 on admission to hospital where a CT scan showed a thin tentorial left sided acute subdural haematoma and PTA of less than 24 hours, indicating a mild head injury. PM had been able to successfully return to work as a chef in a local restaurant and stated that he experienced only mild problems with memory and planning that he was able to easily compensate for. PM was very chatty during test sessions but focused well on the tasks.

Participant 20

CL was 30 when recruited into the study six months post-injury. CL fell down the stairs after an evening out drinking with friends. GCS was 13 on admission to hospital and PTA lasted for 12 hours. CT scan showed a non-displaced right frontal bone fracture extending to the superior lateral orbital ridge with small (5mm) underlying extradural haematoma. CL was living with family at baseline testing due to building works in his own home, which he shared with a friend. CL was subsequently able to move back into his own home prior to first follow-up appointments although both follow-up appointments took place at his mother's home to maintain consistency of testing environment. CL had a successful return to work following his injury, despite temporarily losing his driving license following his head injury impacting his ability to do some activities related to his occupation. CL regained his driving license between first and second follow-up test points. CL competently completed all test measures.

Participant 21

KS was 44 when recruited into the study ten months post-injury. KS had been out cycling with her family when she fell off the bike, with no obvious contributing factors. Other family members report that KS had a short loss of consciousness; KS had no memory immediately before and after the accident indicating a period of anterograde and retrograde amnesia. CT scan conducted in A&E showed no brain changes however KS had difficulty with fatigue, attention, headaches and visual problems on return to work two months post-injury. Following referral to neurorehabilitation services KS altered her working pattern to accommodate her fatigue and cognitive changes; KS was working Monday to Wednesday before the accident, but changed working days to Monday, Wednesday and Friday to allow a rest day between each workday. This remained her work pattern on recruitment to the study. By first follow-up KS was experimenting with returning to a pre-injury working pattern, expressing that she was able to manage but that

fatigue could still be a problem by Wednesday of the working week. At second follow-up KS stated that fatigue could still be a problem at work but that she was pleased overall that she was able to maintain this work pattern.

Participant 22

PP was 27 on admission into the study four months post-injury. PP had been out with friends when he fell down three stairs sustaining a moderate to severe head injury. CT scan showed an acute subarachnoid haemorrhage in the right carotid sulci at the base of the skull next to the cribriform plate, subdural haemorrhage overlaying the right frontotemporal lobe and contusional haemorrhage in right cerebral hemisphere. This was accompanied by left parietal bone fracture and partial effacement of the right lateral ventricle. PP had a right side decompressive craniectomy three days following the original injury and was ventilated for 17 days. Length of PTA is not documented but PP was reported to be orientated to time and place one month following injury. PP suffered from seizures as a result of the head injury.

Two weeks prior to first follow up PP had a series of four seizures in a single day and was admitted to hospital for two nights for observation. As a result of this series of seizures PP had a change to his medication and complained at first follow up that this had made him feel mentally very slow and that he had taken a step backwards in terms of function. Four days after first follow-up PP had his reconstructive cranioplasty surgery. Medication changes had resulted in almost complete management of seizure activity by second follow-up, although PP stated that he still did not feel like himself. PP completed all test measures, although he clearly found them challenging at times.

Participant 23

KN was 40 when recruited into the study 16 months post-injury. KN was disembarking from a coach on holiday when she missed her footing, falling approximately 6 feet face forward onto the pavement. KN had two CT scans and one MRI, all of which were clear with no skull or tissue damage. KN did however develop two black eyes (possible periorbital ecchymosis), which may suggest undetected basilar skull fracture. There is no record of GCS in KN's medical notes and KN self-reported PTA of 6 hours resulting in a diagnosis of symptomatic TBI (Malec et al., 2007). When recruited into the study KN expressed that she suffered from severe fatigue, 'toothache' headaches, visual problems and difficulties with activities of daily living, for example KN visited the hairdresser to have her hair washed as the motion of her head when she washed her own hair caused nausea. Visual problems meant that KN was not able to

complete the full test battery, specifically the Stroop and SRT tasks. KN did not withdraw from the study despite these problems as she felt it was important to contribute to this research, although problems experienced may have had an effect on the effort KN made in completing the tasks.

Participant 24

BMS was 19 when recruited into the study four months post-injury. BMS had been involved in a road traffic accident when out drinking one evening with friends in a nearby city. The injury resulted in frontal contusions with small subarachnoid haemorrhage and diffuse axonal injury. In addition, BMS sustained a large laceration to his right hip requiring a number of stitches. No information on GCS and PTA was available in medical records; as the injury occurred in another city records from the treating hospital were not made available to the neurorehabilitation team. BMS was on a gap year between A-Levels and University when he sustained his head injury and he and his family had made the decision to extend this 'gap' for another year to allow BMS to recover, adjust to cognitive changes, and also to re-evaluate destination University choices. BMS was having memory and word finding difficulties along with some speech problems when recruited into the study, which were being addressed by neurorehabilitation services. BMS was engaged in the tasks and did not present with 'chattiness' or impulsivity in terms of task completion.

Participant 25

KW was 57 when recruited into the study 17 months post-injury. KW had gone to the stables where she kept her horses and when her companion left KW was tacking up the larger horse. Approximately an hour and a half later KW was spotting by a neighbour lying unconscious in a field; the horse's tack was broken as was the back of KW's riding helmet. KW was taken to hospital and observed overnight and discharged the following morning, despite being unable to speak clearly or walk. There is no record of a CT scan. KW has no concrete memories until approximately two weeks after her injury, and this self-report is taken as the length of PTA indicating a moderate head injury. On recruitment into the study KW expressed that she was still having problems with memory and word finding difficulties but had returned to work on the same basis as prior to the accident following an extended return to work process. KW stated that neurorehabilitation service interventions, including speech therapy and neuropsychology and the good response of the workplace following injury were pivotal in this return to work. Notwithstanding between first and second follow-up KW had a physical and mental

collapse culminating with attempting to take her own life. This collapse was partially fatigue related; in retrospect KW stated that she had been so focused on 'returning to normal' that she had ignored the warning signs of exhaustion and low mood until the collapse. At second follow-up KW had not been able to return to work and had taken the decision that she going to leave her current job (in a call centre; high noise and artificial light) and to find an alternative job she was able to manage. KW was having a very hard time adjusting to the 'new person' she was after the injury and stated that she did not like this person. As a result of attempting to take her own life KW had been placed on a waiting list for counselling.

Participant 26

PD was 57 when recruited into the study 17 months post-injury. PD sustained his injury following an accident at work where a large piece of machinery struck him in the back of the head. This resulted in a left occipital & mastoid fracture with associated haemorrhagic contusions to left temporo-occipital lobes, left transverse and sigmoid thrombosis with possible haemorrhagic infarction in the left cerebellar hemisphere. PD underwent left side craniectomy with corrective cranioplasty three months later. PD was aphasic following injury but on recruitment into the study had good speech production with some slowness in word finding. PD had also developed alexia (loss of ability to read) as a result of his injury but was able to recognise letters of the alphabet. PD also had right hemispatial neglect. These deficits meant that PD was unable to complete the full test battery (specifically the Colour Word Interference Test and the Test of Pre-Morbid Intelligence). PD's visual and language problems led to the decision that the WASI-II was not a fair representation of PDs abilities. All reminders about tablet taking and food diary completion were communicated via PD's wife as he was unable to read. Over the time course of PD's involvement in the study he showed improved attention to the right side of space.

Participant 27

LM was 40 when recruited into the study eight months post-injury. LM sustained two head injuries in quick succession (five days apart) following falls, the second resulting in symptoms of head injury without PTA. On CT scan no haemorrhage or skull fracture was detected and no GCS was recorded. Hearing loss following nerve damage was identified at a later medical examination, which clinicians attributed to an undetected skull fracture at the time of injury. LM had a phased return to work three months post-injury, experiencing cognitive slowness and some distractibility. LM stated he was

managing with work, although fatigue was an issue, and this led to some time away from work between baseline testing and first follow-up. At second follow-up testing LM had had no further time away from work, suggesting an overall reduction in fatigue levels although LM stated that fatigue was still a problem in day to day functioning.

Participant 28

MH was 55 on recruitment into the study 17 months post-injury having sustained a depressed skull fracture to the right temporal-parietal region following a piece of metalwork falling from a pile at work. Elevation and washout of the skull fracture was completed surgically, however there was no record of GCS or PTA in MH's medical notes. On recruitment into the study MH expressed frustration with his levels of fatigue and cognitive changes (particularly memory and information processing) which were preventing him returning to work and affecting his ability to function at the same physical and cognitive level as prior to injury. MH required some clarification on test instructions but completed them well once he understood exactly what was required. MH was engaged with the tasks and although he asked questions was not overtly chatty or distractible.

Participant 29

JB was 54 on recruitment into the study ten months post-injury. JB sustained a left occipital non-displaced sphenoid bone fracture with traumatic subarachnoid haemorrhage and bilateral acute subdural haematoma following a trip and fall. GCS was 12 on admission then dropped to 9 initially before going up to 15 on admission to the ward indicating a mild to moderate head injury. There was no reported PTA. JB expressed that although her time in hospital was 'difficult' she felt that she had returned to her normal level of function, if she took her fatigue into consideration. Indications to JB that she was experiencing high levels of fatigue included an increase in tinnitus volume, headache and becoming lachrymose, although she said that she was not explicitly aware that she was fatigued. On recruitment into the study ten months post-injury JB had successfully returned to work in her previous capacity. JB engaged with the study but expressed that she had some difficulty in adhering to the supplementation regime at weekends when her days were less planned. For the second intervention period this was addressed with more frequent reminders, particularly at weekends.

Participant 30

JH was 56 on enrolment into the study seven months after sustaining a mild head injury playing football; he and another player clashed heads when they both went to head

a ball. JH sustained no loss of consciousness at the time of injury but went to the hospital due to severe nosebleed at which point JH was diagnosed with concussion. There was no record in medical notes of GCS or PTA. JH expressed that he was experiencing headaches, fatigue and memory changes and poor attention both misplacing or forgetting items (e.g placing milk in a cupboard rather than the fridge) and repeating sections of music when playing (he was a professional band member). JH had attempted to playing football since his injury but had then made the decision to stop and withdraw from the team as JH stated that he experienced headaches following exercise and was concerned about further head injuries.

6.3. Summary

Participants involved in the study had a diverse range of cognitive impairments, severity of injury and were at different stages of their recovery. Participants were predominantly male (70%), living with family (86.7%) and overall most participants were educated to A-level or undergraduate level (combined total 86.6% of the cohort). The greater proportion of participants sustained their head injury following some form of trip or fall (40%) or as a result of accidents associated with motor vehicles (33.3% in total). This epidemiology is consistent with that found by previous research (Peeters et al., 2015; Tagliaferri et al., 2006). Mean estimated intelligence quotient was in the average range with scores on the Test of Premorbid Intelligence slightly higher than those on the Wechsler Abbreviated Scale of Intelligence, as would be expected following a head injury.

The following chapter provides the results of the study in the traumatically brain injured cohort.

Chapter Seven: Traumatic Brain Injury Study Results and Summary

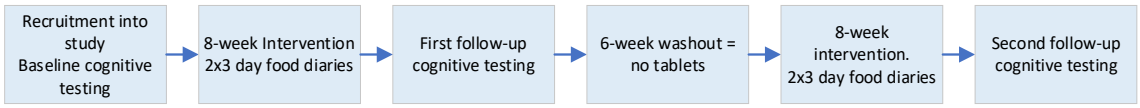
7.1 Introduction

Previous research investigating the effect of micronutrient and omega-3 supplementation following TBI has mainly been in animal models (e.g. Pan et al., 2009; Pu et al., 2013) with few controlled randomised clinical trials in humans to date (e.g. Amen et al., 2011). In the current study 30 human participants were randomly assigned to one of three groups in a double-blind cross-over design with a parallel placebo group. Participants assigned to the multivitamin (intervention MO, n = 10) or omega-3 (intervention OM, n = 10) intervention following baseline testing took the alternative supplement after the first follow-up and wash-out period; in this way participants completed all conditions to account for individual differences in brain trauma sequelae. Participants allocated to the Placebo group (n = 10) following baseline testing took the placebo again following the wash-out period. Each intervention was eight weeks in length, with a wash-out period of six weeks (see Figure 7.1).

During each intervention period participants completed two three-day food diaries covering both week and weekend days. The test battery included measures of memory, executive function, social cognition, mood state, and learning selected on the basis of normative study data. Measures of current and pre-morbid intelligence were also administered at baseline (full details on the methodology can be found in Chapter Five). Two participants withdrew from the study prior to first follow-up (participant 14, intervention OM; participant 16, intervention MO). Participant 14 withdrew as taking the intervention precluded them from drinking fortified protein shakes after gym sessions. Participant 16 did not respond to contact telephone calls, text messages or letters inviting them to make appointments for follow-up sessions. There was a variability in gender split between groups; intervention OM n = 9 (males = 4), intervention MO n = 9 (males = 8), placebo n = 10 (males = 8). Random allocation resulted in a differing number of males and females in each group, consistent with males being up to three times more likely to sustain a TBI (Ponsford et al., 2013) than females.

Figure 7.1

Flow diagram of study procedure



In this chapter baseline demographic analyses are presented followed by analyses of micronutrient intake from food diary entries and from study interventions. Following micronutrient analyses participant performance on behavioural test measures are presented before conclusions from this study are briefly discussed. As sample size has an effect on *p* values, effect size (a measure independent of sample size) is also reported either as η_p^2 (Cohen, 1988; .01 = small, .06 = medium, .14 = large) or Cohen's *d* (Cohen, 1988; .2 = small, .5 = medium, .8 = large) dependent upon the measure reported. All *p* values adhere to the standard convention of two-tailed reporting.

7.2 Results of demographic analyses and descriptive statistics

Cognitive test measures were scored and age-scale adjusted in accordance with the corresponding test administration manuals. Demographic information for the whole cohort can be found in Chapter 6. Behavioural data for the whole cohort were inspected for outliers. A number of outliers, defined as z-scores ±3.29 from the mean (Field, 2009), were identified. After checking each data point to ensure that these were true scores and not inputting errors these values were retained as they reflect the true performance of participants which could be expected to deviate from normality. Data were also inspected for skew; some negatively skewed variables (more than 3.29 SE of skewedness) were identified, however as this cohort was a heterogenous group (acknowledged as a feature of brain injured groups; Maas et al., 2013; Rosenbaum & Lipton, 2012) and all scores were genuine, transformation of data was not conducted. Analyses of variance are known to be robust when group sizes are equal and Pillai's Trace was the criterion used to take a conservative approach (Tabachnick & Fidell, 2001). Descriptive statistics of demographic measures organised by group are presented in Table 7.1 and Appendix E.1.

Table 7.1

Means and standard deviations of demographic measures at baseline by intervention group

Measure	Intervention Group OM Mean (SD) n = 10	Intervention Group MO Mean (SD) n = 10	Placebo Group Mean (SD) n = 10
Time Since Injury (years)	15.00 (6.27)	11.30 (8.86)	11.80 (8.19)
Age (at recruitment)	46.10 (12.81)	36.60 (18.54)	42.80 (16.39)
TOPF	103.50 (10.14)	104.30 (11.82)	105.11 (6.03)
WAIS IQ-4	103.38 (6.95)	98.30 (12.48)	105.78 (9.38)

Note: MO = Multimicronutrient then Omega-3. OM = Omega-3 then Multimicronutrient

Results of one-way ANOVAs showed no significant differences between groups in any of the demographic variables at baseline; time since injury ($F(2,27) = 0.79$, $p = .465$, $\eta_p^2 = .06$), age ($F(2,27) = 0.90$, $p = .419$, $\eta_p^2 = .06$), Test of Premorbid Function (TOPF) estimate of IQ ($F(2,26) = 0.06$, $p = .945$, $\eta_p^2 = .004$) or Wechsler Abbreviated Scale of Intelligence (WAIS) estimate of IQ ($F(2,27) = 0.52$, $p = .600$, $\eta_p^2 = .04$), suggesting that any purported differences in task performance between the groups post-intervention could not be attributed to demographic variation. Descriptive statistics for baseline task performance can be found in Tables 7.2 – 7.5 and Appendix E.2. Test measures were counterbalanced between and within participants at all test points and alternate forms were used where available.

Table 7.2

Memory measures descriptive data for each group. Participants took one supplement for 8 weeks, had a 6-week washout, and then took the other supplement. Participants allocated the placebo took this in both periods. Group OM = omega-3 taken for the first 8 weeks and multimicronutrient taken for the second 8 weeks. Group MO = multimicronutrient taken for the first 8 weeks and omega-3 taken for the second 8 weeks.

	Intervention Group OM			Intervention Group MO			Placebo Group		
Cognitive Measure	Baseline (N = 10) Mean (SD)	T1 Assessment after omega-3 (N = 9) Mean (SD)	T2 Assessment after multivitamin (N = 9) Mean (SD)	Baseline Mean (SD) (N = 10)	T1 Assessment after multivitamin (N = 9) Mean (SD)	T2 Assessment after omega-3 (N = 9) Mean (SD)	Baseline (N = 10) Mean (SD)	T1 Assessment after placebo (N = 10) Mean (SD)	T2 Assessment after the 2nd placebo (N = 10) Mean (SD)
WAIS-IV Digit Span									
Overall Score	7.56 (2.46)	8.33 (3.08)	8.44 (3.43)	10.22 (2.73)	11.00 (2.69)	11.56 (3.09)	10.50 (2.95)	10.30 (2.67)	11.80 (2.86)
WMS-IV Verbal Paired Associates (Verbal Memory)									
Immediate Recall	8.22 (1.56)	10.33 (3.00)	10.11 (3.26)	8.78 (3.35)	10.44 (4.03)	12.00 (3.64)	8.40 (3.27)	10.20 (4.57)	11.90 (4.56)
Delayed Recall	8.00 (2.55)	10.11 (4.01)	9.44 (3.47)	8.89 (4.04)	10.67 (4.03)	11.44 (3.17)	9.50 (3.57)	10.40 (4.38)	11.10 (3.60)
Doors (Visual Recognition)	8.22 (3.80)	9.89 (5.04)	10.11 (5.79)	9.78 (2.99)	10.67 (4.36)	11.75 (4.71)	9.60 (2.76)	9.90 (3.18)	10.89 (2.20)
Rey-Osterrieth Complex Figure (Visual Memory)									
Copy (perceptual organisation)	35.22 (0.83)	34.78 (1.30)	34.78 (1.20)	34.56 (1.59)	34.39 (2.23)	34.67 (1.73)	32.50 (6.19)	32.20 (7.97)	32.60 (5.12)
Immediate Recall	23.72 (5.47)	24.50 (6.54)	23.33 (7.34)	24.56 (5.80)	25.67 (9.51)	27.83 (5.90)	22.65 (9.43)	25.55 (8.44)	26.40 (9.50)
Delayed Recall	22.94 (6.78)	23.50 (6.97)	24.56 (6.86)	22.72 (7.74)	25.72 (9.15)	28.94 (6.15)	21.00 (8.80)	24.35 (8.71)	25.15 (9.62)

Table 7.3

Executive function measures descriptive data for each group. Participants took one supplement for 8 weeks, had a 6-week washout, then took the other supplement. Participants allocated the took this in both periods. Group OM = omega-3 taken for the first 8 weeks and multimicronutrient taken for the second 8 weeks. Group MO = multimicronutrient taken for the first 8 weeks and omega-3 taken for the second 8 weeks.

	Intervention Group OM			Intervention Group MO			Placebo Group		
Cognitive Measure	Baseline (N = 10) Mean (SD)	T1 Assessment after omega-3 (N = 9) Mean (SD)	T2 Assessment after multivitamin (N = 9) Mean (SD)	Baseline Mean (SD) (N = 10)	T1 Assessment after multivitamin (N = 9) Mean (SD)	T2 Assessment after omega-3 (N = 9) Mean (SD)	Baseline (N = 10) Mean (SD)	T1 Assessment after placebo (N = 10) Mean (SD)	T2 Assessment after the 2nd placebo (N = 10) Mean (SD)
Executive Function (DKEFS)									
Trail Making									
Visual Scanning	7.44 (4.61)	9.00 (5.07)	9.22 (4.89)	9.56 (2.83)	10.56 (2.96)	11.56 (1.67)	8.70 (4.69)	8.40 (5.21)	8.90 (4.63)
Number Sequencing	9.67 (4.24)	9.00 (5.52)	9.78 (4.82)	9.44 (2.74)	12.33 (2.06)	11.78 (11.78)	10.00 (4.37)	10.30 (4.30)	10.70 (4.00)
Letter Sequencing	8.89 (4.62)	10.67 (4.74)	11.11 (4.04)	10.67 (2.73)	11.00 (3.12)	12.78 (1.30)	9.70 (4.69)	9.90 (3.54)	11.00 (4.22)
Number/Letter Switching	10.44 (3.12)	10.67 (3.20)	10.67 (3.20)	10.33 (2.96)	11.22 (2.77)	12.33 (2.00)	10.10 (4.07)	10.40 (3.95)	10.90 (3.93)
Motor Speed	9.00 (4.06)	9.33 (4.27)	9.89 (4.37)	11.33 (1.50)	12.11 (0.93)	12.11 (0.78)	10.10 (3.41)	9.70 (3.56)	10.20 (3.49)
Verbal Fluency									
Phonemic Fluency	9.56 (2.65)	9.78 (3.35)	9.56 (3.40)	11.67 (4.61)	12.11 (5.37)	12.44 (5.19)	10.70 (3.23)	10.70 (3.26)	12.20 (3.29)
Semantic Fluency	10.33 (3.43)	10.56 (6.35)	10.33 (5.20)	11.33 (4.36)	11.67 (5.07)	13.00 (5.10)	11.90 (4.95)	10.60 (6.26)	11.90 (3.98)
Semantic Switching	11.33 (1.00)	10.56 (2.79)	10.11 (3.37)	10.89 (3.62)	9.33 (3.54)	12.78 (4.21)	11.40 (4.09)	11.30 (4.32)	12.80 (2.66)
Colour Word Interference									
Naming	7.56 (4.16)	8.11 (4.43)	8.75 (3.73)	8.44 (2.30)	10.11 (2.93)	9.78 (3.60)	7.90 (4.51)	8.40 (4.84)	8.80 (4.52)
Reading	7.89 (4.28)	8.78 (4.63)	9.00 (3.93)	10.00 (2.18)	10.44 (2.13)	10.44 (3.32)	9.67 (3.39)	10.22 (4.49)	10.22 (3.80)
Inhibition	8.75 (4.03)	10.63 (4.31)	10.63 (4.17)	9.44 (3.24)	11.78 (1.56)	11.22 (3.19)	10.33 (4.00)	10.56 (4.95)	10.56 (3.36)
Inhibition Switching	8.38 (4.69)	10.50 (4.04)	10.38 (4.44)	9.56 (4.10)	11.44 (2.46)	11.44 (3.21)	9.67 (4.47)	9.44 (5.46)	11.44 (3.13)

Table 7.4

Processing speed and learning measures descriptive data for each group. Participants took one supplement for 8 weeks, had a 6-week washout, and then took the other supplement. Participants allocated the placebo also took the placebo in the second intervention period. Intervention OM = omega-3 taken for the first 8 weeks and multimicronutrient taken for the second 8 weeks. Intervention MO = multimicronutrient taken for the first 8 weeks and omega-3 taken for the second 8 weeks.

	Intervention Group OM			Intervention Group MO			Placebo Group		
Cognitive Measure	Baseline (N = 10) Mean (SD)	T1 Assessment after omega-3 (N = 9) Mean (SD)	T2 Assessment after multivitamin (N = 9) Mean (SD)	Baseline Mean (SD) (N = 10)	T1 Assessment after multivitamin (N = 9) Mean (SD)	T2 Assessment after omega-3 (N = 9) Mean (SD)	Baseline (N = 10) Mean (SD)	T1 Assessment after placebo (N = 10) Mean (SD)	T2 Assessment after the 2nd placebo (N = 10) Mean (SD)
Processing Speed									
WAIS-IV Symbol Search	9.00 (1.73)	10.11 (3.89)	10.33 (4.50)	8.89 (1.62)	11.00 (3.24)	1.44 (3.32)	8.60 (3.31)	9.90 (4.75)	10.10 (5.61)
Serial Reaction Time Task									
Explicit Learning	3.36 (3.06)	7.03 (3.85)	6.57 (5.16)	7.33 (4.92)	8.83 (5.32)	10.50 (6.07)	6.50 (3.72)	8.65 (4.61)	8.33 (4.64)
Implicit Learning	34.51 (44.69)	38.90 (48.49)	44.16 (36.87)	76.57 (90.43)	21.76 (79.37)	60.68 (40.81)	28.64 (66.21)	79.82 (137.80)	129.24 (171.58)

Table 7.5

Activities of daily living, mood state and social cognition measures descriptive data for each group. Participants took one supplement for 8 weeks, had a 6-week washout, and then took the other supplement. Participants allocated the placebo also took the placebo in the second intervention period. Group OM = omega-3 taken for the first 8 weeks and multimicronutrient taken for the second 8 weeks. Intervention MO multimicronutrient taken for the first 8 weeks and omega-3 taken for the second 8 weeks.

	Intervention Group OM			Intervention Group MO			Placebo Group		
Cognitive Measure	Baseline (N = 10) Mean (SD)	T1 Assessment after omega-3 (N = 9) Mean (SD)	T2 Assessment after multivitamin (N = 9) Mean (SD)	Baseline Mean (SD) (N = 10)	T1 Assessment after multivitamin (N = 9) Mean (SD)	T2 Assessment after omega-3 (N = 9) Mean (SD)	Baseline (N = 10) Mean (SD)	T1 Assessment after placebo (N = 10) Mean (SD)	T2 Assessment after the 2nd placebo (N = 10) Mean (SD)
Activities of Daily Living (ADL)									
Nottingham Extended ADL	50.17 (12.82)	50.11 (14.50)	53.11 (9.91)	53.67 (7.21)	52.67 (9.91)	51.44 (12.41)	48.90 (17.48)	51.10 (19.04)	50.22 (17.44)
Mood State									
PANAS Positive Affect	28.22 (8.87)	33.44 (7.09)	33.44 (7.09)	28.67 (11.91)	32.11 (10.84)	29.33 (10.57)	30.90 (8.72)	31.90 (7.26)	30.50 (8.09)
PANAS Negative Affect	24.00 (10.56)	20.55 (10.33)	25.11 (8.65)	22.89 (7.34)	23.72 (9.33)	22.06 (9.94)	19.30 (5.19)	18.90 (7.56)	18.60 (5.52)
Social Cognition									
Reading the Mind in the Eyes	24.67 (3.94)	22.78 (5.43)	23.22 (5.76)	23.22 (4.27)	24.22 (5.70)	25.00 (5.01)	23.30 (5.89)	24.30 (6.06)	23.78 (5.19)

PANAS = Positive and Negative Affect Schedule

Results of MANOVAs conducted on baseline task performance with supplement group as the independent variable and score on test measures as the dependent variables showed no significant difference between groups (see Table 7.6). This indicates that groups were similar in cognitive status at baseline.

Table 7.6

Table of MANOVAs investigating differences between intervention groups at baseline

Measure	*F*	*df*	*p*	η_p^2
Memory (VPA, ROCFT, Digit Span, Doors)	1.01	14,40	.424	.27
Trail Making	1.64	10,44	.126	.27
Verbal Fluency	0.53	6,48	.780	.06
Colour Word Interference Task	0.50	8,44	.850	.08
Processing Speed and Learning (Symbol Search, SRT)	1.20	6,44	.325	.14
ADL, Mood State and Social Cognition (NEADL, PANAS PA & NA, RME)	0.50	8,46	.847	.08

VPA = Verbal Paired Associates; ROCFT = Rey-Osterrieth Complex Figure Test; NEADL = Nottingham Extended Activities of Daily Living, PANAS = Positive and Negative Affect Schedule; RME = Reading the Mind in the Eyes

7.3 Food diary analyses

All participants completed two three-day food diaries during each intervention period. Three-day food diaries are conventionally accepted as a valid dietary assessment tool (Yang et al., 2010). This enabled a good overview of participant's dietary intake to be obtained without being too onerous on participants with memory deficits. Self-report food diaries are considered to provide a good proxy of micronutrient intake, when compared with physiological biomarkers (Brunner et al., 2001; Sauvageot et al., 2013). Within each eight-week intervention period one food diary was completed during week three, the other was completed during week 6, one during the week (Tuesday, Wednesday, Thursday) the other at the weekend (Friday, Saturday, Sunday). This allowed for the capture of natural variations in food intake. Participants were asked to be as accurate as possible when completing food diaries, including listing all constituent items of recipes, although they were not required to weigh food items. Participants were also asked to fill in the food diary as close in time to eating or drinking as possible to aid recall accuracy (Kirkpatrick et al, 2014). Any queries related to food diary entries were clarified with the participant prior to being entered into analysis software (Nutritics Nutrition Analysis Software v.5.099) and food items not present in the database were added. Participant 3 did not provide a food diary for either intervention period despite 12 months of reminders. Participant 15 did not provide a food diary for the second time period having

misplaced it following a house move. All other participants completed food diaries. Following input the software, Nutritics, calculated mean intake of each micronutrient for each participant across each intervention period; these data were then input into SPSS v24 (IBM Corp., 2016) for statistical analyses. Compliance with interventions (measured as number of tablets remaining as a percentage of total number of tablets) was also very good overall (intervention period 1, m=97.96, SD = 2.69; intervention period 2, m = 98.09, SD = 4.37). Together this indicates that participant own strategies along with regular text reminders were effective in ensuring compliance in both food diary completion and ingesting supplements or placebo. Micronutrients under investigation were all 19 of the essential micronutrients plus omega-3 polyunsaturated fatty acids (see Chapter 2 for review). Iodine was the only micronutrient that was not a component of either of the active interventions. As recommended daily intake levels vary for each micronutrient they were analysed separately.

As in the normative study daily dietary intake of micronutrients was compared to recommended dietary reference intake levels issued by the United States Food and Nutrition Board of the Institute of Medicine (US IoM; Bendich, 2001; Del Valle et al., 2011; IoM, 1998; Monsen, 2000; Trumbo et al., 2001; Trumbo et al., 2002). The comparison of dietary intake with recommended levels was calculated for each of the three groups (intervention MO, intervention OM, Placebo) separately. In addition, total micronutrient intake for each group was calculated from the sum of dietary intake plus micronutrient supplementation following the intervention and again compared with recommended daily intake levels. Differences in dietary intake alone and dietary intake plus supplementation compared to recommended daily amounts were converted to a percentage to account for differences in scale (μg/mg) to enable direct comparison between different micronutrients.

Data were organised by intervention group and inspected for outliers and skew. There were no micronutrient dietary intake outliers (values >±3.29SDs) for either the first or second intervention periods across groups. Some skewed micronutrient variables were detected (above ±3.29 SE of skewedness), these were investigated within the raw data and found to reflect actual intake of participants and as such were left untransformed.

MANOVAs were conducted to investigate any differences in dietary intake between groups in each of the intervention periods, using average daily micronutrient intake taken from food diaries as the independent variable and intervention group as the dependent variable. Results showed no significant differences between groups (Table 7.7). It should be noted that for dietary intake in the second intervention period Box's M

(a test for homogeneity of variance) was not calculated by SPSS for the antioxidants and fat-soluble vitamins analysis. Box's M is, however, considered to be a very sensitive measure (Tabachnick & Fidell, 2001) and there was a slight difference in cohort size for food diaries as one participant did not provide a diary for this period. Pillai's Trace, as the most conservative criterion was therefore reported, following the recommendations of Tabachnick and Fidell (2001).

Table 7.7

Results of MANOVAs investigating differences between groups on micronutrient intake taken from food diaries

Intervention Period	Micronutrients	*F*	*df*	*p*	η_p^2
First intervention period	B Vitamins (B_1, B_2, B_3, B_5, B_6, B_7, B_9, B_{12})	0.56	16,36	.890	.20
	Antioxidants and Fat-Soluble Vitamins (A,C, D, E, K)	0.42	10,42	.927	.90
	Minerals and Omega-3 (Calcium, Iron, Iodine, Magnesium, Selenium, Zinc)	1.58	14,38	.130	.37
Second intervention period	B Vitamins (B_1, B_2, B_3, B_5, B_6, B_7, B_9, B_{12})	0.54	10,40	.850	.12
	Antioxidants and Fat-Soluble Vitamins (A,C, D, E, K)	1.61	16,34	.120	.43
	Minerals and Omega-3 (Calcium, Iron, Iodine, Magnesium, Selenium, Zinc)	1.23	14,36	.299	.32

As a result of these analyses the groups could not be distinguished on dietary micronutrient intake alone, in a similar way to baseline cognitive data, indicating that the groups were similar on variables of interest at the beginning of the study. Participants, except for those taking the placebo, took a different intervention in each 8-week study period. Analyses of differences between dietary intake and recommended daily amounts, and of differences in overall intake once the interventions are taken into account, were therefore conducted separately for each group for both of the intervention periods.

7.3.1. Summary of nutritional status during the first intervention period

All analyses investigating potential differences in average dietary intake to recommended daily intake amounts, assessed from six days of food diary entries, were calculated with differing recommended levels for males and females accounted for in calculations (reflected in means and standard deviations). Descriptive statistics of micronutrient intake for this period can be found in Table 7.8.

Table 7.8

Means and standard deviations of recommended daily amounts (RDA), dietary intake and dietary intake plus supplementation for each group in the first intervention period.

	Intervention Group OM			Intervention Group MO			Placebo Group	
Micro-nutrient	RDA Mean (SD)	Dietary intake mean (SD)	Diet plus supplement mean (SD)	RDA Mean (SD)	Dietary intake mean (SD)	Diet plus supplement mean (SD)	RDA Mean (SD)	Dietary intake mean (SD)
Thiamine	1.14 (0.05)	1.49 (0.29)	-	1.19 (0.04)	1.58 (0.54)	26.58 (0.54)	1.18 (0.04)	1.57 (0.62)
Riboflavin	1.10 (0.00)	1.60 (0.49)	-	1.10 (0.00)	1.80 (0.63)	26.80 (0.63)	1.10 (0.00)	1.83 (0.73)
Niacin	16.00 (0.00)	35.58 (5.14)	-	16.00 (0.00)	40.88 (8.10)	60.88 (8.10)	16.00 (0.00)	36.17 (14.71)
Pantothenic	5.00 (0.00)	5.53 (1.22)	-	5.00 (0.00)	5.76 (1.53)	30.76 (1.53)	5.00 (0.00)	5.69 (2.27)
B_6	1.30 (0.00)	1.73 (0.57)	-	1.30 (0.00)	1.93 (0.45)	11.43 (0.45)	1.30 (0.00)	1.84 (0.63)
Biotin	30.00 (0.00)	41.77 (10.62)	-	30.00 (0.00)	36.24 (11.67)	486.24 (11.67)	30.00 (0.00)	34.21 (17.60)
Folate	400.00 (0.00)	239.56 (61.91)	-	400.00 (0.00)	246.25 (91.25)	646.25 (91.25)	400.00 (0.00)	239.90 (98.32)
B_{12}	2.40 (0.00)	5.06 (2.08)	-	2.40 (0.00)	5.34 (1.76)	125.34 (1.76)	2.40 (0.00)	5.08 (1.84)
Vitamin A	788.89 (105.41)	676.67 (259.11)	-	875.00 (70.71)	687.63 (502.71)	1487.63 (502.71)	860.00 (84.33)	804.80 (310.33)
Vitamin C	81.67 (7.91)	80.26 (48.95)	-	88.13 (5.30)	66.48 (33.70)	146.48 (33.70)	87.00 (6.32)	68.13 (50.99)
Vitamin D	15.00 (0.00)	3.24 (1.90)	-	15.00 (0.00)	2.74 (1.45)	12.74 (1.45)	15.00 (0.00)	2.45 (1.41)
Vitamin E	15.00 (0.00)	8.18 (3.03)	-	15.00 (0.00)	7.43 (3.29)	25.43 (3.29)	15.00 (0.00)	8.17 (3.62)
Vitamin K	103.33 (15.81)	70.13 (71.95)	-	116.25 (10.61)	36.66 (18.51)	116.66 (18.51)	114.00 (12.65)	58.77 (54.28)
Calcium	1000.00 (0.00)	790.44 (292.75)	-	1000.00 (0.00)	945.50 (239.80)	1105.50 (239.80)	1000.00 (0.00)	843.40 (250.22)
Iodine	150.00 (0.00)	142.22 (43.32)	-	150.00 (0.00)	140.75 (45.99)	-	150.00 (0.00)	130.56 (42.00)
Iron	13.56 (5.27)	9.14 (2.60)	-	9.25 (3.54)	9.75 (2.16)	13.95 (2.16)	10.00 (4.22)	10.70 (4.05)
Magnesium	364.44 (52.70)	268.33 (64.83)	-	407.50 (35.36)	220.70 (103.08)	277.70 (103.08)	400.00 (42.16)	261.50 (108.32)
Selenium	55.00 (0.00)	48.68 (13.73)	-	55.00 (0.00)	51.09 (14.64)	151.09 (14.64)	55.00 (0.00)	41.29 (16.78)
Zinc	9.33 (1.58)	7.54 (1.14)	-	10.63 (1.06)	9.58 (2.17)	19.58 (2.17)	10.40 (1.26)	8.84 (3.11)
Omega-3	1.32 (0.26)	1.11 (0.71)	2.01 (0.71)	1.48 (0.23)	0.99 (0.69)	-	1.50 (0.21)	1.29 (1.23)

One-sample t-tests for each group were conducted to analyses differences between intake and recommended daily intake amounts for each micronutrient (Table 7.9; Appendix E.4) with a corrected threshold of $p \leq .010$ to account for multiple comparisons. Results of these analyses found that overall dietary intake of many water-soluble vitamins (vitamin C and B vitamins) were either not significantly different or significantly above RDA amounts (range of p values; vitamin C, $p = .154 - p = .929$; thiamine, $p = .072 - p = .008$; riboflavin, $p = .012 - p = .015$; niacin, $p < .001 - p = .002$; biotin, $p = .010 - p = .469$; pantothenic acid, $p = .202 - p = .632$; B_6, $p = .006 - p = .051$; B_{12}, $p = .001 - p = .005$), only intake of folates were significantly below RDA amounts ($p < .001 - p = .002$). All groups had dietary intake of vitamin A similar to recommended daily intake ($p = .164 - p = .608$), however dietary intake of the other fat-soluble vitamins (D, E, K) was significantly below RDA amounts for all groups ($p < .001$) apart from vitamin K which was only significantly below RDA for group MO (group OM $p = .239$; Placebo $p = .017$), however it should be noted that intake of vitamin K in the Placebo group was close to significantly below RDA and would have reached significance level without the correction.

Analyses of essential mineral dietary intake found no significant differences to RDA amount for intake of calcium, iodine, iron and selenium in all groups, however dietary intake of magnesium was significantly below recommended intake. The findings for zinc intake mirrored that of thiamine with there being no significant difference between intake and RDA amounts apart from in group OM where the lower RDA for women may have resulted in this group having intake that was significantly below RDA. It should, however, be noted that dietary intake of zinc in this group (OM) was lower than the other two groups and may have been significantly below RDA with a mainly male group as recommended daily intake of zinc is different for males and females (11mg and 8mg respectively). Finally, dietary intake of omega-3 polyunsaturated fatty acids was not significantly different to recommended daily amounts across all groups. To represent this data more clearly these differences to RDA were converted to a percentage and are presented in Figure 7.2. It should be noted that for many of the micronutrients where intake was not statistically significantly different to RDA this intake was still below RDA levels.

Table 7.9

Analyses of difference between dietary intake of micronutrients and recommended daily amounts during the first intervention period.

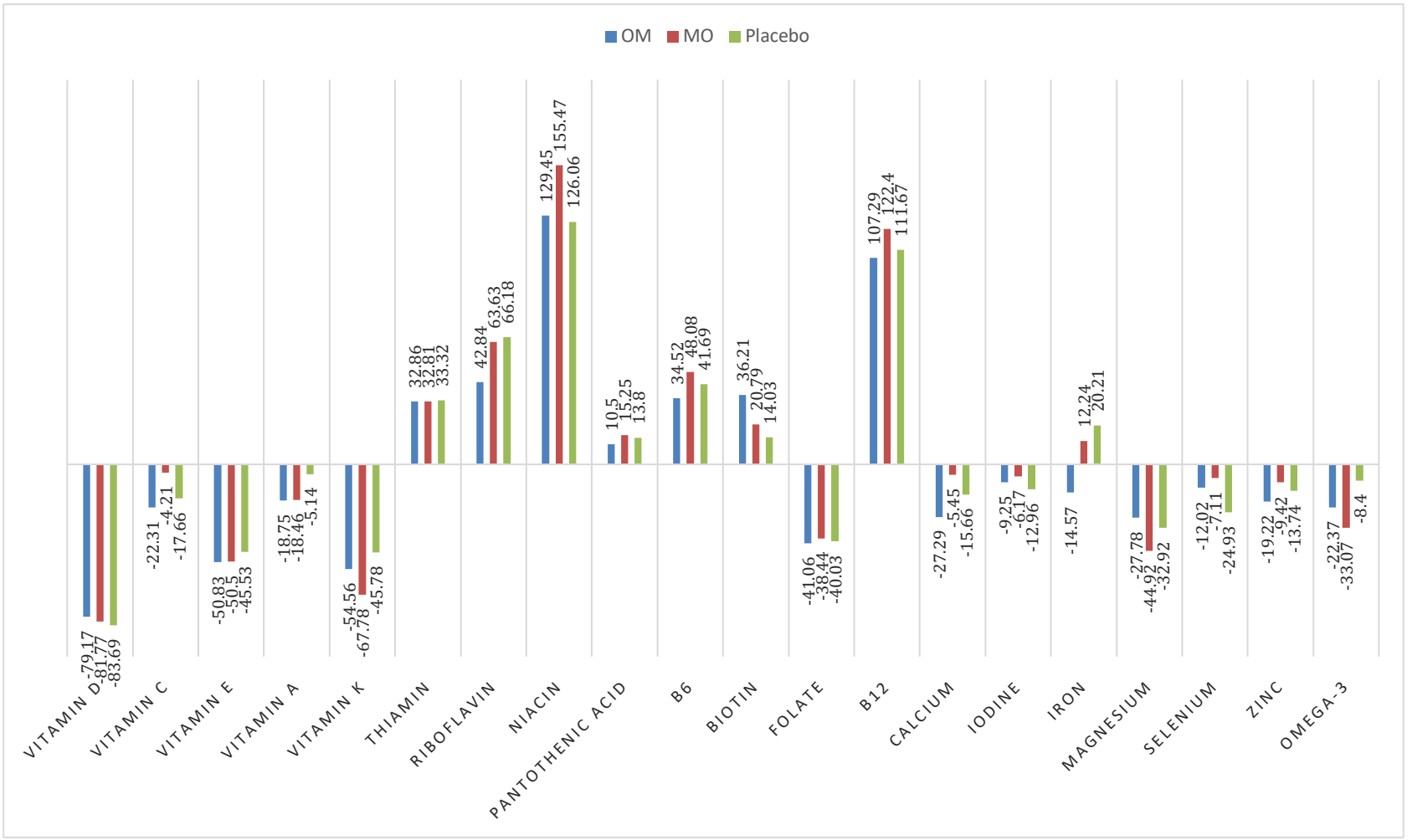
	Intervention OM			Intervention MO			Placebo		
Micronutrient	*t* (df = 8)	*p*	*d*	*t* (df = 7)	*p*	*d*	*t* (df = 9)	*p*	*d*
Thiamine	3.54	.008*	1.21	2.11	.072	0.74	1.94	.084	0.63
Riboflavin	3.07	.015	1.02	3.14	.016	1.11	3.16	.012	1.00
Niacin	11.43	<.001*	3.81	8.86	<.001*	3.07	4.34	.002*	1.37
Pantothenic Acid	1.32	.225	0.43	1.41	.202	0.50	0.96	.632	0.30
B_6	2.30	.051	0.75	3.93	.006*	1.40	2.74	.023*	0.86
Biotin	3.23	.010*	1.11	1.51	.174	0.54	4.21	.469	0.24
Folate	7.78	<.001*	2.59	4.77	.002*	1.69	5.15	.001*	1.63
B_{12}	3.83	.005*	1.28	4.72	.002*	1.67	4.61	.001*	1.46
Vitamin A	1.53	.164	0.51	0.98	.360	0.40	0.53	.608	0.18
Vitamin C	0.09	.929	0.03	1.60	.154	0.74	1.06	.318	0.41
Vitamin D	18.60	<.001*	6.19	23.94	<.001*	8.46	28.16	<.001*	8.90
Vitamin E	6.74	<.001*	2.24	6.52	<.001*	2.30	5.96	<.001*	1.89
Vitamin K	1.27	.239	0.48	9.58	<.001*	4.21	2.92	.017	1.08
Calcium	2.15	.064	0.72	0.64	.541	0.23	1.98	.079	0.63
Iodine	0.54	.605	0.18	0.57	.587	0.20	1.46	.177	0.46
Iron	2.08	.074	0.84	0.39	.710	0.14	0.36	.729	0.13
Magnesium	5.07	.001*	1.69	4.57	.003*	1.83	3.43	.007*	1.34
Selenium	1.38	.205	0.46	0.76	.474	0.27	2.58	.030	0.82
Zinc	3.38	.010*	1.13	1.37	.214	0.48	1.49	.171	0.47
Omega-3	0.86	.413	0.28	2.07	.078	0.74	0.52	.617	0.18

*$p \leq .01$

Figure 7.2 presents visual comparison of difference to RDA from dietary intake as a percentage for each group during the first intervention.

Figure 7.2

Percentage difference to RDA for each group from dietary intake alone during the first intervention period.



Results of MANOVAs following the intervention with average daily micronutrient intake taken from food diaries plus supplement as the independent variable and group as the dependent variable (Table 7.10; Appendix E.5) showed significant effects of intervention group on overall micronutrient intake (dietary intake plus intervention). As no iodine was present in any of the interventions it was not included in these analyses.

Table 7.10

Results of MANOVAs (Pillai's Trace) investigating differences between groups on overall micronutrient intake taken from food diaries plus intervention during the first intervention period.

Micronutrients	*F*	*df*	*p*	η_p^2
B Vitamins (B_1, B_2, B_3, B_5, B_6, B_7, B_9, B_{12})	2.83	16,36	.005	.56
Antioxidants and Fat-Soluble Vitamins (A,C, D, E, K)	4.31	10,42	<.001	.51
Minerals and Omega-3 (Calcium, Iron, Magnesium, Selenium, Zinc)	8.04	12,40	<.001	.71

Results of between group ANOVAs were significant at the <.050 level indicating a significant difference in intake between groups following the interventions, as was expected. The exceptions to this were vitamin K, $F(2, 24) = 2.75$, $p = .084$, $\eta_p^2 = 0.19$, magnesium, $F(2, 24) = 0.07$, $p = .937$, $\eta_p^2 = 0.01$, and omega-3, $F(2, 24) = 2.71$, $p = .087$, $\eta_p^2 = 0.18$. For vitamin K this lack of statistical difference between groups following the intervention is likely to be the result of the lower dietary intake of vitamin K from diet in group MO. Supplementation in this group therefore did not result in a significant difference when compared to dietary intake of group OM and Placebo group. For magnesium the level of supplementation (57mg) was small compared to the level of average dietary intake and therefore did not result in a significant difference between groups. This seems to be the same for omega-3 where the level of supplementation (0.90g) was lower than the RDA and this affected the level of significance between groups.

Further analyses using *post-hoc* independent samples *t*-tests (Appendix E.6) found no significant difference between group OM and the placebo group for omega-3 intake, $t(17) = 1.54$, $p = .142$, $d = 0.72$. Intervention group OM did however have a significantly higher intake of omega-3 ($m = 2.01$, $SD = 0.71$) than group MO ($m = 0.99$, $SD = 0.69$), $t(15) = 2.98$, $p = .009$, $d = 1.45$.

As group MO received the multimicronutrient intervention in this period they had significantly greater intake of those micronutrients compared with groups OM and Placebo with a number of exceptions; there were no significant differences in overall intake (diet plus intervention) of vitamin K ($t(15) = 1.77$, $p = .097$, $d = 0.89$) or magnesium ($t(15) = 0.23$, $p = .823$, $d = 0.11$) between group MO and group OM. Similarly, group MO had higher total intake of vitamins and minerals than the placebo group apart from magnesium ($t(16) = 0.32$, $p = .752$, $d = 0.15$) and iron ($t(16) = 2.04$, $p = .058$, $d = 1.00$). There was also no significant difference between group MO and the Placebo group on intake of omega-3 ($t(16) = 0.60$, $p = .555$, $d = 0.30$). Paired *t*- tests conducted to investigate whether the multimicronutrient intervention resulted in total intake above recommended daily amounts in group MO. The intervention resulted in intake significantly above RDA levels for all micronutrients except for from vitamins D, K and the minerals calcium and magnesium (Table 7.11). The omega-3 intervention resulted in total intake significantly above recommended daily intake levels in group OM.

Figure 7.11

t-tests with effects sizes investigating difference to RDA of intervention plus dietary intake in the first intervention period.

Micronutrient	Difference to RDA Diet + Supplement		
	t (*df* = 7)	*p*	*d*
Intervention MO			
Thiamine	136.36	<.001*	48.19
Riboflavin	115.35	<.001*	40.79
Niacin	15.66	<.001*	5.54
Pantothenic Acid	47.61	<.001*	16.84
B_6	63.70	<.001*	22.51
Biotin	110.60	<.001*	39.10
Folate	7.63	<.001*	2.70
B_{12}	197.50	<.001*	69.85
Vitamin A	3.21	.015*	0.51
Vitamin C	4.30	.004*	1.89
Vitamin D	4.42	.003*	1.56
Vitamin E	8.97	<.001*	3.17
Vitamin K	0.50	.962	0.02
Calcium	1.24	.253	0.44
Iron	3.64	.008*	1.29
Magnesium	3.18	.0168	1.52
Selenium	18.57	<.001*	6.56
Zinc	11.65	<.001*	4.11
Intervention OM	(*df* = 8)		
Omega-3	3.70	.008*	0.92

*$p \leq .050$

7.3.2. Summary of nutritional status during the second intervention period

All analyses investigating potential differences in average dietary intake to recommended daily intake amounts were calculated with differing recommended intake levels for males and females accounted for in calculations. Descriptive statistics of micronutrient intake can be found in Table 7.12.

One-sample t-tests conducted to analyse differences between average intake and recommended daily intake amounts for each micronutrient (with corrected *p* of .010 for multiple comparisons) followed a similar pattern to the first intervention period (Table 7.13, Appendix E.7). Dietary intake of vitamin C and many of the B vitamins were either not significantly different or significantly above RDA (vitamin C, thiamine, riboflavin, niacin, biotin, pantothenic acid, B_6, B_{12}), with intake of folates significantly below RDA. For fat-soluble vitamins all groups had dietary intake of vitamins D, E, and K significantly below RDA. Average vitamin A dietary intake was not significantly different to recommended intake for group OM and the Placebo group but was significantly below RDA in group MO, with a smaller variation in intake when compared with other groups.

Results of analyses of dietary intake of the essential minerals found slight differences to intake during the first intervention period. There was no significant difference to recommended intake of iodine or iron in all groups. Groups OM and MO had dietary magnesium intake significantly below recommended intake levels, with the Placebo group's intake close to significantly below (without the correction). Group OM and MO's intake of selenium was not significantly different to recommended intake, with intake in the Placebo group significantly below recommended levels for this mineral. The reverse finding was found for dietary intake of calcium, with intake similar to recommended levels in the placebo group but significantly below recommended levels in groups OM with intake in group MO significant without the correction. Zinc intake in group MO and the placebo group was not significantly different to recommended daily intake levels, however average intake was significantly below recommended levels in group OM. Finally, dietary intake of omega-3 polyunsaturated fatty acids was significantly below recommended daily intake levels in both group OM and MO, but not significantly different in the placebo group. These data were again converted to a percentage to allow for clearer visual comparison and are presented in Figure 7.3. What should also be considered is that no physiological measures of micronutrient levels were taken. This is particularly relevant when assessing vitamin D levels as the majority of vitamin D in the body is as the result of sun exposure rather than dietary intake (Pittas et al., 2010). As the research was conducted through a number of seasons in a double-blind

randomised sample then the effect of sun exposure on vitamin D levels could have been evened out in the sample, however without a physiological measure of serum vitamin D levels overall intake may have been underestimated by the metrics presented.

Table 7.12

Means and standard deviations of recommended daily amounts (RDA), dietary intake, and dietary intake plus supplementation for each group in the second intervention period.

	Intervention OM			Intervention MO			Placebo	
Micro-nutrient	RDA Mean (SD)	Dietary intake mean (SD)	Diet plus supplement mean (SD)	RDA Mean (SD)	Dietary intake mean (SD)	Diet plus supplement mean (SD)	RDA Mean (SD)	Dietary intake mean (SD)
Thiamine	1.15 (0.05)	1.31 (0.30)	26.31 (0.30)	1.19 (0.04)	1.22 (0.30)	-	1.18 (0.04)	1.46 (0.61)
Riboflavin	1.10 (0.00)	1.49 (0.36)	26.49 (0.36)	1.10 (0.00)	1.59 (0.43)	-	1.10 (0.00)	1.72 (0.68)
Niacin	16.00 (0.00)	34.03 (6.05)	54.03 (6.05)	16.00 (0.00)	32.82 (9.38)	-	16.00 (0.00)	32.85 (8.56)
B_5	5.00 (0.00)	4.85 (1.12)	29.85 (1.12)	5.00 (0.00)	4.70 (0.90)	-	5.00 (0.00)	5.62 (2.19)
B_6	1.30 (0.00)	1.43 (0.47)	10.93 (0.47)	1.30 (0.00)	1.64 (0.32)	-	1.30 (0.00)	1.59 (0.65)
Biotin	30.00 (0.00)	38.09 (13.19)	488.09 (13.19)	30.00 (0.00)	31.00 (12.57)	-	30.00 (0.00)	33.60 (18.06)
Folate	400.00 (0.00)	245.38 (111.55)	645.38 (111.55)	400.00 (0.00)	185.88 (39.42)	-	400.00 (0.00)	227.20 (111.46)
B_{12}	2.40 (0.00)	4.11 (1.31)	124.11 (1.31)	2.40 (0.00)	5.03 (2.09)	-	2.40 (0.00)	4.16 (1.77)
Vitamin A	875.00 (106.90)	654.88 (393.74)	1454.88 (393.74)	875.00 (70.71)	582.00 (180.27)	-	860.00 (84.33)	719.00 (426.92)
Vitamin C	82.50 (8.02)	74.96 (46.04)	154.96 (46.04)	88.13 (5.30)	63.60 (59.14)	-	87.00 (6.32)	88.39 (73.44)
Vitamin D	15.00 (0.00)	2.14 (0.53)	12.14 (0.53)	15.00 (0.00)	1.95 (1.14)	-	15.00 (0.00)	1.92 (0.71)
Vitamin E	15.00 (0.00)	8.58 (3.91)	26.58 (3.91)	15.00 (0.00)	6.79 (1.97)	-	15.00 (0.00)	6.74 (1.86)
Vitamin K	105. 00 (16.04)	33.51 (30.45)	113.51 (30.45)	116.25 (10.61)	33.98 (33.09)	-	114.00 (12.65)	57.66 (90.81)
Calcium	1000.00 (0.00)	733.38 (161.60)	893.40 (161.60)	1000.00 (0.00)	754.38 (281.80)	-	1000.00 (0.00)	827.40 (321.63)
Iodine	150.00 (0.00)	112.25 (66.70)	-	150.00 (0.00)	103.41 (56.47)	-	150.00 (0.00)	104.98 (50.09)
Iron	13.00 (5.35)	9.51 (2.20)	13.71 (2.20)	9.25 (3.53)	9.31 (2.50)	-	10.00 (4.21)	9.98 (4.56)
Magnesium	370.00 (53.45)	260.00 (89.80)	317.00 (89.80)	407.50 (35.35)	230.63 (61.30)	-	400.00 (42.16)	269.00 (116.95)
Selenium	55.00 (0.00)	45.60 (13.04)	145.60 (13.04)	55.0 (0.00)	43.00 (14.96)	-	55.00 (0.00)	33.58 (10.46)
Zinc	9.50 (1.60)	7.59 (1.77)	17.59 (1.77)	10.63 (1.06)	8.96 (3.24)	-	10.40 (1.26)	8.18 (3.05)
Omega-3	1.35 (0.27)	0.73 (0.33)	-	1.48 (0.23)	0.74 (0.46)	1.48 (0.46)	1.50 (0.21)	0.94 (0.99)

Table 7.13

Analyses of difference between dietary intake of micronutrients and recommended daily amounts during the second intervention period.

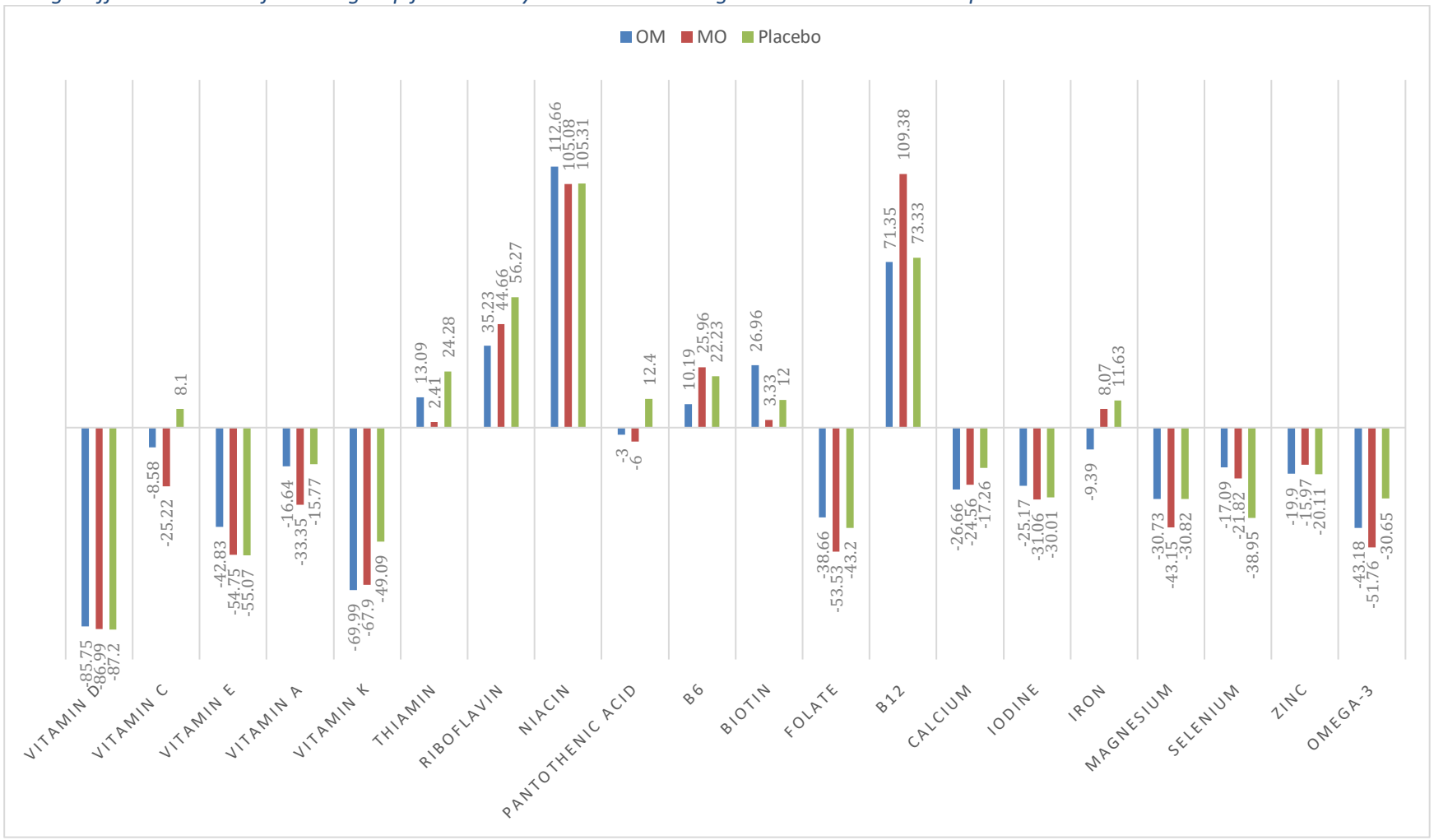
	Intervention OM			Intervention MO			Placebo		
Micronutrient	*t* (df = 7)	*p*	*d*	*t* (df = 7)	*p*	*d*	*t* (df = 9)	*p*	*d*
Thiamine	1.69	.135	0.61	0.31	.765	0.11	1.46	.178	0.46
Riboflavin	3.08	.018	1.08	3.21	.015	1.14	2.86	.019	0.91
Niacin	8.43	.002*	2.98	5.07	.001*	1.79	6.22	<.001*	1.97
Pantothenic Acid	0.38	.715	0.13	0.94	.378	0.33	0.89	.396	0.28
B_6	0.79	.454	0.28	2.94	.022	1.06	1.41	.193	0.45
Biotin	1.73	.126	0.61	0.23	.828	0.08	0.63	.544	0.20
Folate	3.92	.006*	1.39	15.36	<.001*	5.43	4.90	.001*	1.55
B_{12}	3.70	.008*	1.31	3.56	.009*	1.26	3.16	.012	0.99
Vitamin A	1.00	.352	0.36	4.57	.003*	1.62	1.03	.329	0.33
Vitamin C	0.46	.660	0.16	1.11	.302	0.44	0.06	.957	0.42
Vitamin D	68.08	<.001*	24.26	32.23	<.001*	11.45	57.88	<.001*	18.42
Vitamin E	4.64	.002*	1.64	11.79	<.001*	4.17	14.02	<.001*	4.44
Vitamin K	8.63	<.001*	3.05	5.41	.001*	3.46	1.95	.083	0.62
Calcium	4.67	.002*	1.65	2.47	.043	0.87	1.70	.124	0.54
Iodine	1.60	.153	0.57	2.33	.052	0.83	2.84	.019	0.90
Iron	1.41	.201	0.83	0.04	.968	0.01	0.01	.992	<0.01
Magnesium	5.02	.002*	1.78	7.58	<.001*	2.68	3.02	.015	1.19
Selenium	2.04	.081	0.72	2.27	.058	0.80	6.48	<.001*	2.05
Zinc	3.77	.007*	1.33	1.56	.163	0.55	2.14	.061	0.68
Omega-3	3.70	.008*	1.70	5.74	.001*	2.03	1.60	.144	0.62

*$p \leq .01$

The following figure (7.3) presents visual comparison of difference to RDA from dietary intake as a percentage for each group during the second intervention.

Figure 7.3

Percentage difference to RDA for each group from dietary intake alone during the second intervention period.



Results of MANOVAs following the intervention (Table 7.14) showed significant effects of intervention group on overall micronutrient intake (dietary intake plus intervention). Pillai's Trace was again reported as the most conservative criterion. Iodine was not included in these analyses as there was no iodine included in any of the interventions.

Table 7.14

MANOVAs investigating differences between groups on overall micronutrient intake taken from food diaries plus intervention during the second intervention period.

Micronutrients	*F*	*df*	*p*	η_p^2
B Vitamins (B_1, B_2, B_3, B_5, B_6, B_7, B_9, B_{12})	6.31	16,34	<.001	.75
Antioxidants and Fat-Soluble Vitamins (A,C, D, E, K)	4.54	10,40	<.001	.53
Minerals and Omega-3 (Calcium, Iron, Magnesium, Selenium, Zinc)	7.69	12,38	<.001	.71

Results of between group ANOVAs were significant at the <.050 level, indicating a significant difference in intake between groups following the interventions as was expected (Appendix E.5). The exceptions to this were calcium, $F(2, 23) = 0.53$, $p = .594$, $\eta_p^2 = 0.04$, and magnesium, $F(2, 23) = 1.68$, $p = .207$, $\eta_p^2 = 0.13$. Calcium intake from diet in group OM was lower than dietary intake in the other two groups. When the level of calcium present in the intervention given to group OM in this period was factored into the analyses this did not result in group OM having a significantly greater intake than the other two groups. For magnesium the results reflected those reported for the first intervention period; the level of supplementation (57mg) was small compared to the level of average dietary intake and therefore did not result in a significant difference between groups.

Results of *post-hoc* independent samples *t*-tests (Appendix E.9) found significant differences between group OM, given the multimicronutrient intervention, and the other groups for all vitamins and minerals except for calcium and magnesium. There were no significant differences in intake plus supplement of calcium between groups OM and MO, $t(14) = 1.21$, $p = .246$, $d = 0.61$, and group OM and placebo, $t(14) = 0.53$, $p = .605$, $d = 0.26$. There was also no difference in total intake (diet plus supplement) of magnesium between group OM and the placebo group, $t(14) = 0.96$, $p = .354$, $d = 0.46$. The only other micronutrient where significant differences were found was for intake of omega-3.

Group MO received omega-3 as the intervention in this period had significantly higher intake (m = 1.64, SD = 0.46), than group OM (m = 0.73, SD = 0.33), $t(14) = 4.60$, $p <$ .001, $d = 2.30$, but not significantly higher than the Placebo group (m = 0.94, SD = 0.99), $t(16) = 1.85$, p .083, $d = 0.91$. There were no other significant differences between groups. Results of paired t-tests conducted to investigate whether the interventions resulted in total intake above recommended daily amounts in group OM found significant differences for all micronutrients apart from vitamin D, vitamin K, and calcium. The omega-3 intervention in group MO resulted in participants in that group having an average total intake 10.88% above recommended amounts, although this did not reach statistical significance (Table 7.15).

Table 7.15

t-tests with effects sizes investigating difference to RDA of intervention plus dietary intake in the second intervention period

Micronutrient	Difference to RDA Diet + Supplement		
	t (df = 7)	p	d
Intervention OM			
Thiamine	269.90	<.001*	70.78
Riboflavin	201.52	<.001*	70.53
Niacin	17.79	<.001*	6.29
Pantothenic Acid	62.90	<.001*	22.19
B_6	57.59	<.001*	20.49
Biotin	118.73	<.001*	41.97
Folate	6.22	<.001*	2.20
B_{12}	262.62	<.001*	92.91
Vitamin A	4.50	.003*	1.62
Vitamin C	4.42	.003*	1.56
Vitamin D	15.15	<.001*	5.40
Vitamin E	8.37	<.001*	2.96
Vitamin K	1.03	.338	0.36
Calcium	1.87	.104	0.66
Iron	0.29	.782	0.17
Magnesium	2.42	.046*	0.86
Selenium	19.66	<.001*	6.95
Zinc	15.96	<.001*	5.64
Intervention MO	(df = 7)		
Omega-3	1.29	.238	0.44

*$p < .050$

Overall findings from food diary analyses were very similar over the two intervention periods. These findings indicate that individuals' dietary intake maintained a consistent pattern with few variations over the course of this study. Some slight differences in diet over time was expected, particularly in a population where variations in feelings of wellbeing affected appetite (as evidenced in food diaries). In addition, participants did not weigh food portions which may also have resulted in some variability. Participants had dietary intake not significantly different to recommended daily amount for most of the water-soluble vitamins (vitamin C and B vitamins) with intakes of folate

the notable exception. Analyses of fat-soluble vitamin intake showed that participants had insufficient levels of vitamins D and E, with average intake levels of vitamin K varying from adequate to insufficient across the two intervention periods. Magnesium was the only mineral that participants consistently had intake significantly below recommended levels. Intake levels of the other minerals fluctuating in relation to recommended levels but were consistently low even when not significantly different to recommended amounts. Intake of omega-3 was consistently low over the two intervention periods, however the extent to which intake was statistically significantly below RDI varied. The interventions resulted in a significant difference in overall intake of micronutrients with very few exceptions; vitamin K, magnesium and iron during intervention period 1, and calcium and magnesium during intervention period 2, this lack of significant increase reflecting either the low levels of supplement or differences in dietary intake.

7.4 Summary of cognitive task performance findings

Cognitive data were analysed separately for each group as total intake of micronutrients from diet and supplements meant that groups were nutritionally distinct. Analyses of cognitive task performance was conducted in line with the methodology described by Jones and Kenward (1996). These analyses tested whether carryover effects were equal for all groups, whether there was an effect of intervention, and whether there was an effect of when the intervention was taken (period 1 or period 2). As this study will be used to form hypotheses for future research investigating micronutrient interventions in TBI no corrections for multiple testing were applied so that potentially useful findings and avenues for future research were not discarded because of possible type II errors (Perneger, 1998; Rothman, 1990; Streiner& Norman, 2011).

7.4.1 Analyses of carry over effects

Assessment of the effect of treatment can only be conducted if carry over effects are equal. If there is differing carry over effect from intervention one to intervention two, effects of treatment may potentially be the result of this carry over (Jones & Kenwood, 1996). To test whether carry over effects of interventions were equal for all groups the sum of cognitive test scores from follow up test points one and two were calculated for each variable. Independent t-tests were then conducted with group as the independent variable and total behavioural test measure score as dependent variables (Appendix E.9). To ensure that any skew in the data did not have an effect on findings, both non-parametric Mann-Whitney and parametric independent *t*-tests were conducted. Results from these analyses were consistent and did not produce diverge interpretations (see

Appendix E.10). Results of these analyses showed no significant carryover effects for any of the groups from intervention 1 to intervention 2 for any behavioural test measure, with the highest *p* value .057 when comparing Group OM with Group MO on Digit Span, therefore further analyses investigating treatment effects are valid.

7.4.2 Analyses of treatment effects.

Differing interventions resulted in groups being nutritionally distinct at each follow up test point as intended. Comparison of each group's cognitive test performance from baseline testing to follow up one, and then follow up one to follow up two were therefore conducted using paired *t*-tests. T-tests were bootstrapped using 2000 samples (sampling with replacement) with bias corrected and accelerated confidence intervals (Efrom & Tibshirani, 1993). Use of bootstrapping in clinical samples provides a more robust estimate of the properties of the sampling distribution from the sample data given that sample sizes are often smaller with non-normal distribution in these populations (Wright, London & Field, 2011). Full outputs of analyses along with paired *t*-tests without bootstrapping and non-parametric equivalents (for comparison) can be found in Appendices E.11-14.

7.4.2.1 Group OM Intervention 1 (Omega-3)

Results of cognitive task performance in Group OM following the omega-3 intervention are presented in Tables 7.16 and 7.17. Analyses of performance on memory tasks (Table 7.16) showed no significant change in performance on any of the memory measures between baseline and first follow-up testing for group OM when taking the omega-3 intervention. Of note is that although the overall significance value for immediate verbal recall of orally presented word pairs (WMS Verbal Paired Associates) is above the two-tailed $p \leq .05$ threshold the effect size is moderate with a confidence interval that does not straddle 0. The confidence interval suggests the improvement is a consistent and stable effect. A similar finding was also seen for the delayed recall condition of this task; the p value is not significant; however, the effect size is moderate with confidence interval upper and lower limits that do not straddle 0.

Table 7.16

Bootstrapped paired t-tests analysing differences in memory performance between baseline and first follow-up in group OM after taking the omega-3 supplement

Measure/Function	Baseline mean (SD)	Time 1 mean (SD)	*t* (8)	*p*	*d*	BCa 95% CI LL	BCa 95% CI UL
Memory:							
WAIS-IV Digit Span							
Overall Score	7.56 (2.46)	8.33 (3.08)	1.21	.283	.20	-2.11	0.44
WMS-IV Verbal Paired Associates (Verbal Memory)							
Immediate Recall	8.22 (1.56)	10.33 (3.00)	2.27	.078	**.61**	**-4.00**	**-0.44**
Delayed Recall	8.00 (2.55)	10.11 (4.01)	1.85	.133	.58	**-4.00**	**-0.11**
Doors (Visual Recognition)	8.22 (3.80)	9.89 (5.04)	1.70	.144	.54	-3.56	0.11
Rey-Osterrieth Complex Figure (Visual Memory)							
Copy (perceptual organisation)	35.22 (0.83)	34.78 (1.30)	1.41	.197	.43	-0.11	1.11
Immediate Recall	23.72 (5.47)	24.50 (6.54)	1.57	.197	.50	-1.87	0.17
Delayed Recall	22.94 (6.78)	23.50 (6.97)	0.65	.547	.21	-2.61	1.28

Note: BCa = Bias-corrected and accelerated. CI = confidence interval. LL = lower limit. UL = Upper limit.
Note: *p* values significant to ≤.05 in **bold.**
Note: effect size > 0.60 in **bold**
Note: confidence interval does not straddle 0 in **bold**

No significant changes were seen when looking at executive function components of the DKEFS Trail Making or Verbal Fluency tasks, however the Visual Scanning condition of the Trail Making task had confidence intervals with upper and lower limits that were both negative and moderate effect size (Table 7.17). There was a significant improvement in speed of completion of the Colour Word Naming and Reading conditions of the DKEFS Colour Word Inhibition task. Performance on the Inhibition and Inhibition Switching conditions of this task showed moderate effect sizes with confidence intervals suggesting the improvement was consistent and stable despite a not significant *p* value.

Processing speed, as measured by the WAIS-IV Symbol Search task (Table 7.17), was significantly improved in group OM following the omega-3 intervention There was also a significant improvement in explicit awareness of the presented pattern sequence on the Serial Reaction Time task with a large associated effect size. There was no change in participants' self-reported ability to complete extended activities of daily living (NEADL) or subjective feeling of negative affect (PANAS). Improvement in positive affect was close to significance with a large effect size with confidence interval upper and lower limits both negative, indicating this change in positive mood state would be mirrored in the population.

Table 7.17

Bootstrapped paired t-tests analysing differences in executive function, processing speed, learning, activities of daily living, affect and social cognition scores between baseline and first follow-up in group OM following the omega-3 supplement

Measure/Function	Baseline mean (SD)	Time 1 mean (SD)	*t* (8)	*p*	*d*	BCa 95% CI LL	BCa 95% CI UL
Executive Function (DKEFS)							
Trail Making							
Visual Scanning	7.44 (4.61)	9.00 (5.07)	1.84	.232	.57	**-4.00**	**-0.11**
Number Sequencing	9.67 (4.24)	9.00 (5.22)	0.80	.486	.25	-0.56	2.33
Letter Sequencing	8.89 (4.62)	10.67 (4.74)	0.42	.382	.45	-4.78	0.22
Number/Letter Switching	10.44 (3.12)	10.67 (3.20)	0.73	.499	.24	-0.67	0.22
Motor Speed	9.00 (4.06)	9.33 (4.27)	0.68	.535	.21	-1.33	0.78
Verbal Fluency							
Phonemic Fluency	9.56 (2.65)	9.78 (3.35)	0.28	.793	.09	-1.44	1.11
Semantic Fluency	10.33 (3.43)	10.56 (2.79)	0.10	.932	.03	-3.89	3.56
Semantic Switching	11.33 (1.00)	10.56 (2.79)	0.87	.453	.28	-0.56	2.11
Colour Word Interference							
Naming	7.56 (4.16)	8.11 (4.43)	3.83	**.008**	**1.22**	**-0.88**	**-0.38**
Reading	7.89 (4.28)	8.78 (4.63)	4.05	**.002**	**1.32**	**-1.25**	**-0.75**
Inhibition	8.75 (4.03)	10.63 (4.31)	1.61	.245	.55	**-4.38**	**0.00**
Inhibition Switching	8.38 (4.69)	10.50 (4.04)	1.65	.345	.57	**-4.75**	**-0.38**
Processing Speed							
WAIS-IV Symbol Search Correct	9.00 (1.73)	10.11 (3.89)	4.67	**.004**	**1.66**	**-3.14**	**-1.14**
Learning:							
SRT Explicit Learning	3.36 (3.06)	7.03 (3.85)	3.00	**.042**	**1.04**	**-5.63**	**-1.89**
SRT Implicit Learning	34.51 (44.69)	38.90 (48.50)	0.16	.906	.09	-49.10	41.99
Activities of Daily Living							
NEADL	50.17 (12.82)	50.11 (14.50)	0.02	.986	<.01	-4.67	5.80
Affect:							
PANAS Positive Affect	28.22 (8.87)	33.44 (7.09)	2.35	.059	**.74**	**-9.91**	**-1.00**
PANAS Negative Affect	24.00 (10.56)	20.56 (10.33)	0.83	.488	.27	-3.78	12.93
Social Cognition:							
Reading the Mind in the Eyes	24.67 (3.94)	22.78 (5.43)	1.73	.137	.54	-0.22	4.00

Note: BCa = Bias-corrected and accelerated. CI = confidence interval. LL = lower limit. UL = Upper limit.
Note: *p* values significant to <.050 in **bold.**
Note: effect size > 0.60 in **bold**
Note: confidence interval does not straddle 0 in **bold**

7.4.2.2 Group OM Intervention 2 (Multimicronutrient)

Results of cognitive task performance in Group OM following the multimicronutrient intervention are presented in Tables 7.18 and 7.19. Analyses of performance on memory tasks (Table 7.18) showed no significant change in performance

between first and second follow-up test points on any of the assessed memory tasks for this group. Effect sizes were all small with confidence intervals that straddled 0.

Table 7.18

Bootstrapped paired t-tests analysing differences in measures of memory performance between first and second follow-up in group OM following the multimicronutrient supplement

Measure/Function	Follow-up 1 mean (SD)	Follow-up 2 mean (SD)	*t* (8)	*p*	*d*	BCa 95% CI LL	UL
Memory:							
WAIS-IV Digit Span							
Overall Score	8.33 (3.08)	8.44 (3.43)	0.22	.854	.07	-1.11	0.89
WMS-IV Verbal Paired Associates (Verbal Memory)							
Immediate Recall	10.33 (3.00)	10.11 (3.26)	0.28	.810	.09	-1.56	1.78
Delayed Recall	10.11 (4.01)	9.44 (3.47)	0.94	.382	.32	-0.67	2.11
Doors (Visual Recognition)	9.89 (5.04)	10.11 (5.80)	0.68	.751	.11	-1.44	0.89
Rey-Osterreith Complex Figure (Visual Memory)							
Copy (perceptual organisation)	34.78 (1.30)	34.78 (1.20)	0.00	1.00	<.01	-0.89	0.89
Immediate Recall	24.50 (6.54)	23.33 (7.34)	0.84	.462	.26	-1.72	3.98
Delayed Recall	23.50 (6.97)	24.56 (6.86)	0.72	.530	.23	-4.17	1.89

Note: BCa = Bias-corrected and accelerated. CI = confidence interval. LL = lower limit. UL = Upper limit.

Results of analyses of cognitive task performance on measures of executive function, processing speed, explicit and implicit learning, and social cognition found no significant changes after the multimicronutrient intervention (Table 7.19). There were also no significant differences in reported ability to complete extended activities of daily living (NEADL). Self-reported feelings of positive and negative affect (PANAS) did not reach significance at the .050 level, however effect sizes for these measures were moderate to large with confidence interval upper and lower limits that did not straddle 0. It should be noted that the changes in affect were not in the direction that would be expected, with reductions in ratings of positive affect and increased ratings of negative affect.

Table 7.19

Bootstrapped paired t-tests analysing differences in scores of executive function, processing speed, learning, activities of daily living, affect and social cognition between first and second follow-up in group OM following the multimicronutrient supplement

Measure/Function	Follow-up 1 mean (SD)	Follow-up 2 mean (SD)	*t* (8)	*p*	*d*	BCa 95% CI LL	UL
Executive Function (DKEFS)							
Trail Making							
Visual Scanning	9.00 (5.07)	9.22 (4.89)	0.58	.572	.19	-0.89	0.33
Number Sequencing	9.00 (5.52)	9.78 (4.82)	0.85	.476	.27	-2.56	0.78
Letter Sequencing	10.67 (4.74)	11.11 (4.04)	0.54	.637	.17	-2.36	1.14
Number/Letter Switching	10.67 (3.20)	10.67 (3.20)	0.00	1.00	<.01	-0.44	0.56
Motor Speed	9.33 (4.27)	9.89 (4.37)	1.41	.223	.45	-1.22	0.11
Verbal Fluency							
Phonemic Fluency	9.78 (3.35)	9.56 (3.40)	0.32	.763	.10	-1.22	1.55
Semantic Fluency	10.56 (6.35)	10.33 (5.20)	0.23	.824	.08	-2.00	2.44
Semantic Switching	10.56 (2.79)	10.11 (3.37)	0.81	.490	.26	-0.56	1.56
Colour Word Interference							
Naming	9.00 (3.78)	8.75 (3.73)	0.75	.486	.24	-0.25	0.75
Reading	9.75 (3.85)	9.00 (3.93)	1.73	.309	.54	0.25	1.38
Inhibition	10.63 (4.31)	10.63 (4.17)	0.00	1.00	<.01	-0.38	0.38
Inhibition Switching	10.50 (4.04)	10.38 (4.44)	0.24	.821	.08	-0.88	1.13
Processing Speed							
WAIS-IV Symbol Search Correct	10.11 (3.89)	10.33 (4.50)	0.55	.608	.19	-1.28	0.71
Learning:							
SRT Explicit Learning	7.03 (3.85)	6.57 (5.16)	0.26	.896	.09	-4.20	4.71
SRT Implicit Learning	38.90 (48.50)	44.16 (36.87)	0.31	.775	.11	-35.70	22.12
Activities of Daily Living							
NEADL	50.11 (14.50)	53.11 (9.91)	0.96	.383	.30	-11.00	3.89
Affect:							
PANAS Positive Affect	33.44 (7.09)	28.22 (6.74)	2.08	.103	**.69**	**0.67**	**10.33**
PANAS Negative Affect	20.56 (10.33)	25.11 (8.65)	2.06	.117	**.64**	**-9.11**	**-0.31**
Social Cognition:							
Reading the Mind in the Eyes	22.78 (5.43)	23.22 (5.76)	0.49	.630	.16	-2.33	1.00

Note: BCa = Bias-corrected and accelerated. CI = confidence interval. LL = lower limit. UL = Upper limit.
Note: *p* values significant to <.050 in **bold.**
Note: effect size > 0.60 in **bold**
Note: confidence interval does not straddle 0 in **bold**

7.4.2.3 Group MO Intervention 1 (Multimicronutrient)

Results of cognitive task performance in Group MO following the multimicronutrient intervention are presented in Tables 7.20 and 7.21. Analyses of cognitive performance on memory measures in this group found a significant improvement on immediate verbal memory as measured by WMS Verbal Paired Associates (Table 7.20). Improvements in delayed verbal memory on the same task were approaching significance with a similar effect size and confidence intervals with negative upper and lower limits. Delayed recall of a visually presented stimulus (Rey Osterreith

Complex Figure) followed the same pattern of findings, suggesting that improvements in delayed visual and verbal recall is a consistent and stable effect that would be seen in TBI populations after this intervention. There was no significant improvement in working memory (Digit Span) and confidence interval upper and lower limits were either side of the 0 mark.

Table 7.20

Bootstrapped paired t-tests analysing differences in memory performance between baseline and first follow-up in group MO after the multimicronutrient supplement

Measure/Function	Baseline mean (SD)	Time 1 mean (SD)	*t* (8)	*p*	*d*	BCa 95% CI LL	BCa 95% CI UL
Memory:							
WAIS-IV Digit Span							
Overall Score	10.22 (2.73)	11.00 (2.69)	1.99	.098	**.60**	-1.67	0.11
WMS-IV Verbal Paired Associates (verbal memory)							
Immediate Recall	8.78 (3.35)	10.44 (4.03)	2.95	**.026**	**.89**	**-2.78**	**-0.56**
Delayed Recall	8.89 (4.04)	10.67 (4.03)	2.43	.053	**.76**	**-3.44**	**-0.22**
Doors (visual recognition)	9.78 (2.99)	10.67 (4.36)	1.13	.335	.35	-2.56	0.67
Rey-Osterreith Complex Figure (visual memory)							
Copy (perceptual organisation)	34.56 (1.59)	34.39 (2.23)	0.20	.837	.06	-1.33	1.56
Immediate Recall	24.56 (5.80)	25.67 (9.51)	0.72	.507	.22	-4.33	2.42
Delayed Recall	22.72 (7.74)	25.72 (9.15)	2.00	.112	**.62**	**-6.71**	**-0.28**

Note: BCa = Bias-corrected and accelerated. CI = confidence interval. LL = lower limit. UL = Upper limit.
Note: *p* values significant to <.050 in **bold.**
Note: effect size > 0.60 in **bold**
Note: confidence interval does not straddle 0 in **bold**

Results of analyses of performance on executive function tasks showed a significant improvement in speed of Number Sequencing (measuring response inhibition and processing speed) subtest of the DKEFS Trail Making task with an improvement close to significance on the Number/Letter Switching (set shifting) condition (Table 7.20). The effect size for the Number/Letter Switching condition was large with a confidence interval limits that were both negative values, however this change reflected an average reduction in speed of completion of the task. There was also a significant change on the Switching condition of the Verbal Fluency task, but this change again related to an average reduction in number of words generated when switching between semantic categories. There were no significant findings on the Colour Word Inhibition task of the DKEFS, however the effect size for the Inhibition condition of the task was large with a confidence interval that did not straddle 0 indicating that the improvement found for this measure is reliable.

An improvement in processing speed (WAIS-IV Symbol Search) was found following the multimicronutrient intervention in group MO, however this improvement did not reach a significant level despite a large associated effect size and confidence interval that did not straddle 0. The larger variability in scores across the group at first follow-up compared to baseline on this measure may have had an effect on this statistic. There were no significant findings on measures of learning, activities of daily living, affect or social cognition (Table 7.21). There was a large effect size in the improvement in implicit learning for the Serial Reaction Time (SRT) task, however the confidence interval straddled 0 indicating that this change in reaction time is not a reliable effect.

Table 7.21

Bootstrapped paired t-tests analysing differences in performance on measures of executive function, processing speed, learning, activities of daily living, affect and social cognition between baseline and 1st follow-up in group MO following the multimicronutrient supplement

Measure/Function	Baseline mean (SD)	Time 1 mean (SD)	*t* (8)	*p*	*d*	BCa 95% CI LL	BCa 95% CI UL
Executive Function (DKEFS)							
Trail Making							
Visual Scanning	9.56 (2.83)	10.56 (2.96)	1.19	.298	.38	-3.11	0.78
Number Sequencing	9.44 (2.74)	12.33 (2.06)	4.29	**.003**	**1.35**	**-4.44**	**-1.44**
Letter Sequencing	10.67 (2.74)	11.00 (3.12)	0.46	.677	.14	-1.56	1.33
Number/Letter Switching	10.33 (2.96)	11.22 (2.77)	2.43	.052	**.76**	**-1.67**	**-0.11**
Motor Speed	11.33 (1.50)	12.11 (0.93)	1.35	.302	.45	-2.00	0.11
Verbal Fluency							
Phonemic Fluency	11.67 (4.61)	12.11 (5.37)	0.64	.543	.20	-1.89	1.00
Semantic Fluency	11.33 (4.35)	11.67 (5.07)	0.32	.762	.11	-2.56	2.00
Semantic Switching	10.89 (3.62)	9.33 (3.54)	2.68	**.047**	**.86**	**0.44**	**2.67**
Colour Word Interference							
Naming	8.44 (2.29)	10.11 (2.93)	1.87	.342	.59	**-3.56**	**-0.44**
Reading	10.00 (2.18)	10.44 (2.13)	0.52	.627	.16	-2.33	1.00
Inhibition	9.44 (3.24)	11.78 (1.56)	2.12	.103	**.66**	**-4.56**	**-0.44**
Inhibition Switching	9.56 (4.10)	11.44 (2.46)	1.38	.380	.42	-5.00	0.11
Processing Speed							
WAIS-IV Symbol Search Correct	8.89 (1.62)	11.00 (3.24)	2.42	.061	**.75**	**-3.67**	**-0.78**
Learning:							
SRT Explicit Learning	7.33 (4.92)	8.83 (5.32)	0.78	.470	.18	-5.50	3.33
SRT Implicit Learning	76.57 (90.43)	21.76 (79.37)	1.14	.318	**.70**	-28.78	153.21
Activities of Daily Living							
NEADL	53.67 (7.21)	52.67 (9.91)	0.34	.752	.11	-4.45	7.33
Affect:							
PANAS Positive Affect	28.67 (11.91)	32.11 (10.84)	1.19	.304	.37	-10.67	2.31
PANAS Negative Affect	20.89 (7.24)	23.72 (9.33)	1.80	.128	.56	-5.56	0.00
Social Cognition:							
Reading the Mind in the Eyes	23.22 (4.27)	24.22 (5.70)	0.75	.474	.24	-3.56	1.67

Note: BCa = Bias-corrected and accelerated. Note: *p* values significant to <.050 in **bold.**
Note: effect size > 0.60 in **bold.** Note: confidence interval does not straddle 0 in **bold**

7.4.2.4 Group MO Intervention 2 (Omega-3)

Results of *t*-tests after participants in group MO had taken the omega-3 supplement are presented in Tables 7.22 and 7.23. On assessed measures of memory performance group MO showed a significant improvement in immediate verbal memory as measured by the WMS-IV Verbal Paired Associates (Table 7.22), there was no significant improvement on the delayed condition of this task. There was a significant improvement in delayed recall of a complex figure (Rey-Osterreith), however there was no significant change in immediate recall of this figure. There was an improvement in visual recognition of previously presented stimuli ('Doors' task from Doors and People) that showed a moderate effect size with a confidence interval that did not straddle 0. This suggests that this improvement is stable and consistent, despite the lack of significant *p* value.

Table 7.22

Bootstrapped paired t-tests analysing differences in memory performance between first and second follow-up in group MO after taking the omega-3 supplement

Measure/Function	Follow-up 1 mean (SD)	Follow-up 2 mean (SD)	*t* (8)	*p*	*d*	BCa 95% CI LL	BCa 95% CI UL
Memory:							
WAIS-IV Digit Span							
Overall Score	11.00 (2.69)	11.56 (3.09)	1.19	.329	.32	-1.44	0.22
WMS-IV Verbal Paired Associates (verbal memory)							
Immediate Recall	10.44 (4.03)	12.00 (3.64)	5.67	**.001**	**1.78**	**-2.11**	**-1.00**
Delayed Recall	10.67 (4.03)	11.44 (3.17)	1.52	.183	.48	-1.89	0.33
Doors (visual recognition)	10.38 (4.57)	11.75 (4.71)	1.88	.123	**.62**	**-2.75**	**0.00**
Rey-Osterreith Complex Figure (visual memory)							
Copy (perceptual organisation)	34.39 (2.23)	34.67 (1.73)	0.40	.728	.13	-2.33	1.11
Immediate Recall	25.67 (9.51)	27.83 (5.90)	1.27	.266	.40	-5.90	1.12
Delayed Recall	25.72 (9.15)	28.94 (6.15)	2.57	**.048**	**.81**	**-5.89**	**-0.67**

Note: BCa = Bias-corrected and accelerated. CI = confidence interval. LL = lower limit. UL = Upper limit.
Note: *p* values significant to <.050 in **bold.**
Note: effect size > 0.60 in **bold**
Note: confidence interval does not straddle 0 in **bold**

Results of analyses of the three DKEFS measures found a significant improvement in the Letter Sequencing subtest (measuring response inhibition and processing speed for letters) and Number/Letter Switching subtest (measuring the ability to shift set and maintain the other set in mind) of the Trail Making task (Table 7.23). The Visual Scanning condition of this measure did not reach significance; however, the effect size was moderate with an upper and lower confidence interval limits both with negative

values, indicating that increased speed would be consistently be seen in the population. Participants showed a significant improvement in Semantic Category Switching (ability to switch set when retrieving words belonging to particular categories) on the Verbal Fluency task, with performance on the Semantic Fluency subtest nearing significance with a large effect size and confidence interval that did not straddle zero. No significant improvements were observed for any conditions of the Colour Word Interference task which measures ability to inhibit cognitive interference of a second stimulus (the presence of a word when naming a colour).

No significant improvements were found for processing speed (Symbol Search), learning (Serial Reaction Time task), extended activities of daily living (NEADL), positive and negative affect (PANAS), or social cognition (Table 7.23). It should be noted that a large effect size was found for the improvement in Implicit learning reaction times on the SRT task, however the confidence interval straddled 0 indicating that this finding is not reliable. The effect size for the change in Positive Affect reported on the PANAS was large with positive upper and lower limits for the confidence interval, however participants reported on average a reduction in positive affect.

Table 7.23

Bootstrapped paired t-tests analysing difference in performance on measures of executive function, processing speed, learning, activities of daily living, affect and social cognition between first and second follow-up in group MO after the omega-3 supplement

Measure/Function	Baseline mean (SD)	Time 1 mean (SD)	*t* (8)	*p*	*d*	BCa 95% CI LL	BCa 95% CI UL
Executive Function (DKEFS)							
Trail Making							
Visual Scanning	10.56 (2.96)	11.56 (1.67)	1.89	.263	**.61**	**-2.00**	**-0.22**
Number Sequencing	12.33 (2.06)	11.78 (2.59)	0.98	.645	.30	-0.67	1.78
Letter Sequencing	11.00 (3.12)	12.78 (1.30)	2.78	**.044**	**.87**	**-3.08**	**-0.67**
Number/Letter Switching	11.22 (2.77)	12.33 (2.00)	2.87	**.035**	**.88**	**-1.78**	**-0.44**
Motor Speed	12.11 (0.93)	12.11 (0.78)	0.00	>.999	<.01	-0.33	0.33
Verbal Fluency							
Phonemic Fluency	12.11 (5.37)	12.44 (5.20)	0.37	.730	.12	-2.22	1.24
Semantic Fluency	11.67 (5.07)	13.00 (5.10)	2.32	.066	**.71**	**-2.56**	**-0.11**
Semantic Switching	9.33 (3.53)	12.78 (4.21)	3.21	**.021**	**1.00**	**-5.22**	**-1.78**
Colour Word Interference							
Naming	10.11 (2.93)	9.78 (3.60)	0.97	.383	.30	-0.22	0.89
Reading	10.44 (2.13)	10.44 (3.32)	0.00	1.00	<.01	-1.11	1.11
Inhibition	11.78 (1.56)	11.22 (3.19)	1.02	.368	.32	-0.22	1.33
Inhibition Switching	11.44 (2.46)	11.44 (3.21)	0.00	>.999	<.01	-0.78	0.78
Processing Speed							
WAIS-IV Symbol Search Correct	11.00 (3.24)	11.44 (3.32)	0.39	.696	.13	-1.38	0.88
Learning:							
SRT Explicit Learning	7.31 (2.91)	10.50 (6.07)	1.51	.183	.50	-8.19	0.94
SRT Implicit Learning	9.16 (74.60)	60.68 (40.81)	1.48	.206	**.84**	-114.76	7.16
Activities of Daily Living							
NEADL	52.67 (9.91)	51.44 (12.41)	0.38	.727	.10	-5.22	8.33
Affect:							
PANAS Positive Affect	32.11 (10.84)	29.33 (10.57)	2.29	.103	**.73**	1.11	4.56
PANAS Negative Affect	23.72 (9.33)	22.06 (9.94)	0.96	.376	.28	-1.44	4.67
Social Cognition:							
Reading the Mind in the Eyes	23.38 (5.45)	25.00 (5.01)	1.20	.286	.03	-4.37	1.25

Note: BCa = Bias-corrected and accelerated. CI = confidence interval. LL = lower limit. UL = Upper limit.
Note: *p* values significant to <.050 in **bold.**
Note: effect size > 0.60 in **bold**
Note: confidence interval does not straddle 0 in **bold**

7.4.2.5 Placebo Group Period 1

Results of analyses of the placebo group's task scores following the first intervention period are presented in Tables 7.24 and 7.25. On tasks of memory participants in this group showed significant improvements in immediate recall of verbally presented word pairs (WMS-IV Verbal Paired Associates; Table 7.24) and delayed recall of a previously presented complex figure (Rey-Osterreith). Immediate recall of the complex figure had a moderate effect size and a confidence interval with

upper and lower limits both with negative values. There were no significant improvements seen for Digit Span (measuring working memory) or visual recognition ('Doors' task).

Table 7.24

Bootstrapped paired t-tests analysing differences in memory performance between baseline and first follow-up in the placebo group

Measure/Function	Baseline mean (SD)	Time 1 mean (SD)	*t* (8)	*p*	*d*	BCa 95% CI LL	BCa 95% CI UL
Memory:							
WAIS-IV Digit Span							
Overall Score	10.50 (2.95)	10.30 (2.67)	0.38	.726	.11	-1.00	1.30
WMS-IV Verbal Paired Associates (verbal memory)							
Immediate Recall	8.40 (3.27)	10.20 (4.57)	3.19	**.010**	**.97**	**-2.90**	**-0.60**
Delayed Recall	9.50 (3.57)	10.40 (4.38)	1.31	.277	.39	-2.59	0.70
Doors (visual recognition)	9.60 (2.76)	9.90 (3.18)	0.35	.728	.10	-2.20	1.50
Rey-Osterreith Complex Figure (visual memory)							
Copy (perceptual organisation)	32.50 (6.19)	32.20 (7.97)	0.42	.742	.13	-1.00	2.00
Immediate Recall	22.65 (9.43)	25.55 (8.44)	2.08	.103	**.62**	**-5.50**	**-0.45**
Delayed Recall	21.00 (8.80)	24.35 (8.71)	3.18	**.021**	**.95**	**-5.40**	**-1.15**

Note: BCa = Bias-corrected and accelerated. CI = confidence interval. LL = lower limit. UL = Upper limit.
Note: *p* values significant to <.050 in **bold.**
Note: effect size > 0.60 in **bold**
Note: confidence interval does not straddle 0 in **bold**

Results of analyses of scores on all other measures (executive function, processing speed, learning, affect, and social cognition) showed no significant improvements on any measures with predominantly small effect sizes (Table 7.25).

Table 7.25

Bootstrapped paired t-tests analysing differences in measures of executive function, processing speed, learning, activities of daily living, affect and social cognition between baseline and first follow-up in the placebo group.

Measure/Function	Follow-up 1 mean (SD)	Follow-up 2 mean (SD)	*t* (9)	*p*	*d*	BCa 95% CI LL	UL
Executive Function (DKEFS)							
Trail Making							
Visual Scanning	8.70 (4.69)	8.40 (5.21)	0.48	.670	.14	-1.00	1.80
Number Sequencing	10.00 (4.37)	10.30 (4.30)	0.34	.756	.10	-2.20	1.70
Letter Sequencing	9.70 (4.69)	9.90 (3.54)	0.27	.804	.08	-2.20	1.60
Number/Letter Switching	10.10 (4.07)	10.40 (3.95)	0.53	.615	.16	-1.60	1.00
Motor Speed	10.10 (3.41)	9.70 (3.56)	1.40	.203	.41	**0.00**	**0.80**
Verbal Fluency							
Phonemic Fluency	10.70 (3.23)	10.70 (3.27)	0.00	1.00	<.01	-1.10	0.90
Semantic Fluency	11.90 (4.95)	10.60 (6.26)	1.18	.296	.34	-0.90	3.32
Semantic Switching	11.40 (4.09)	11.30 (4.32)	0.16	.896	.05	-1.10	1.30
Colour Word Interference							
Naming	7.90 (4.51)	8.40 (4.84)	1.68	.158	.54	**-1.00**	**-0.11**
Reading	9.67 (3.39)	10.22 (4.49)	0.96	.386	.30	-1.33	0.33
Inhibition	10.33 (4.00)	10.56 (4.95)	0.35	.703	.11	-1.00	0.67
Inhibition Switching	9.67 (4.47)	9.44 (5.46)	0.54	.615	.18	-0.44	0.89
Processing Speed							
WAIS-IV Symbol Search Correct	8.60 (3.31)	9.90 (4.75)	1.75	.283	.51	-3.30	0.00
Learning:							
SRT Explicit Learning	6.50 (3.72)	8.65 (4.61)	1.29	.266	.39	-7.12	1.45
SRT Implicit Learning	28.64 (66.21)	79.82 (137.80)	0.92	.421	.42	-168.23	32.63
Activities of Daily Living							
NEADL	48.90 (17.48)	51.10 (19.40)	1.23	.283	.37	-5.40	1.05
Affect:							
PANAS Positive Affect	30.90 (8.72)	31.90 (7.26)	0.49	.681	.15	-4.40	3.40
PANAS Negative Affect	19.30 (5.19)	18.90 (7.56)	0.14	.894	.04	-4.90	5.30
Social Cognition:							
Reading the Mind in the Eyes	23.30 (8.89)	24.30 (6.06)	1.34	.245	.40	-2.40	0.30

Note: BCa = Bias-corrected and accelerated. CI = confidence interval. LL = lower limit. UL = Upper limit.

7.4.2.5 Placebo Group Period 2

Results of analyses of cognitive test performance and self-report measure following the second intervention period for the placebo group are reported in Tables 7.26 and 7.27. On tasks of memory there was a significant improvement in Digit Span (measuring working memory) at the second follow-up. There were also improvements in immediate and delayed Verbal Memory, these did not reach significance but did have moderate to large effect sizes with confidence interval upper and lower limits both with negative values. No improvements were seen on visual recognition of previously presented stimuli (the 'Doors') or on immediate or delayed visuo-spatial recall of the Rey-Osterreith Complex Figure (Table 7.26).

Table 7.26

Bootstrapped paired t-tests analysing differences in memory performance between first and second follow-up in the placebo group.

Measure/Function	Follow-up 1 mean (SD)	Follow-up 2 mean (SD)	*t* (9)	*p*	*d*	BCa 95% CI LL	BCa 95% CI UL
Memory:							
WAIS-IV Digit Span							
Overall Score	10.33 (2.67)	11.80 (2.86)	3.20	**.013**	**.95**	**-2.50**	**-0.60**
WMS-IV Verbal Paired Associates (verbal memory)							
Immediate Recall	10.20 (4.57)	11.90 (4.56)	2.44	.073	**.74**	**-3.20**	**-0.50**
Delayed Recall	10.40 (4.38)	11.10 (3.60)	2.21	.055	**.65**	**-1.20**	**-0.30**
Doors (visual recognition)	9.56 (3.17)	10.89 (2.20)	1.20	.362	.37	-3.67	0.44
Rey-Osterreith Complex Figure Test (visual memory)							
Copy (perceptual organisation)	32.20 (7.97)	32.60 (5.12)	0.43	.668	.13	-2.45	1.10
Immediate Recall	25.55 (8.43)	26.40 (9.50)	0.67	.535	.20	-2.90	1.76
Delayed Recall	24.35 (8.70)	25.15 (9.62)	0.81	.464	.24	-2.85	1.30

Note: BCa = Bias-corrected and accelerated. CI = confidence interval. LL = lower limit. UL = Upper limit.
Note: *p* values significant to <.050 in **bold.**
Note: effect size > 0.60 in **bold**

Participants in the Placebo group also showed a significant improvement in number of words generated that began with a specified letter (Phonemic Fluency measuring strategy generation) and an improvement in generation of words belonging to alternate categories (Semantic Switching) that was just above the $p \leq .05$ cut-off. There were no other significant improvements in task performance on the DKEFS measures administered, however Number and Letter Sequencing on the Trail Making task, Semantic Switching on Verbal Fluency and Inhibition Switching all had effect sizes that were moderate to large with confidence intervals that did not straddle zero. No improvements were seen on measures of processing speed, social cognition or on self-reported measures of extended activities of daily living and mood state in this group during the second intervention period (Table 7.27).

Table 7.27

Bootstrapped paired t-tests analysing differences in measures of executive function, processing speed, learning, activities of daily living, affect and social cognition between first and second follow-up in the placebo group.

Measure/Function	Follow-up 1 mean (SD)	Follow-up 2 mean (SD)	*t* (9)	*p*	*d*	BCa 95% CI LL	BCa 95% CI UL
Executive Function (DKEFS)							
Trail Making							
Visual Scanning	8.40 (5.21)	8.90 (4.63)	0.58	.624	.17	-2.10	0.90
Number Sequencing	10.30 (4.30)	10.70 (4.00)	0.88	.444	.27	-1.50	0.40
Letter Sequencing	9.90 (3.54)	11.00 (4.22)	2.22	.135	**.66**	**-1.70**	**-0.40**
Number/Letter Switching	10.40 (3.95)	10.90 (3.93)	2.40	.106	**.71**	**-0.80**	**-0.20**
Motor Speed	9.70 (3.56)	10.20 (3.49)	1.11	.318	.33	-1.20	0.10
Verbal Fluency							
Phonemic Fluency	10.70 (3.27)	12.20 (3.29)	3.37	**.033**	**.99**	**-2.20**	**-0.80**
Semantic Fluency	10.60 (6.26)	11.90 (3.98)	1.27	.263	.38	-3.26	0.90
Semantic Switching	11.30 (4.32)	12.80 (2.66)	2.39	.052	**.73**	**-2.80**	**-0.10**
Colour Word Interference							
Naming	8.40 (4.84)	8.80 (4.52)	1.14	.290	.37	-1.11	0.22
Reading	10.22 (4.49)	10.22 (3.80)	0.00	1.00	<.01	-0.56	0.56
Inhibition	10.56 (4.95)	10.56 (3.36)	0.00	1.00	<.01	-1.76	1.33
Inhibition Switching	9.44 (5.46)	11.44 (3.13)	2.40	.058	**.74**	**-3.78**	**-0.22**
Processing Speed							
WAIS-III Symbol Search Correct	9.90 (4.75)	10.10 (5.61)	0.70	.504	.22	-1.89	0.89
Learning:							
SRT Explicit Learning	8.28 (4.72)	8.33 (4.64)	0.05	.960	.02	-1.83	2.00
SRT Implicit Learning	81.22 (146.08)	129.24 (171.58)	1.13	.329	.35	-113.97	24.84
Activities of Daily Living							
NEADL	51.10 (19.40)	50.20 (17.74)	0.59	.615	.26	-1.20	3.20
Affect:							
PANAS Positive Affect	31.90 (7.26)	30.50 (8.09)	1.07	.324	.32	-0.90	3.90
PANAS Negative Affect	18.90 (7.56)	18.60 (5.52)	0.18	.860	.06	-3.93	4.60
Social Cognition:							
Reading the Mind in the Eyes	23.67 (6.06)	23.78 (5.19)	0.13	.911	.04	-1.44	1.33

Note: BCa = Bias-corrected and accelerated. CI = confidence interval. LL = lower limit. UL = Upper limit.
Note: *p* values significant to <.050 in **bold.**
Note: effect size > 0.60 in **bold**

7.4.3 Effect of Period When Supplement Taken

MANOVAs were conducted to evaluate whether there was a change in cognitive test performance over time irrespective of the intervention. This was calculated by comparing the difference in scores or ratings between Omega-3 and Multivitamin (A-B) irrespective of the order that these interventions were taken in. For the purposes of these analyses the placebo group were excluded as the focus of these analyses are to ensure that

the time point the supplement was taken was not a contributory factor in findings. MANOVAs showed no significant effect of time period of intervention on test scores, with the largest $p \geq .108$ (See Appendix E.15).

7.5 Conclusion

7.5.1 Dietary intake

Analyses of dietary intake of micronutrients showed fairly consistent findings over the two intervention periods, with intake of water-soluble vitamins at or above recommended daily levels with the exception of folate which was low. Intake of fat-soluble vitamins were found to be significantly lower than recommended levels, with the exception of vitamin A (intake similar to recommended levels). Mineral intake was found to be not different to recommended daily levels apart from magnesium intake which was consistently insufficient. Intake of omega-3 polyunsaturated fatty acids was found to be at recommended daily intake levels over the first intervention period, and below recommended levels in the second intervention period.

Micronutrient intake levels of traumatically brain injured participants were similar to that of participants involved in the normative study. This was unexpected as it had been hypothesised that head injured participants would have diets that were poorer and therefore lower in micronutrient content than the general population, based on previous literature (Duraski et al., 2014; Wahls et al., 2014). A potential mediating factor in these findings is that the majority of participants (86%) were living with other family members. Further research needs to be undertaken looking at the diet of people with TBI living alone compared to those living with family.

The findings of this study support the findings of the normative study showing that individuals have insufficient levels of key micronutrients in their diet (Denniss et al., 2019). This also supports the 'hidden hunger' findings of Biesalski (2013), specifically for fat-soluble vitamins, folates and magnesium. In addition to the long-term health implications of dietary micronutrient insufficiencies raised in Chapter 4, micronutrient insufficiency is of particular concern in a head injured population where low levels of essential micronutrients have the potential to negatively affect the recovery process within neurons and glial cells in addition to affecting baseline physiological functioning of the brain (e.g. Bailey et al., 2015; Dauncey, 2014; Ueland et al., 2016). The multimicronutrient and omega-3 interventions changed the nutritional profile of the two active supplement groups (OM and MO) in both intervention periods, with the

multimicronutrient intervention resulting in a much broader change in nutritional profile compared to participants taking the omega-3 or placebo.

7.5.2 Cognitive performance

Differing effects on cognition of the two supplements (multimicronutrient and omega-3) were found in this study. Improvements in cognition when participants took the omega-3 supplement were predominantly in executive functions including processing speed (Symbol Search), attention (Trail Making sequencing and Colour Word Naming and Reading), response inhibition (Colour Word Inhibition) and set shifting (Trail Making Number/Letter Switching, Verbal Fluency Switching). Some improvements in memory (Verbal Paired Associates) were also seen in both groups when taking the omega-3 supplement. Fewer improvements were seen when participants took the multimicronutrient compared with the omega-3 supplement. Group MO showed improvements in both immediate and delayed verbal memory (Verbal Paired Associates) and delayed visuo-spatial recall (Rey-Osterreith Complex Figure) when taking the multimicronutrient. This group also showed improvements in attention (number sequencing sub-test of Trail making), set-shifting (Switching subtest of Trail Making), inhibition of a pre-potent response (Inhibition subtest of the Colour Word Interference Test) and processing speed (Symbol Search) which were not found when group OM took the multimicronutrient. The Placebo group also showed improvements in visual and verbal recall, motor speed (Trail Making), working memory (Digit Span) at both follow-up test points. These findings are suggestive of a robust placebo effect. A summary table of these findings are presented in Table 7.28.

In conclusion this study has demonstrated that supplementation, particularly with omega-3 polyunsaturated fatty acids, results in cognitive improvements in memory and executive function after a relatively short period of time. Micronutrient interventions therefore offer a low-cost adjunct to standard care with the potential to positively improve cognitive recovery post-TBI. The mean time since injury in this cohort was 12 months, indicating that the improvements in cognition demonstrated were not limited to the immediate post-injury period and were seen after the point where large improvements related to spontaneous recovery might be expected. Further discussion of the findings from this study, along with a discussion of thesis findings as a whole and directions for future research, will be explored in Chapter 8.

Table 7.28

Visual summary of changes in cognition following each intervention period

	Change in scores at first test post baseline following first 8-week intervention			Change in scores at second test post baseline following 6-week washout and second 8-week intervention		
	Group			Group		
Function	OM (omega-3)	MO (multi-micronutrient)	Placebo	OM (multi-micronutrient)	MO (omega-3)	Placebo
Memory						
Working Memory (Digit Span)						✓*
Immediate Verbal Memory (Verbal Paired Associates)	✓	✓*	✓*		✓*	✓
Delayed Verbal Memory (Verbal Paired Associates)	✓	✓				✓
Visual Recognition ('Doors' from Doors and People)					✓	
Perceptual Organisation (copy Rey-Osterreith)						
Immediate Visuo-Spatial Recall (Rey-Osterreith Figure)			✓			
Delayed Visuo-Spatial Recall (Rey-Osterreith Figure)		✓	✓*		✓*	
Executive Function (DKEFS) Trail Making						
Visual Scanning	✓				✓	
Number Sequencing		✓*				
Letter Sequencing					✓*	✓
Number/Letter Switching		✓			✓*	✓
Motor Speed			✓			

Note: ✓* $p \leq .050$. ✓ moderate to large effect size. **X** = significant decrease ($p \leq .050$)

	Change in scores at first test post baseline following first 8-week intervention			Change in scores at second test post baseline following 6-week washout and second 8-week intervention		
	Group			Group		
Function	OM (omega-3)	MO (multi-micronutrient)	Placebo	OM (multi-micronutrient)	MO (omega-3)	Placebo
Verbal Fluency						
Phonemic Fluency						✓*
Semantic Fluency					✓	
Semantic Switching		**X***			✓*	✓
Colour Word Interference						
Naming	✓*	✓	✓			
Reading	✓*					
Inhibition	✓	✓				
Inhibition Switching	✓					✓
Processing Speed						
WAIS-IV Symbol Search Correct	✓*	✓				
Learning:						
SRT Explicit Learning	✓*					
SRT Implicit Learning						
Activities of Daily Living						
NEADL						
Affect:						
PANAS Positive Affect	✓			**X**		
PANAS Negative Affect				**X**		
Social Cognition:						
Reading the Mind in the Eyes						

Note: ✓* $p \leq .050$. ✓ moderate to large effect size. **X** = significant decrease ($p \leq .050$)

Chapter Eight – General Discussion

8.1 Overview

This chapter summarises, evaluates and discusses the findings of the studies conducted for this thesis. The aims of this thesis were two fold; (i) to investigate the levels of dietary intake of micronutrients in the general population and in individuals who had experienced a traumatic brain injury (TBI), and (ii) to investigate whether there were any positive effects of supplementation on cognitive function in these two populations, with the aim of establishing whether micronutrients were suitable candidate treatments for aiding cognitive recovery after brain trauma. Previous research has investigated Western diets and the health implications of poor micronutrient intake (Ames, 2006; Biesalski, 2013; Monteiro, 2009). There has also been interest in the role of micronutrients in recovery post-TBI with the majority of research in this field in pre-clinical models (rodents) and limited human trials (Amen et al., 2011; Pillsbury et al., 2011; Sen & Gulati, 2010; Wu et al., 2013).

Chapters Three and Four present the study whereby healthy participants were randomly allocated to one of three interventions (vitamin D, multimicronutrient, vitamin C) for an eight-week period during which time participants also completed a 14-day food diary. At baseline and following the intervention participants completed a randomised and counterbalanced battery of cognitive test measures that assessed memory, executive function, social cognition, processing speed, and explicit and implicit learning.

Findings from the normative study showed that the general population were not meeting recommended daily intake of a number of micronutrients based on food diary records; they were below RDA for all minerals (calcium, iron, magnesium, selenium, zinc) along with fat-soluble vitamins (A, D, E) and the B vitamins pantothenic acid and folate. Findings from analyses of cognitive test performance showed improvement in all groups on a number of measures following the intervention period, specifically verbal memory (immediate and delayed; Logical Memory test), delayed visual recall (Visual Reproduction test), visual and verbal learning and memory (Doors and People overall score), visuomotor processing speed (Symbol Search) and social cognition (Movie for the Assessment of Social Cognition). The vitamin D group alone showed improvement in number sequencing on the Trail Making task. Both the Vitamin D and Multivitamin groups showed significantly improved performance on the Perceptual Reasoning sub-tests of the WASI-II, resulting in improved overall IQ score. The Multivitamin and

Vitamin C groups showed significant improvements on tasks of motor planning (Tower mean 1st move), visual strategy generation (Design Fluency with a distractor) and explicit awareness of a pattern (SRT task), however the Multivitamin group alone showed improvements on visual spatial working memory on the Symbol Span task and implicit awareness of the presented pattern on the SRT task. These findings show an unexpected deficiency in micronutrient intake and an improvement in cognition following micronutrient intervention across all three groups – which was unexpected for quasi-placebo vitamin C group (Denniss et al., 2019). These findings provided a rationale for the study in a TBI population, who based on this data were likely to have low micronutrient levels before injury which would be further depleted by the effects of the brain trauma and secondary biochemical cascade.

Study two investigated putative effects of micronutrient interventions in a TBI population (Chapters Five, Six and Seven). Based on results from an eight-week intervention period in the normative study, the same length of intervention was used along with a cross-over design in the patient study. Participants were randomly allocated (double-blind) to either group OM (omega-3 followed by multimicronutrient), MO (multimicronutrient followed by omega-3) or to the parallel placebo group (sucrose in a cellulose capsule). Groups OM and MO took part in the cross-over, each taking the two interventions in turn with a six-week wash-out period between interventions. Participants in the parallel placebo group took the placebo at both time points, still with a wash-out period due to the double-blind nature of the study. Some changes to the test battery were made for this study to reduce the number of test measures, however the same functions assessed in the normative study were also assessed in the TBI cohort (memory, executive function, social cognition, processing speed, and explicit and implicit learning and awareness). Reduction in overall number of test measures was to accommodate levels of fatigue experienced by individuals following traumatic brain injury (e.g. Ouellet & Morin, 2006) and to eliminate redundancy based on findings from the normative study. Food diary completion rates were shortened from 14 to two 3-day diaries over each intervention period to make this task less onerous for patients yet still adequately provide a snapshot of general eating habits (note - diets tend to be uniform over time and resistant to change to this period of data collection was considered adequate taking into consideration patient's difficulties; Hughes et al., 2012; Whyte et al., 2016; Zweers et al., 2018). Overall dietary intake of micronutrients over the two intervention periods followed a similar pattern to that seen in the normative group. Intake of water-soluble vitamins (Vitamin C and the B-complex) was at or above recommended daily amounts apart from

folate. Intake of fat-soluble vitamins was found to be significantly lower than recommended daily levels with the exception of vitamin A. Mineral intake was found to be not different to recommended daily levels, apart from magnesium intake, which was consistently insufficient.

As described in Chapter 7 the effects of each intervention on mean group cognitive performance differed across groups in this study and also from the normative study. In the cross-over part of the study group OM took the omega-3 first and the multimicronutrient second, and group MO took the multimicronutrient first and the omega-3 second. In group OM improvements were seen in executive functions including processing speed, attention and set-shifting as measured by WAIS-IV Symbols Search and DKEFS Trail Making, Verbal Fluency, and Colour Word Interference when taking the omega-3 supplement in the first intervention period. Group MO, taking the multimicronutrient in the first intervention period, showed improvement on a number of memory measures (immediate and delayed Verbal Paired Associates verbal memory, delayed recall of the Rey-Osterrieth Complex figure) along with improvements on some of the DKEFS measures (Number Sequencing and Switching subtests of Trail Making, Naming and Inhibition subtests of the Colour Word Interference) and processing speed (WAIS-IV Symbol Search). Group MO also showed improvements in verbal memory (Verbal Paired Associates), visual recognition ('Doors' from Doors and People) and delayed visuo-spatial recall (Rey-Osterreith complex Figure) after taking the omega-3 supplement in the second intervention period. Group OM, who completed the multimicronutrient intervention second, after the omega-3, showed no further improvements on test measures following the multimicronutrient supplement phase when comparing follow-up 1 (post omega-3) to follow-up 2 scores (post multimicronutrient).

Unexpectedly the Placebo group showed some improvement in memory and executive function over the two intervention periods, for example delayed visuo-spatial recall (Rey-Osterreith Complex Figure Test) and verbal switching inhibition (Colour Word Interference Test). There are a number of contributory factors in this research study that may have resulted in this effect. These include the act of participants volunteering for research with an expectation of potential improvement, dedicated cognitive assessment and encouragement without time constraints, which may have led to increased effort (Enck & Zipfel, 2019). It has also been previously found that the expectation of a stimulant effect in a placebo improves aspects of cognition including working memory and executive function (Ashor, 2011; Foroughi et al., 2016). In addition, natural recovery cannot be excluded as a factor in these findings.

There were no significant improvements seen in any group following any of the interventions for the measures of social cognition (Reading the Mind in the Eyes) and extended activities of daily living (NEADL). The Nottingham Extended Activities of Daily Living scale covered many aspects of daily living that are affected following traumatic brain injury. As a self-report measure individual's confidence in completing the stated activities measured by the Nottingham Extended Activities of Daily Living scale is a factor in participants' responses. Responses may therefore have been affected by other factors in their daily lives, for example physical setbacks or completion of an activity, resulting in slight individual variations in scores but no overall improvement at the group level.

As there was no difference in cognitive test performance between groups at baseline the difference in response to the omega-3 and multimicronutrient supplements in terms of cognitive improvement is an important finding. Taking the omega-3 supplement improved participant's cognitive function, regardless of intervention order (in the first or second intervention periods) with improvements seen on measures of learning, attention, processing speed and set shifting. Levels of omega-3 have been shown to be reduced in cortical tissue following TBI, potentially through increased utilisation in regions of damage (Wu et al., 2013; 2014) as they are involved in a number of underlying cellular mechanisms initiated by the secondary biochemical cascade. These include increasing numbers of precursors for protectins and resolvins that mediate the neuroinflammatory response to injury (Serhan et al., 2008; Weylandt et al., 2012), decreasing production of reactive oxygen species (Pan et al., 2009), and stimulation of oligodendrocyte progenitor cells (Salvati et al., 2008). Boosting omega-3 levels has been demonstrated to reduce levels of neurofilament light which is a biomarker for axonal damage (Oliver et al., 2016). This has the potential to attenuate the on-going neuroinflammatory response and oxidative stress within cells (as described by Ramlackhansingh et al., 2011) and support myelin maintenance and repair. Supporting these processes improves cellular function and communication between neurons, with better cognition as the outcome.

Group MO showed greater improvements, compared to Group OM, when taking the omega-3 intervention after the multimicronutrient intervention. It may be the case that the multimicronutrient intervention may have upregulated cellular function within the brain. Although speculative the multimicronutrient taken first may have provided a foundation for the omega-3 intervention, the wash out period not reversing underlying cellular change. At the cellular level B vitamins, calcium, iron, magnesium and selenium

are all required for competent cellular energy production in the mitochondria to produce ATP for all cellular processes. When considering secondary cascade mechanisms following traumatic brain injury a spectrum of micronutrients are required to reduce oxidative stress (vitamins C, E, riboflavin, vitamin K and calcium) and inflammatory processes (vitamin D, B_6, selenium and zinc). Repair of axonal injury is also vital following TBI. Biotin, B_{12}, vitamin K and iron are involved in the biosynthesis of fatty acids, sphingolipids, and proteins for myelin (Brito et al., 2016; Ferland et al., 2012; Möller et al., 2019; Tourbah, 2015). Biotin, B12, and vitamin K are not stored in the brain and require regular intake and inflammatory processes following trauma can lead to anaemia (Abbaspour et al., 2014; Ferland, 2012; Von Drygalski & Adamson, 2012). Vitamin A is involved in remyelination processes (Huang et al., 2011) and iodine is involved in stimulation of oligodendrocyte progenitor cells (Calzà et al., 2010; Dugas et al., 2012). Supplementation with the multimicronutrient could have therefore boosted cellular energy production, reduced neuroinflammation, and initiated myelin synthesis and repair to provide a foundation that the omega-3 supplement then built on, however more research would be required to test this hypothesis. It is currently unclear why in group OM taking the omega-3 supplement, which is anti-inflammatory and is involved in myelin production and repair, did not produce a similar foundation for the multimicronutrient supplement, if this is the case. It may be that in group MO the multimicronutrient supplement corrected any deficiencies resulting in the subsequent omega-3 supplement having maximum effect. According to this hypothesis in group OM micronutrient deficiencies had not been corrected, therefore the omega-3 less of an effect on cognition. Omega-3 has, however, been shown to increase resting and active metabolism (Gammone et al., 2019; Logan & Spriet, 2015) which may have resulted in increased utilization of micronutrients. The subsequent multimicronutrient supplement may have addressed any resulting deficiencies but to less of an extent than in group MO, affecting any associated cognitive improvement. Again, more research would be required to test this hypothesis.

8.2 Micronutrient intake in normative and TBI samples

Controlling neuroinflammation, along with supporting mitochondrial function and maintenance and repair of myelin, are all vital in recovery of the injured brain. Therefore, gaining information on dietary micronutrient intake in both the general population and those with head injuries is a key component of assessing nutritional status. It is important to know micronutrient intake levels in the general population as pre-

clinical studies have highlighted that micronutrient status prior to TBI has implications for recovery from injury. For example, low levels of omega-3 and zinc pre-injury have been shown to result in poorer motor and cognitive recovery along with increased necrotic cell death in rodents (Cope et al., 2012; Desai et al., 2014). Although based on animal data which limits comparisons with humans these findings lend support that omega-3 and micronutrient supplementation are potentially reparative and would provide a useful dietary adjunct to traditional therapies which may have a significant impact on cognitive outcome after TBI.

In the normative study dietary intake of fat-soluble vitamins, folate, pantothenic acid, and all minerals apart from iodine were significantly below recommended daily intake amounts. In short, individuals in the general population who have, on average, low dietary micronutrient levels may potentially have worse comparative outcomes following head injury compared to those in the population that meet all dietary intake requirements. To put this into context, in the normative sample there was only one participant (out of 60 individuals) whose dietary micronutrient intake met or exceeded RDI for all vitamins and minerals. Based on the combined data from the normative and patient study it may be a beneficial therapeutic intervention to provide multimicronutrient and omega-3 supplements as soon as possible post-injury given that it is possible that individuals are potentially deficient any ways, regardless of injury.

Importantly after TBI a number of micronutrients become depleted, either through increased metabolic demand or through renal clearance[23] including vitamins C, D, and E, magnesium, zinc, and omega-3 clearance (e.g. McClain et al., 1986; Sen & Gulati, 2010). If individuals also have pre-existing poor nutrition, this additional depletion will further impact capacity for competent cellular function and neural (and body) repair following traumatic brain injury. This has implications wider than TBI; micronutrient support is potentially also important following stroke to address associated secondary cascade mechanisms. Analyses of food diary entries in the TBI study found the same pattern of dietary intake as the normative group for vitamins (sufficient levels of most B-vitamins, insufficient intake of most fat-soluble vitamins), but on average sufficient intake of minerals with the exception of magnesium. In addition to vitamins and minerals dietary intake of omega-3 was also assessed from food diaries in this study. Intake of omega-3 was found to be low during each of the intervention periods in the TBI sample, although whether this was statistically significant varied as even occasional intake of foods high in

[23] rate at which micronutrients are cleared from the body in urine

omega-3 resulted in a significant change to overall average intake. The consistent findings from food diaries across the normative and TBI cohorts suggests normative findings were not isolable to the normative sample, but instead suggests that micronutrient deficiency is common in otherwise healthy westerners consuming standard diets. Similarity in dietary intake of micronutrients across patients and the normative group is an unexpected finding as previous research has indicated that dietary micronutrient intake is poorer in people after TBI compared to the general population (Duraski et al., 2014; Wahls et al., 2014). This can be due to a number of factors including executive dysfunction and poor appetite. Put into the wider context of the population of people with TBI, pre-existing and ongoing levels of micronutrient insufficiency may be resulting in sub-optimal levels of recovery, this could be easily addressed at relatively low cost.

8.3 The role of micronutrients in cognition

Arguably one strength of the research methodology used across both studies in the present research is the inclusion of selective micronutrients as interventions. It was therefore possible to begin to tease out any putative effect of select micronutrients on cognition compared to multimicronutrient interventions. The information gathered from food diary analyses resulted in a fuller picture of the changes in overall micronutrient profile resulting from these types of interventions. Previous research has not typically included measurement of dietary intake alongside interventions and cognitive test measures, although some research has included physiological measures alongside supplementation and cognitive test measures (e.g. Amen et al., 2013).

8.3.1 Vitamin C

As part of the normative study vitamin C was selected for use as the control supplement as previous research (e.g. Arlt et al., 2012) had indicated that 200mg of this vitamin would be unlikely to affect cognition. Improved cognition in the Vitamin C group was therefore an unexpected finding. A number of contributory factors may offer an explanation for this. As discussed in Chapter Four research investigating the relationship between fruit and vegetable consumption and cognitive decline has been conducted in aging populations (e.g. Gale et al., 1996). This has indicated that vitamin C deficiency is a contributory factor in cognitive decline. Further research has highlighted a strong relationship between higher levels of vegetable consumption (compared to fruit) and slower cognitive decline (Loef & Walach, 2012; Morris et al., 2006). More recently cross-sectional research has found a link between plasma vitamin C levels measured by biochemical analysis and performance on a range of cognitive tasks (Travica et al.,

2019; Travica et al., 2020). The research conducted by Travica and colleagues had similar findings to the current normative research: participants who had adequate vitamin C plasma levels performed better on tasks of memory, attention, choice reaction time and inhibition compared to those who were deficient (Travica et al., 2019; Travica et al., 2020). Considering other research and the findings of study one it is reasonable to suggest that in participants with low levels of fruit and vegetables in their diets increased vitamin C intake via supplements may result in improvements in cognition. It should be noted that in the normative study the supplement given was five times RDA (200mg supplement vs 40mg RDA), however this was the lowest dose supplement available at the time, with 'max strength' over-the-counter supplements providing 1500mg of vitamin C; in this case the quasi-placebo was actually demonstrably active based on cognitive data.

As discussed in Chapter Two vitamin C is involved in a number of cellular processes within the brain. These processes include transport of lipids for catabolism (breakdown and energy release) in the mitochondria improving cellular energy production (Covarrubias-Pinto et al., 2015; Harrison & May, 2009), along with enhancing iron absorption and metabolism (Lane & Richardson, 2014). Iron is required by oligodendrocytes to maintain myelin integrity (Crichton et al., 2012; Möller et al., 2019) and participants in the normative study did not meet RDI of iron from diet alone. It is therefore plausible that increasing vitamin C intake through supplementation resulted in more efficient uptake and metabolism of iron potentially available in participants' diets. As such the vitamin C intervention may have contributed to cognitive improvements via efficient cellular energy production and neuronal transmission in the normative group but failed as an inert placebo and should be avoided as a potential economical placebo in future work.

8.3.2 Vitamin D

Vitamin D was selected as one of the supplements for the normative study (study one). Vitamin D deficiency is common in the UK, even in the summer months when the levels of UV sunlight is at high enough levels for vitamin D conversion in the skin to occur (Webb et al., 2010). Neurons express vitamin D receptors which stimulate intracellular signalling pathways in the hypothalamus, substantia nigra, cortex, and hippocampus (Annweiler et al., 2009; Garcion et al., 2002; Oudshoorn et al., 2008). The majority of previous research investigating the role of vitamin D in cognition has been in older adults (e.g. Buell et al., 2009; Laughlin at al., 2017), however some research has used younger cohorts (e.g. Pettersen, 2017). This research has indicated that higher

plasma vitamin D levels is related to better performance on tasks of executive function, attention and processing speed in normative groups.

Findings from study one data are inconsistent with some earlier findings showing no effect on memory (e.g. McGrath et al., 2007) with improvements seen for a number of memory measures, including delayed non-verbal memory which was similarly found in the Pettersen (2017) study. Although participants in the vitamin D group did not show improvements on the same number of cognitive tasks as the multimicronutrient group in the normative study these data support the notion that individual micronutrients can significantly improve cognitive function. It may be the case that some individual micronutrients have a greater capacity for effecting cognitive change than others. Individual micronutrient research and micronutrient interactions in normal and pathological conditions is an area for future research.

8.3.3 Multimicronutrient

In both the normative and TBI studies a multimicronutrient was selected as one of the supplements under investigation. For the normative study an over the counter preparation was selected that contained levels of micronutrients that met RDA requirements as far as was possible. This approach was taken to ensure that participants allocated to this intervention met recommended daily intake for micronutrients but did not exceed it to a large amount once dietary levels were included. Findings from the normative study, alongside research highlighting micronutrient depletion following traumatic brain injury, led to the decision to select a multimicronutrient intervention for the TBI study with micronutrient levels higher than RDA amounts.

Multimicronutrient formulations have a number of advantages when trying to improve cognitive function. The first is that absorption, retention and activation of some vitamins and minerals are improved by the presence of another. As examples, vitamin C increases iron absorption (Pehlivan, 2017), magnesium and vitamin B_6 mutually increase uptake (Abraham et al., 1981; Pouteau et al., 2018), and vitamin D increases absorption of calcium (Christakos et al., 2020). Beyond uptake of vitamins and minerals in the gut, zinc is required for vitamin A transport (Christian & West, 1998), and magnesium is required to convert thiamine (B_1) into its biologically active form and is a co-factor in vitamin D conversion reactions (Fleet, 2017; Osiezagha et al., 2013). Nutrient matching may therefore offer another area for future research exploring optimising nutrition and cognitive outcome.

In diet micronutrients are not absorbed and metabolized singly, but instead in a complex matrix along with other macro and micronutrients that interact (Goyal, 2018),

multimicronutrient formulations mimic this to some extent. One example is the B-complex of vitamins which are grouped together based on their interdependent functions in cellular energy production (Kennedy, 2016; Tardy, 2020), with this inter-relatedness of function particularly important in the nervous system where they are involved in myelin and neurotransmitter synthesis (Calderón-Ospina & Nava-Mesa, 2020). Other micronutrients have interdependent functions with vitamin C, iron and magnesium involved with cellular energy production, and niacin, pantothenic acid, iron, magnesium and zinc required for neurotransmission (Tardy et al., 2020). As part of the secondary biochemical cascade oxidative stress, microglial activation and neuroinflammation are interconnected (Solleiro-Villavicencio & Rivas-Arancibia, 2018) with oxidative stress leading to chronic inflammation. Vitamins D and B_6, along with selenium and zinc are integral to a balanced inflammatory response to traumatic brain injury (McAllister & Dyck, 2017; Pearce & Cheetham, 2010; Roman et al., 2014; Ueland et al., 2016). The multimicronutrient supplement therefore ensured that absorption, retention and biochemical function of the micronutrients was optimised.

In both the normative and TBI studies the multimicronutrient supplement may have boosted cellular energy production and improved neurotransmission with the outcome of improved cognition. In the TBI group this supplement may also have reduced neuroinflammatory processes. Further research still needs to be conducted using multimicronutrient interventions in both normative and clinical groups to establish the most effective dosage, to use physiological indices, and to clarify what other factors may affect levels of cognitive change.

8.3.4 Omega-3

In the TBI study a one-a-day high dose omega-3 supplement providing 580mg of EPA and 320mg of DHA was taken by participants. Findings showed cognitive improvements in memory (immediate verbal and delayed visual), processing speed (Symbol Search), semantic fluency, set shifting (semantic and number/letter), and learning. These results replicated findings from previous research in other populations (Stavrinou et al., 2020; Witte et al., 2014; Yurko-Mauro et al., 2010) and also indicated that additional functions are improved (for example processing speed). For example, semantic fluency and switching improved from the average to high average range, and verbal recall improved from below average to average at the group level. These findings of improvements in processing speed, executive function and memory (functions associated with white matter and frontotemporal functionality) correspond well to findings of improved white matter tract integrity in frontal, temporal and limbic regions

of the brain in older adults following a 26-week omega-3 intervention (Witte et al., 2014). Although the intervention in the current study was not as long, the research by Witte et al., (2014) demonstrates a relationship between improvement in function and underlying brain changes.

The underlying mechanism for improvements in white matter integrity is associated with omega-3 polyunsaturated fatty acids constituting 50% of the phospholipid composition of neuronal membranes, as well as being involved in synaptogenesis (Dyall & Michael-Titus, 2008). Omega-3 PUFAs are also required for efficient oligodendrocyte function. Findings from animal research with rodents indicate that omega-3 interventions following injury can attenuate damage to white matter pathways by stimulating oligodendrocyte progenitor cells (Pu et al., 2013). Chemically omega-3 PUFAs also act as precursors to anti-inflammatory mediators involved in the resolution of neuroinflammation following TBI (Serhan et al., 2008; Weylandt et al., 2012). The omega-3 supplement taken by participants in the TBI study may therefore have improved white matter integrity and reduced neuroinflammation, improving cognition as the behavioural outcome. Notably, the current research can only speculate about any purported biological or reparative brain changes as a result of intervention.

8.4 Limitations

8.4.1 Sample size

Due to the time scale of doctoral research the sample sizes for both studies conducted was smaller than initial projections. The ideal sample size for a normative cohort is considered to be around 70 participants in line with recommendations for small scale studies (Teare et al., 2014). So, although cohort size did not meet this criteria, sixty participants completed the normative study with an even number in each group. This sample size compared favourably to other recent studies (e.g. Harris et al., 2011, Macpherson et al., 2012, Scholey et al., 2013, Von Armin et al., 2013, Whyte et al., 2016).

In regard to the TBI study, comparable research suggests this sample size is sufficient for a pilot cross-over study, with 10 participants recruited in each group (Garcia et al., 2004; Julious, 2005). There was some attrition in the present study (2 participants; 1 in group OM and 1 in group MO), which for a longitudinal study in a clinical population was a good outcome (Richter et al., 2020). The Consort diagram (Appendix C1) highlights that 69 people were identified by clinicians as suitable for the research. Some of the referring Trusts preferred to approach potential participants with the Participant Information document themselves, gaining verbal consent from individuals that they

wished to be involved in the study before referring them. Other Trusts made the initial contact with individuals and gave a general overview of the study, individuals were then referred to me to make contact and to follow-up once the Participant Information had been sent. This second method was more successful as it often required many days of regular telephone calls from myself to get participants to read the documentation and to talk through what was required so that an informed decision to participate could be made. Obviously, NHS Trust collaborators did not have the time to make daily telephone calls to follow-up with individuals and this perhaps resulted in fewer individuals being involved in the study than may have otherwise been the case.

Another issue related to the sample size of the TBI study was the inclusion/exclusion criteria. This in and of itself is not a limitation of the research but a strength as it was constructed to introduce a level of homogeneity in a very heterogeneous population. The criteria stated that only those with a single TBI could be involved in the research, thus excluding a large proportion of sport-related injuries (although several cyclists were participants). This exclusion criterion removed the confound of effects of multiple concussive events on findings. Individuals who were already taking over the counter micronutrient supplements were also excluded from the study as it would not have been possible to parse out the effects of the study interventions from the effects from supplements participants were already taking. It was also a safety measure to ensure that participants did not exceed upper tolerable limits for any micronutrient. These and the other exclusion criteria (specifically exclusion of those with drug or alcohol problems) put limitations on the potential participant pool but imposed a level of homogeneity on the sample.

8.4.2 Testing for biomarkers

As was discussed in Chapters Four and Seven one potential limitation of both studies in this PhD is the lack of testing for biomarkers of micronutrient status, and for inflammatory markers in the TBI study. Individual micronutrient status can be assessed via a number of physiological matrices including urine, saliva, nails and hair, depending on the individual micronutrient, however a blood draw is often required (Höller et al., 2018). Blood draws are invasive and the prospect of a number of blood draws may have dissuaded people from participating in the research, particularly as a number of samples is often needed to test levels of multiple micronutrients. There is currently debate over the most effective assessment technique for each micronutrient (Höller et al., 2018), in addition it was not clear which micronutrients would be the best targets for this kind of investigation when planning the normative study.

The lack of testing for inflammatory markers is another limiting factor in being able to evidence physiological changes following interventions in the TBI study. One contributing issue to this limitation is sufficient evidence for the presence of inflammatory markers (e.g. the cytokines interferon (IFN)-γ, tumour necrosis factor (TNF)-α, IL1b, IL6) in blood serum at time points further than six months post-injury (Licastro et al., 2016). Another biomarker of neuroinflammation, the protein neurofilament light (NfL), has been found to be elevated following severe TBI up to 17 months post-injury (Bagnato et al., 2017) and can be effectively measured in blood plasma in levels equivalent to that found in CSF (Novakova et al., 2017; Rubin et al., 2019). Gaining samples of blood plasma is comparatively much less invasive than CSF, however, carries the same limitations on recruitment as previously discussed. Taking blood samples requires laboratory space and human tissue approvals, with the additional costs that this would incur this was beyond the scope of the current research. Future studies should, however, include analysis of blood plasma for inflammatory biomarkers in the design.

8.4.3 Food diary analyses

The use of different software in the two studies to analyse food diary entries is another possible limitation of this research as it potentially prevents direct comparison of micronutrient intake between studies. The change in software usage was due to the university acquiring the license to Nutritics as an alternative to Netwisp (which was no longer supported by the university) just prior to commencement of the TBI study. Nutritics uses newer food composition information, compared to Netwisp, and is therefore potentially more accurate in the analyses of micronutrient content of food items. Recent research has however used both pieces of software as alternates to analyse food diaries (McCrink et al., 2020), indicating the perceived equivalence of the databases within nutrient research.

8.4.4 Multimicronutrient interventions

One potential limitation of using over the counter formulations for this programme of research is that it was not possible to source a formulation that completely met requirements. For the normative study the aim was to find a formulation that delivered RDA amounts for each of the essential vitamins and minerals. The Boots A-Z (Appendix A.1) was the closest to this requirement but did not contain RDA levels of some micronutrients, e.g. vitamin C, D, calcium. This formulation also contained small amounts of minerals that were outside the remit of this study (chromium, copper, manganese, molybdenum). For the TBI study the aim was to find a formulation that provided levels of vitamins and minerals that were at or above RDA. The Swisse

Women's 50+ Ultivite (Appendix C.2) delivered much of what was required, however levels of some micronutrients (e.g. magnesium, calcium) were lower and others higher (e.g. most B vitamins) than would have been ideal. There were also a number of 'extracts' in this formulation that were again outside the remit of this study and the potential for these having had an effect on participants' cognition or levels of fatigue cannot be excluded. This all has to be placed in the context of costs, which would have been prohibitive to create bespoke formulations for this research, but a bespoke product would be optimal in future work to address this limitation.

8.5 Directions for future research

The findings highlighted by this programme of PhD research represent a robust start point for future work with a number of potential avenues for research in both normative and head injured populations.

8.5.1 Future normative research

8.5.1.1 Vitamin C

One of the novel findings of the normative study were improvements in immediate and delayed verbal and recognition memory, delayed visual memory, cognitive flexibility and processing speed seen in normal participants taking a relatively low dose (200mg) of vitamin C. Since conclusion of the normative study cross-sectional research has found a relationship between higher plasma levels of ascorbate (vitamin C) and performance on similar cognitive tasks (recognition memory, verbal memory, choice reaction time; Travica et al., 2019; 2020) in healthy adults (range 24-95, mean 60.97, SD 15.76 years). It might therefore be useful to investigate the role of vitamin C in cognition combining the methodologies of both research studies; a longitudinal study taking measures of plasma vitamin C along with measures of cognitive performance at baseline and following the intervention. Vitamin C is a water-soluble vitamin and therefore higher levels of vitamin C could be administered than were used in the normative study without risk of toxicity, as excess is excreted.

8.5.1.2 Vitamin D

Participants allocated to the vitamin D intervention in the normative study did not show the expected improvements in cognition. To investigate this further dosage could be manipulated; the dosage administered (10µg) may not have been sufficient to have an observable effect on cognition, with research indicating that 25µg might be a more effective dosage (Llewellyn et al., 2010) and it would be useful to take blood plasma to

gain a measure of vitamin D hormone status. This would be of particular relevance for a vitamin D intervention as the majority of this seco-steriod is manufactured within the body following exposure to UVB light (Pittas et al., 2010). As vitamin D is intimately connected with calcium homeostasis it would also be useful to look at 'nutrient matching' and assess calcium levels in relation to the vitamin D intervention. Comparing relative changes in cognitive performance with two different dosages of vitamin D, plus a placebo group, would be a good way to fully investigate whether vitamin D dose produces different outcome with respect to cognitive change. Additionally, absorption of vitamin D is known to be affected by the size of the meal ingested, with research showing that uptake of the vitamin is increased by 50% percent if it is taken with the largest meal of the day, compared to taking it with breakfast or lunch (Mulligan & Licata, 2010), although this may reflect other circadian factors too. This could be introduced as a variable, with matched participants (gender, age, IQ) taking the vitamin D intervention with either breakfast or with their main meal and cognitive outcome compared.

8.5.2.3 Multimicronutrient

In the normative study the greatest level of improvement was seen in the group allocated to the multimicronutrient intervention. What cannot be established from this finding is which micronutrients, or combination of micronutrients were the drivers of this effect. An additional question is whether supplementing individuals so that total intake greatly exceeds recommended intake amounts (set at a level to meet the requirements of 98% of the population) is beneficial, specifically in terms of cognitive function. To start to unpick this it would be necessary to conduct a number of comparison studies. One way forward would be to conduct studies involving vitamins and minerals that have inter-related functionality within the brain, with the hypotheses of targeting specific cognitive domains or cellular processes. For example, the B-complex vitamins are inter-related in the roles they play in cellular energy function, this inter-relationship the reason why they are grouped together. Magnesium and selenium have both been implicated in memory function (Cardoso et al., 2014; Durlach, 1990; Slutsky et al., 2010), and magnesium is a co-factor in reactions to form vitamin D binding protein (Gröber et al., 2015). These three micronutrients may therefore work well together as an intervention, particularly as these micronutrients are typically at low levels in peoples' diets. The effect on cognition of more targeted micronutrient interventions could then be compared with a broad-spectrum multimicronutrient intervention. Another variable that has not been investigated in sufficient depth is the effect of micronutrient interventions in young adults (those between 18 and 30), with the majority of micronutrient research being in children and the elderly.

Early adulthood is a key period in brain maturation and targeted micronutrient research targeted at this age range would fill a gap in the literature.

8.5.2 Head Injury Research

The underlying pathophysiological response to traumatic brain injury is complex with a large number of contributory factors affecting outcome (Ponsford, 2013). The research conducted during this PhD has provided evidence that micronutrient interventions have a role to play in cognitive recovery post injury and this work provides a foundation for future studies. There are a number of ways that micronutrient research in TBI populations could be explored in the future, particularly by taking a more holistic approach to understanding and treating individuals. By taking the research from this thesis forwards and treating the individual as a whole, rather than simply focusing on cognitive issues, it may be possible to further improve outcomes. This is becoming of greater importance as there is growing acceptance that TBI is not a single disease process, but instead that there are a number of endophenotypes (Hannawi & Stevens, 2016). It therefore stands to reason that a more holistic approach to treatment is required to fully address the different underlying problems that individuals experience after head trauma.

8.5.2.1 Interventions

Multimicronutrient supplementation provided varied findings in cognitive performance in the normative and TBI studies. As has been previously discussed there are a number of potential underlying factors that may have affected these findings. Participants in the TBI study, however, consistently showed improvements in cognition when taking the omega-3 intervention. In future, research in TBI populations could combine these two interventions (multimicronutrient and omega-3) and compare this with omega-3 alone. This would be worthwhile to investigate whether a multimicronutrient intervention would provide further cellular support with the outcome of greater improvements in cognition when compared with omega-3 supplementation alone.

8.5.2.2 Lifestyle changes

Evidence from sports research has highlighted the positive effect of delayed exercise on recovery following traumatic brain injury (Leddy et al., 2015). The general physiological process produces excitotoxicity as a consequence of the initial insult, followed by depressed brain activity. Exercise increases expression of BDNF (brain-derived neurotrophic factor), a protein that improves synaptic plasticity, increasing brain activation (Griesbach et al., 2004). An exercise intervention could therefore improve learning and memory in TBI, which could be assessed using a cognitive test battery to

measure these functions. Factors that would need to be considered in an exercise intervention is severity of injury and activity level prior to injury, as these dictates when exercise interventions are effective (Griesbach, 2012). An exercise intervention could then be a variable manipulated alongside micronutrient supplementation, with participants taking the micronutrient intervention alone or paired with a tailored exercise regime. One consideration in this kind of study is the participant's willingness to engage with an exercise intervention as there is evidence from rodents indicating that forced exercise may result in elevated release of stress hormones affecting BDNF expression (Griesbach et al., 2012; Ke et al., 2011). Improvements in cognition would be measured using a test battery including measures of processing speed, memory and executive function; the cognitive domains where improvements were seen during study two.

8.5.2.3 Gut brain axis

Providing micronutrient interventions to ameliorate secondary cascade mechanisms in TBI is potentially ignoring an important determinant of the effectiveness of uptake of such interventions; gut function. The gut-brain-axis (GBA) is a bidirectional pathway; healthy gut microbiota are important in regulation of neurotransmitters, neurogenesis, microglial activation and the neuro-endocrine stress response (Barker & Jordan, 2020; Carabotti et al., 2015; Mayer et al., 2015; Sampson & Mazmanian, 2015; Sherwin et al., 2016). The brain in turn modulates gastrointestinal motility and secretion, and maintenance of the mucus bilayer and biofilm which provide the correct environment for microbiota (Macfarlane & Dillon, 2007). A recognised consequence of TBI is intestinal barrier dysfunction resulting in structural and functional changes to gut epithelial tissue (Bansal et al., 2009; Hang et al., 2003; Kharrazian, 2015). More specifically TBI can lead to altered gastrointestinal function through disruption to afferent and efferent circuits including the enteric nervous system and vagal complex. One outcome of this is TBI-induced intestinal permeability. This is followed by a systemic immune response evidenced by elevation in a number of inflammatory cytokines including CD40, NK-kβ, TNF-α, IL-6, along with increased priming of microglia which are already reactive following damage to brain tissue (Finnie, 2013; Kharrazian, 2015). The result of this is an inflammatory cascade loop between the brain and the gut; addressing compromised gut function could potentially offer one route to reduce the neuroinflammatory cascade.

Compromised gut function can be addressed in two ways; increasing fibre intake (prebiotics) to provide nutrients for gut microbiota (Desai et al., 2016), and by introducing more live microbiota into the gut (probiotics). Probiotics have also been shown to tighten

gap junctions within the intestine (Hsieh et al., 2015), reducing gut permeability and subsequent overall health (Zhang & Jiang, 2015). Importantly improving gut function may result in more efficient uptake of micronutrients, potentially increasing the effects of these types of intervention. Future research could compare one group of TBI individuals taking a complete intervention composed of pre- and pro-biotics with a micronutrient intervention (omega-3 plus multimicronutrient) with another TBI group only taking the micronutrient intervention. It would also be useful to gain a measure of participants inflammatory status from blood plasma to compare changes in this measure between groups. A parallel study design with matched controls would need to be employed for this study rather than a cross-over design as improvements to the microbiome would not be reversed with a wash-out period. Again, cognitive improvements would be assessed via a test battery focusing on the domains of processing speed, memory and executive function.

8.6 Summary and Conclusions

The aim of this thesis was to evaluate cognitive function under normal conditions and following traumatic brain injury, and to understand the potential role of micronutrient intervention to cognitive outcome. The research conducted investigated whether supporting general health with micronutrients had an impact on cognition; study one assessed purported cognitive change in a normative cohort following either a vitamin D, multimicronutrient or vitamin C eight-week intervention. Study two assessed cognitive change in a TBI cohort following a cross-over study with an omega-3 and multimicronutrient intervention with a parallel placebo condition, again each intervention period was eight weeks long. Participants in both studies completed food diaries to provide an estimate of dietary micronutrient and omega-3 intake with a six-week washout period between interventions in study two.

Study one (Chapter Four) demonstrated that the general population had dietary intake significantly below recommended dietary amounts for folate, riboflavin, most fat-soluble vitamins and most essential minerals. Following the intervention period there were improvements in a number of cognitive functions for each of the intervention groups, including visual and verbal recall, learning and memory, processing speed and social cognition. The multimicronutrient intervention showed the greatest number of improvements over the widest range of cognitive functions. Participants taking vitamin C showed improvements in motor planning, visual strategy generation and explicit awareness of a presented pattern in addition to the improvements seen in all groups. The

Multimicronutrient group alone showed improvements in visual spatial working memory and implicit awareness of a presented pattern on a serial reaction time task.

Study two (Chapter Seven) had similar findings to study one in terms of dietary intake of micronutrients by participants, with folate, riboflavin, many fat-soluble vitamins and essential minerals all significantly below recommended daily intake. The multimicronutrient intervention did not consistently result in the same level of cognitive improvements in groups OM and MO, when compared with the normative population; only group MO showing cognitive improvements following taking the multimicronutrient supplement. It has been hypothesised that this difference in findings between the two groups may be an effect of a differing response between the sexes, however this requires further research to clarify this. There were, however, consistent improvements in both groups OM and MO following the omega-3 intervention with improvements seen in processing speed, visual and verbal memory and executive functions. The Placebo group also showed some improvements, focused in the domain of memory. This study has demonstrated that micronutrient interventions have the capacity to improve cognitive function following TBI, even at time points distal to the original insult. This emphasises the need to carry out further research in this area and to include information about the advantages of healthy eating in brain recovery to hospital discharge information.

To conclude the thesis has made an original contribution to knowledge by directly comparing the effect of single micronutrient interventions with multimicronutrients to cognitive outcome in both normative and clinical populations using a standardised procedure for all participants. To the knowledge of the researcher this is the first time that a standardised intervention involving micronutrients has been administered in a TBI population. It is also the first time that a multimicronutrient intervention has been compared with an omega-3 intervention with cognitive function as the outcome measure. This thesis also compared dietary intake of micronutrients in both these populations, highlighting the similarity between the two and confirming previous research of a level of 'hidden hunger' for some essential B vitamins, fat-soluble vitamins and also minerals. This research has highlighted that individuals eating a 'normal' diet have levels of intake of micronutrients that are insufficient to meet recommended guidelines, which may have long-term health consequences. Placed into the wider context of the population of people with a TBI, pre-existing and ongoing levels of micronutrient insufficiency may be resulting in sub-optimal levels of recovery, this could be easily addressed at relatively low cost. A good diet with supplements is therefore important following TBI and should

be highlighted to individuals who have experienced brain trauma in hospital discharge information.

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Appendix A

A.1 Supplement Composition

Boots A-Z Vitamin

Micronutrient	Quantity
Vitamin A	400µg RE
Vitamin D	5µg
Vitamin E	12mg α-TE
Vitamin C	80mg
Thiamin (B1)	1.1mg
Riboflavin (B2)	1.4mg
Niacin (B3)	16mg NE
Vitamin B6	1.4mg
Folic Acid	200µg
Vitamin B12	2.5µg
Biotin	50µg
Pantothenic Acid	6mg
Vitamin K	75µg
Calcium	200mg
Iron	14mg
Magnesium	60mg
Zinc	10mg
Iodine	150µg
Chromium	40µg
Copper	0.5mg
Manganese	0.5mg
Molybdenum	50µg
Selenium	55µg

Vitamin D Supplement 10µg
Vitamin C Supplement 200mg

A.2 Example Food Diary Page

Date_____

Try to provide portion sizes wherever possible and also give all brand names.

Breakfast. Include all food and drinks *(example: 8am - 1 piece of brown toast and butter, 2 eggs scrambled, 1 cup of black coffee with 1 sugar)* **Time:**
Lunch. Include all food and drinks *(example: 12.30pm - 1 small plate of lettuce and tomatoes, 1/2 tin tuna in brine, 2 small new potatoes - boiled, small portion of full-fat salad dressing, and 1 can of Coke)* **Time:**
Evening meal. Include all food and drinks *(example: 7pm - Beef chilli con carne with white rice (average portion). Cup of black coffee with one sugar)* **Time:**
Snacks and drinks (not taken at mealtimes) *(example: 1 apple, 1 bar of chocolate (Mars bar), 1 small glass of full fat milk, 1 plain biscuit, 1 large glass of white wine)* **Is this day typical of your usual food intake? YES……NO……..**

A.3 Participant Materials

A.3.1 Participant Information

Sheffield Hallam University

Rebecca Denniss
Sheffield Hallam University
Department of Psychology, Sociology and Politics
Collegiate Crescent Campus
Oak Lodge
Sheffield S10 2 BP

Telephone: 0114 225 5580
Email: r.denniss@shu.ac.uk

Participant Information Sheet

Hello. I am conducting research for my PhD qulaification. This is a voluntary study, you are not obliged to take part and you may refuse to take part at any point during the research. This sheet outlines why the research is being conducted and what you, as a participant, would be required to do. If you have any questions, or you do not fully understand something, feel free to ask me at any point.

What is this study about?
Research has suggested that certain micronutrients (vitamins and minerals) may improve performance of individuals with head injuries. To investigate this we are going to compare people taking different vitamin supplements to see which shows greater improvement on task performance. As such it is important that you are not currently taking any multivitamin supplements to be a participant in this study.

Do I have to take part?
This study is voluntary and you decide whether you want to take part in the research. If you do decide to participate then you will be asked to sign a written consent form to show that you are fully informed and willing to take part. Please be aware that if you do participate you are able to stop taking part in the research at any time without question. You do not have to divulge any information or answer any questions that you feel uncomfortable with. You are also able to withdraw any of your results up to two weeks after they have been collected. It will not be possible to withdraw results after two weeks as your data will have been collated with the other participants and analysed. If after reading this sheet you do not want to take part in the research then that is also fine, no questions will be asked and you will be free to leave.

What will I have to do if I say yes?
If you want to take part then you will be asked to attend four test sessions in two groups of two, six months apart. These test sessions will take place either at Sheffield Hallam University or at your home, at your discretion. During the first two sessions you will then be given some tasks that will calculate your IQ, assess your memory and problem solving abilities and some social skills. During the second set of sessions you will do the same

tasks, or variants of them, assessing the same abilities. Between these two test sessions you will be asked to take one vitamin tablet a day with a meal for the six month period and keep a food diary for the first two weeks. The food diary will require you to note everything that you eat and drink over the two week period, being as accurate as you can and including brand names. Full instructions on how to fill in the food diary will be given to you by the experimenter and will also be written in the food diary booklet. You will be reminded by email each day to complete your food diary, and then twice a week to take your supplement.

Who is the Sheffield Hallam research team?
There are four researchers involved in this Sheffield Hallam research. As previously stated this research is being conducted by Rebecca Denniss. Rebecca is a PhD student with a MSc in Cognitive Neuroscience with full training in the correct administration of psychological tests and experience working with people who have had head injuries. Overseeing this research is:
Dr. Lynne Barker, Senior Lecturer in Cognitive Neuroscience
Dr John Francis, Principal Lecturer in Psychology and Food Behaviours
Dr Catherine Day, Senior Lecturer in Psychology and Food Choices

Where will all of this take place?
Research will take place either on the Sheffield Hallam University Collegiate campus in the specially designed psychology research labs, or the researcher can travel to your home for testing.

How long will the study take?
From when you begin the study you will be involved for a maximum of seven months. Over this time period you will be asked to attend 4 sessions in total with the researcher with an 6 month gap between session pairs. Each testing session may last for approximately 2 .5 hours with rest breaks determined by you.

What will be done with my results?
All of your results will be anonymised, this means that your name will not appear anywhere on your results. Participants will be given numbers and not be identified by their names. All data collected will be stored in a locked filing cabinet within a restricted access building or encrypted and stored on a password protected PC. Your anonymous data will be kept on a database so that other researchers can refer to it. Your results will be added to other participant's results and the researcher will look for patterns within these. The overall result of the research will be published in a scientific journal. If you would like to receive copies of any publications arising from this research you may request them from the researchers involved.

Is this study safe?
Yes. This research has been reviewed and approved by the Faculty Research Ethics Committee (FREC) at Sheffield Hallam University. All vitamin tablets contain no more than World Health Organisation recommended daily amounts. However, should you experience any negative effects related to the tablets you should discontinue taking them and inform the study team that you wish to withdraw from the study.

Pregnant or breast-feeding women should not take part in this study.

What are the advantages of taking part?
You will receive an evaluation of your cognitive functions and we are happy to provide a breakdown of scores. Findings of this research may also expand knowledge of how

nutrition affects cognition. The data collected from this study will be used to provide information to rehabilitation teams and the health service into how nutritional supplements could help those who suffer head injuries.

What are the disadvantages of taking part?

There are no foreseeable risks to this research and none of the tasks should cause you any discomfort or any distress, although they make you feel a little tired. If you experience any adverse reactions to the supplement you are given you are entitled to discontinue your participation in the study.

Can I know my results?

You can request a feedback form that will tell you how well you did on the tasks. Unfortunately you won't be able to have the form straight away, as the tests require scoring. You can collect a feedback sheet at the next session or they can be posted to you. We will not be able to tell you if you have done the same as other participants as we are not allowed to discuss other people's results.

When can I ask questions?

You are free to ask any questions at any point during the research. If you have any questions now please feel free to ask. If you think of any questions after you leave here today please feel free to contact me using the details at the top of the front page.

PLEASE REMEMBER THAT ALL RESULTS WILL STAY CONFIDENTIAL AND ANONYMOUS. YOU ARE FREE TO WITHDRAW FROM THIS STUDY AT ANY TIME DURING THE RESEARCH.

Thank you for taking the time to read this.

Researcher: Rebecca Denniss. Rebecca.j.denniss@student.shu.ac.uk
If you wish to query this further and do not wish to speak to the researcher please contact:
Dr Lynne Barker,
Senior Lecturer in Cognitive Neuroscience,
Department of Psychology,
Southbourne,
37, Clarkehouse Road,
Collegiate Campus,
Sheffield Hallam University,
Sheffield
S10 2LD
Telephone Number: 0114 225 5379
email: l.barker@shu.ac.uk

A.3.2 Consent Form

Sheffield Hallam University

Optimising nutrition: Can dietary supplementation enhance general cognitive function in traumaticall brain injured populations?

Please read the questions below very carefully and circle your answer. If you do not understand any of the questions please ask the researcher.

Have you read and understood the participant information sheet?	Yes	No
Have all of your questions been answered sufficiently?	Yes	No
Do you understand why the study is being done and what is required of you as a participant?	Yes	No
Are you currently taking any vitamin supplements?	Yes	No
Do you understand that you will be required to take one tablet each day for 8 weeks and keep a food diary for 2 weeks?	Yes	No
Do you understand that if you experience any negative effects from taking the supplements you are free to withdraw from the study?	Yes	No
Do you understand that if you are pregnant or breastfeeding you should not take part in this study?	Yes	No
Do you understand that this research is voluntary and you are free to withdraw from the research at any point during the testing phase and withdraw your results up to two weeks after testing without question or any negative consequences?	Yes	No
Do you understand that all your results will be anonymous and will stay confidential and secure throughout the research process although they will be made available for other researchers to refer to?	Yes	No
Do you know how to contact the researcher after the study if you have any questions or wish to withdraw?	Yes	No
Do you agree to take part in this research?	Yes	No

Name (Printed) ----------

Signature ----------

Date ----------

Email Address ----------

If you would like to be contacted about published results and where you can find them then please indicate here Yes/No

Researcher contact details:

Rebecca Denniss (e-mail Rebecca.j.denniss@student.shu.ac.uk)

If you have any questions about the research and you do not wish to discuss them with the researcher then please contact:

Dr Lynne Barker, Senior Lecturer in Cognitive Neuroscience,

Department of Psychology,

Southbourne,
37, Clarkehouse Road,
Collegiate Campus,
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Sheffield
S10 2LD
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A.3.3 Debrief

Sheffield Hallam University

Rebecca Denniss
Sheffield Hallam University,Department of Psychology,
Heart of Campus Building, Collegiate Campus,
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Optimising nutrition: Can dietary supplementation enhance general cognitive function in normal groups? Evaluating potential clinical applications

Thank you for participating in this research. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information.

The purpose of this research is to investigate whether vitamin supplements can improve an individual's ability to process certain kinds of information. You were allocated to the _____ condition. It was necessary that both you and the person administering the tests were unaware of the tablet you were taking to ensure that there was no bias in the results, either from your expectations or from the expectations of the experimenter. This form of study is known as a randomised clinical trial.

During this research you initially completed a number of tasks to test general levels of cognitive ability, memory capability and problem solving ability. You were then asked to take a tablet once a day for 8 weeks and keep a food diary. Finally you have completed a number of the same kinds of tasks as you did in the first session.

All information provided by you will remain confidential and will be stored anonymously in accordance with the Data Protection Act 1998. Only members of the research team will have access to your data. Hard copies of data will be stored in locked cabinet in a key-card only building. Data transferred onto a computer will be password protected and stored on Sheffield Hallam University's secure network.

The results from the analysis of this research will be written up as an internal report and may also be submitted to an academic journal for publication. Results from this study will also be used to inform further research into nutrition and cognition in people with neurological conditions.

If you have any concerns about the experiment, the research or the researcher and you do not wish to discuss them with the researcher then please contact:

Dr Lynne Barker, Senior Lecturer in Cognitive Neuroscience
Department of Psychology,
Heart of Campus Building,
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Appendix B: Chapter 4 SPSS Outputs

B1. Descriptive statistics of baseline cognitive task performance by group.

Cognitive Measure	Group		
	Vitamin D (n = 20)	Multivitamin (n = 20)	Vitamin C (n = 20)
	Mean (SD)	Mean (SD)	Mean (SD)
PANAS Positive Affect Rating	33.60 (7.35)	36.30 (6.14)	35.50 (5.49)
PANAS Negative Affect Rating	19.50 (6.42)	17.45 (5.42)	17.65 (6.38)
WASI-II FSIQ-4	113.15 (10.41)	110.40 (12.07)	114.15 (11.56)
WAIS-III Symbol Search Correct	12.75 (3.52)	12.05 (2.67)	13.60 (2.04)
WAIS-III Digit Span	10.85 (3.03)	10.15 (2.96)	11.50 (2.21)
WMS-IV Logical Memory Immediate Recall	11.61 (2.26)	10.80 (2.59)	11.75 (2.53)
WMS-IV Logical Memory Delayed Recall	11.35 (3.13)	11.00 (2.64)	11.45 (2.61)
WMS-IV Visual Reproduction Immediate Recall	12.40 (2.74)	12.25 (2.34)	12.30 (2.87)
WMS-IV Visual Reproduction Delayed Recall	11.55 (3.65)	10.95 (2.35)	13.05 (3.25)
WMS-IV Symbol Span Correct Recall	11.75 (3.04)	11.80 (3.58)	12.25 (2.95)
Doors and People Overall Score	12.35 (3.27)	12.05 (2.63)	12.65 (2.35)
DKEFS Trail Making Visual Scanning	12.60 (1.60)	12.65 (1.27)	12.45 (1.43)
DKEFS Trail Making Number Sequencing	11.40 (2.19)	11.80 (2.33)	11.95 (1.54)
DKEFS Trail Making Letter Sequencing	12.45 (1.64)	12.65 (1.87)	12.60 (1.64)
DKEFS Trail Making Number/Letter Switching	12.05 (1.39)	11.75 (1.92)	12.45 (1.28)
DKEFS Trail Making Motor Speed	11.75 (2.40)	11.55 (1.88)	12.20 (1.20)
DKEFS Verbal Fluency Phonemic Fluency	13.10 (2.55)	11.90 (3.67)	12.65 (3.47)
DKEFS Verbal Fluency Semantic Fluency	14.40 (3.07)	12.80 (3.86)	15.25 (2.69)
DKEFS Verbal Fluency Semantic Switching	14.85 (3.18)	12.85 (3.22)	14.75 (2.99)
DKEFS Design Fluency Total Correct Designs	8.25 (2.51)	7.90 (1.55)	8.35 (1.39)
DKEFS Tower Total Score	12.50 (2.74)	12.30 (2.56)	12.75 (2.17)
DKEFS Tower Time per Move	11.15 (1.14)	11.02 (1.65)	10.90 (1.33)
DKEFS Tower Mean 1st Move Time	11.50 (1.36)	10.95 (2.37)	11.70 (2.11)
DKEFS Tower Move Accuracy	11.00 (1.30)	10.50 (1.73)	10.40 (1.60)
Serial Reaction Time Test Explicit Learning	11.05 (4.47)	11.15 (5.33)	9.80 (3.32)
Serial Reaction Time Test Implicit Learning	79.52 (38.90)	64.74 (63.25)	89.22 (41.08)
Serial Reaction Time Test Implicit Learning Outliers Removed	79.52 (38.90)	81.14 (31.87)	89.22 (41.08)
Reading the Mind in the Eyes	27.95 (2.50)	27.20 (3.97)	27.65 (3.39)
Movie for the Assessment of Social Cognition	36.10 (2.86)	36.00 (3.55)	36.75 (2.69)

B2 Baseline Descriptive Analyses

Baseline ANOVA – IQ

Levene's Test of Equality of Errors Variances

F	*df1*	*df2*	*p*
0.90	2	57	.413

Test of Between Subject Effects

Source	Type III Sum of Squares	df	Mean Square	*F*	*p*	Partial eta^2
Corrected model	150.83	2	75.417	.598	.553	.021
Intercept	760275.267	1	760275.267	6025.625	.000	.991
Intervention	150.833	2	75.417	.598	.553	.021
Error	7191.900	57	126.174			
Total	767618.000	60				
Corrected Total	7342.733	59				

Baseline ANOVA – Age

Levene's Test of Equality of Errors Variances

F	*df1*	*df2*	*p*
2.003	2	57	.144

Test of Between Subject Effects

Source	Type III Sum of Squares	df	Mean Square	*F*	*p*	Partial eta^2
Corrected model	193.433	2	96.717	.730	.486	.025
Intercept	91572.267	1	91572.267	691.313	.000	.924
Intervention	193.433	2	96.717	.730	.486	.025
Error	7550.300	57	132.461			
Total	99316.000	60				
Corrected Total	7743.733	59				

B3 Baseline MANOVA – Cognitive Variables

Effect		Value	*F*	Hypothesis *df*	Error *df*	*p*	Partial Eta^2
Intercept	Pillai's Trace	.998	710.95	27	31	.000	.99
	Wilk's Lambda	.002	710.95	27	31	.000	.99
	Hotelling's Trace	619.218	710.95	27	31	.000	.99
	Roy's Largest Root	619.218	710.95	27	31	.000	.99
Intervention	Pillai's Trace	.984	1.15	54	64	.296	.49
	Wilk's Lambda	.233	1.23	54	62	.214	.52
	Hotelling's Trace	2.362	1.31	54	60	.153	.54
	Roy's Largest Root	1.861	2.21	27	32	.017	.65

B4: Baseline MANOVA Micronutrient Intake

Box's Test of Equality of Covariances Matrix

Box's M	1224.610
F	1.61
*df*1	38
*df*2	8473.98
p	<.001

Effect		Value	*F*	Hypothesis *df*	Error *df*	*p*	Partial Eta^2

Intercept	Pillai's Trace	.978	89.35	19	39	.000	.98
	Wilk's Lambda	.002	89.35	19	39	.000	.98
	Hotelling's Trace	43.529	89.35	19	39	.000	.98
	Roy's Largest Root	43.529	89.35	19	39	.000	.98
Intervention	Pillai's Trace	.600	.90	38	80	.632	.30
	Wilk's Lambda	.490	.88	38	78	.664	.30
	Hotelling's Trace	.857	.86	38	76	.695	.30
	Roy's Largest Root	.449	.94	19	40	.538	.31

B5: Analysis of micronutrients at baseline

Vitamins:

Vitamin D

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	0.38	7.74	2.91	1.71
	Intake + Supplement	10.38	17.74	12.91	1.71
Multivitamin	Intake Alone	0.15	9.60	2.46	2.24
	Intake + Supplements	5.15	14.60	7.46	2.24
Vitamin C	Intake Alone	0.32	5.64	2.50	1.26
	Intake + Supplements	0.32	5.64	2.50	1.26

ANOVA

	Levene Statistic	df1	df2	p

Intake Alone	0.96	2	57	.390	
Intake plus supplement	0.96	2	57	.390	

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	2.49	2	1.25	0.39	.677
	Within groups	181.23	57	3.18		
	Total	183.73	59			
Diet + Supplement	Between Groups	1084.49	2	542.25	170.54	.000
	Within Groups	181.23	57	3.18		
	Total	1265.73	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	12.91	1.71	0.38
Multivitamin	7.46	2.24	0.50

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.17	.687	8.64	38	.000	4.17	6.73
Equal variances not assumed			8.64	35.55	.000	4.17	6.73

Group	Mean	SD	Std Error of Mean
Vitamin D	12.91	1.71	0.38
Placebo	2.50	1.26	0.28

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	1.34	.255	21.92	38	.000	9.45	11.37
Equal variances not assumed			21.92	34.85	.000	9.45	11.37

Group	Mean	SD	Std Error of Mean
Multivitamin	7.46	2.24	0.50
Placebo	2.50	1.26	0.28

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	1.67	.204	8.63	38	.000	3.79	6.12
Equal variances not assumed			8.63	29.86	.000	3.78	6.13

Vitamin C

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	22.00	304.18	86.31	62.44
	Intake + Supplement	22.00	304.18	86.31	62.44
Multivitamin	Intake Alone	22.00	459.00	109.70	102.03

	Intake + Supplements	102.00	539.00	189.70	102.03
Vitamin C	Intake Alone	21.00	187.00	84.35	42.01
	Intake + Supplements	221.00	387.00	284.35	42.01

ANOVA

	Levene Statistic	df1	df2	p
Intake Alone		2	57	
Intake plus supplement		2	57	

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	7957.33	2	3978.66	0.74	.480
	Within groups	305403.35	57	5357.95		
	Total	313360.68	59			
Diet + Supplement	Between Groups	392457.06	2	196228.53	36.62	.000
	Within Groups	305403.35	57	5357.95		
	Total	697860.41	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	86.31	62.44	13.96
Multivitamin	189.70	102.03	22.81

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	1.38	.248	-3.87	38	.000	-157.54	-49.24

Equal variances not assumed			-3.87	31.48	.001	-157.91	-48.87

Group	Mean	SD	Std Error of Mean
Vitamin D	86.31	62.44	13.96
Placebo	284.35	42.01	9.39

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.95	.336	-11.77	38	.000	-232.11	-163.97
Equal variances not assumed			-11.77	33.28	.000	-232.27	-163.82

Group	Mean	SD	Std Error of Mean
Multivitamin	189.70	102.03	22.81
Placebo	284.35	42.01	9.39

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	3.65	.064	-3.84	38	.000	-144.60	-44.70
Equal variances not assumed			-3.84	25.26	.001	-145.44	-43.86

Vitamin E

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	4.52	12.99	7.04	2.43
	Intake + Supplement	4.52	12.99	7.04	2.43
Multivitamin	Intake Alone	2.93	21.07	7.86	3.68
	Intake + Supplements	14.93	33.07	19.86	3.68
Vitamin C	Intake Alone	2.85	12.21	7.99	2.66
	Intake + Supplements	2.85	12.21	7.99	2.66

ANOVA

	Levene Statistic	df1	df2	p
Intake Alone		2	57	
Intake plus supplement		2	57	

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	10.58	2	5.29	0.60	.553
	Within groups	504.20	57	8.85		
	Total	514.78	59			
Diet + Supplement	Between Groups	2041.30	2	1020.65	115.39	.000
	Within Groups	504.20	57	8.85		
	Total	2545.50	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	7.04	2.43	0.54
Multivitamin	19.86	3.68	0.82

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.49	.488	-13.00	38	.000	-14.82	-10.82
Equal variances not assumed			-13.00	32.94	.000	-14.83	-10.81

Group	Mean	SD	Std Error of Mean
Vitamin D	7.04	2.43	0.54
Placebo	7.99	2.66	0.60

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.56	.46	-1.18	38	.247	-2.58	0.68
Equal variances not assumed			-1.18	37.69	.247	-2.58	0.68

Group	Mean	SD	Std Error of Mean
Multivitamin	19.86	3.68	0.82
Placebo	7.99	2.66	0.60

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.04	.851	11.69	38	.000	9.82	13.93
Equal variances not assumed			11.69	34.63	.000	9.81	13.93

Vitamin A

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	342.00	2147.00	812.35	448.21
	Intake + Supplement	342.00	2147.00	812.58	448.21
Multivitamin	Intake Alone	265.00	2262.00	877.10	538.44
	Intake + Supplements	65.00	2662.00	1277.00	538.44
Vitamin C	Intake Alone	227.00	1420.00	750.10	252.16
	Intake + Supplements	227.00	1420.00	750.10	252.16

ANOVA

	Levene Statistic	df1	df2	p
Intake Alone		2	57	
Intake plus supplement		2	57	

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	161310.83	2	80655.42	0.44	.648
	Within groups	10533394.20	57	184796.39		
	Total	10694705.00	59			
Diet + Supplement	Between Groups	3317310.83	2	1658655.42	8.98	.000
	Within Groups	10533394.20	57	184796.39		

Total	13850705.0	59

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	812.35	448.21	100.22
Multivitamin	1277.10	538.44	120.40

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.31	.581	-2.97	38	.005	-781.88	-147.62
Equal variances not assumed			-2.97	36.79	.005	-782.22	-147.28

Group	Mean	SD	Std Error of Mean
Vitamin D	812.35	448.21	100.22
Placebo	750.10	252.16	56.38

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	4.05	.051	0.54	38	.591	-170.54	295.04
Equal variances not assumed			0.54	29.93	.592	-172.62	297.12

Group	Mean	SD	Std Error of Mean
Multivitamin	1277.10	538.44	120.40
Placebo	750.10	252.16	56.38

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	5.52	.024	3.96	38	.000	257.86	796.12
Equal variances not assumed			3.96	26.95	.000	254.19	799.81

Thiamine

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	0.66	1.99	1.21	0.32
	Intake + Supplement	0.66	1.99	1.21	0.32
Multivitamin	Intake Alone	0.87	5.59	1.56	1.04
	Intake + Supplements	1.97	6.69	2.66	1.04
Vitamin C	Intake Alone	0.74	7.37	1.82	1.58
	Intake + Supplements	0.74	7.37	1.82	1.58

ANOVA

	Levene Statistic	df1	df2	p
Intake Alone				
Intake plus supplement				

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	3.12	2	1.56	1.67	.197

	Within groups	53.11	57	0.93		
	Total	56.22	59			
Diet + Supplement	Between Groups	20.19	2	10.09	10.83	.000
	Within Groups	53.11	57	0.93		
	Total	73.29	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	1.21	0.32	0.07
Multivitamin	2.62	0.86	0.19

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	3.46	.070	-6.83	38	.000	-1.83	-0.99
Equal variances not assumed			-6.83	24.26	.000	-1.84	-0.98

Group	Mean	SD	Std Error of Mean
Vitamin D	1.21	0.32	0.07
Placebo	1.76	1.39	0.31

Riboflavin

Descriptives

Group	Minimum	Maximum	Mean	SD

Vitamin D	Intake Alone	0.56	2.03	1.25	0.34
	Intake + Supplement	0.56	2.03	1.25	0.34
Multivitamin	Intake Alone	0.59	2.43	1.41	0.51
	Intake + Supplements	1.99	3.83	2.81	0.51
Vitamin C	Intake Alone	0.57	2.86	1.35	0.55
	Intake + Supplements	0.57	2.86	1.35	0.55

ANOVA

	Levene Statistic	df1	df2	p
Intake Alone				
Intake plus supplement				

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	0.27	2	0.14	0.60	.553
	Within groups	13.00	57	0.23		
	Total	13.27	59			
Diet + Supplement	Between Groups	30.60	2	15.30	67.10	.000
	Within Groups	13.00	57	0.23		
	Total	43.59	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	1.25	0.34	0.08
Multivitamin	2.81	0.51	0.11

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	3.77	.060	-11.40	38	.000	-1.84	-1.29
Equal variances not assumed			-11.40	32.97	.000	-1.84	-1.28

Group	Mean	SD	Std Error of Mean
Vitamin D	1.25	0.34	0.08
Placebo	1.35	0.55	0.12

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	2.21	.145	-0.71	38	.483	-0.40	0.19
Equal variances not assumed			-0.71	31.44	.484	-0.40	0.19

Group	Mean	SD	Std Error of Mean
Multivitamin	2.81	0.51	0.11
Placebo	1.35	0.55	0.12

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.01	.910	8.66	38	.000	1.12	1.80
Equal variances not assumed			8.66	37.76	.000	1.12	1.80

Niacin

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	11.40	68.20	30.77	11.40
	Intake + Supplement	11.40	68.20	30.77	11.40
Multivitamin	Intake Alone	16.40	72.20	32.28	12.39
	Intake + Supplements	32.40	88.20	48.28	12.39
Vitamin C	Intake Alone	15.00	49.50	30.68	8.49
	Intake + Supplements	15.00	49.50	30.68	8.49

ANOVA

	Levene Statistic	df1	df2	p
Intake Alone				
Intake plus supplement				

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	32.53	2	16.26	0.14	.872
	Within groups	6756.88	57	118.54		
	Total	6789.40	59			
Diet + Supplement	Between Groups	4111.46	2	2055.73	17.34	.000
	Within Groups	6756.88	57	118.54		

Total	10868.34	59

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	30.77	11.40	2.55
Multivitamin	48.28	12.39	2.77

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.30	.587	-4.65	38	.000	-25.14	-9.89
Equal variances not assumed			-4.65	37.74	.000	-25.14	-9.89

Group	Mean	SD	Std Error of Mean
Vitamin D	30.77	11.40	2.55
Placebo	30.68	8.49	1.90

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.07	.787	0.03	38	.978	-6.34	6.52
Equal variances not assumed			0.03	35.13	.978	-6.36	6.54

Group	Mean	SD	Std Error of Mean
Multivitamin	48.28	12.39	2.77
Placebo	30.68	8.49	1.90

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.89	.350	5.24	38	.000	10.80	118.92
Equal variances not assumed			5.24	33.62	.000	10.78	24.43

Pantothenic Acid

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	1.61	5.79	3.97	0.94
	Intake + Supplement	1.61	5.79	3.97	0.94
Multivitamin	Intake Alone	2.78	8.82	4.58	1.35
	Intake + Supplements	8.78	14.82	10.58	1.35
Vitamin C	Intake Alone	1.71	6.71	3.95	1.26
	Intake + Supplements	1.71	6.71	3.95	1.26

ANOVA

	Levene Statistic	df1	df2	p
Intake Alone				
Intake plus supplement				

	Sum of Squares	*df*	Mean Square	*F*	*p*

Diet	Between groups	5.14	2	2.57	1.80	.175
	Within groups	81.55	57	1.43		
	Total	86.69	59			
Diet + Supplement	Between Groups	584.42	2	292.21	204.24	.000
	Within Groups	81.55	57	1.43		
	Total	665.97	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	3.97	0.94	0.21
Multivitamin	10.58	1.35	0.30

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	1.41	.243	-17.99	38	.000	-7.36	-5.87
Equal variances not assumed			-17.99	33.80	.000	-7.36	-5.86

Group	Mean	SD	Std Error of Mean
Vitamin D	3.97	0.94	0.21
Placebo	3.95	1.26	0.28

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	2.46	.125	0.05	38	.962	-0.69	0.73
Equal variances not assumed			0.05	35.06	.962	-0.70	0.73

Group	Mean	SD	Std Error of Mean
Multivitamin	10.58	1.35	0.30
Placebo	3.95	1.26	0.28

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.03	.869	16.04	38	.000	5.79	7.47
Equal variances not assumed			16.04	37.82	.000	5.79	7.47

B_6

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	.94	2.58	1.57	0.41
	Intake + Supplement	.94	2.58	1.57	0.41
Multivitamin	Intake Alone	1.15	3.99	1.78	0.65
	Intake + Supplements	2.55	5.39	3.18	0.65
Vitamin C	Intake Alone	0.73	3.24	1.55	0.58

	Intake + Supplements	0.73	3.24	1.55	0.58

ANOVA

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	0.56	2	0.28	0.97	.385
	Within groups	16.54	57	0.29		
	Total	17.10	59			
Diet + Supplement	Between Groups	34.36	2	17.18	59.19	.000
	Within Groups	16.54	57	0.29		
	Total	50.90	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	1.57	0.41	0.09
Multivitamin	3.16	0.61	0.14

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	1.14	.292	-9.79	38	.000	-1.60	0.16
Equal variances not assumed			-9.79	33.29	.000	-1.60	0.16

Group	Mean	SD	Std Error of Mean
Vitamin D	1.57	0.41	0.09

Placebo	1.55	0.58	0.13

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	2.22	.144	.10	38	.923	-0.31	0.34
Equal variances not assumed			.10	34.04	.923	-0.31	0.34

Group	Mean	SD	Std Error of Mean
Multivitamin	3.16	0.61	0.14
Placebo	1.55	0.58	0.13

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	.05	.821	8.59	38	.000	1.23	1.99
Equal variances not assumed			8.59	37.94	.000	1.23	1.99

Biotin

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	14.00	48.30	30.82	10.61
	Intake + Supplement	14.00	48.30	30.82	10.61
Multivitamin	Intake Alone	19.40	65.20	36.05	13.56
	Intake + Supplements	69.40	115.20	86.05	13.56

Vitamin C	Intake Alone	16.60	61.40	32.16	12.84
	Intake + Supplements	16.60	61.40	32.16	12.84

ANOVA

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	294.60	2	147.30	0.96	.390
	Within groups	8765.67	57	153.78		
	Total	9060.27	59			
Diet + Supplement	Between Groups	39701.26	2	19850.63	129.08	.000
	Within Groups	8765.67	57	153.78		
	Total	58466.932	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	30.82	10.61	2.37
Multivitamin	86.05	13.56	3.03

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	1.31	.259	-14.34	38	.000	-63.02	-47.43
Equal variances not assumed			-14.34	35.91	.000	-63.03	-47.42

Group	Mean	SD	Std Error of Mean
Vitamin D	30.82	10.61	2.37
Placebo	32.16	12.84	2.87

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.29	.593	-0.36	38	.721	-8.88	6.20
Equal variances not assumed			-0.36	36.69	.721	-8.89	6.20

Group	Mean	SD	Std Error of Mean
Multivitamin	86.05	13.56	3.03
Placebo	32.16	12.84	2.87

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	.25	.618	12.90	38	.000	45.43	62.34
Equal variances not assumed			12.90	37.89	.000	45.43	62.34

Folic Acid

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	123.00	404.00	223.35	79.75
	Intake + Supplement	123.00	404.00	223.35	79.75
Multivitamin	Intake Alone	132.00	470.00	212.00	84.57
	Intake + Supplements	332.00	670.00	412.00	84.57
Vitamin C	Intake Alone	114.00	299.00	195.85	55.92
	Intake + Supplements	114.00	299.00	195.85	55.92

ANOVA

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	7639.30	2	3819.65	0.69	.506
	Within groups	316167.10	57	5546.79		
	Total	323806.40	59			
Diet + Supplement	Between Groups	553772.63	2	276886.32	49.92	.000
	Within Groups	316167.10	57	5546.79		
	Total	869939.73	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	223.35	79.75	17.83
Multivitamin	412.00	84.57	18.91

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper

Equal variances assumed	0.02	.900	-7.26	38	.000	-241.27	-136.03
Equal variances not assumed			-7.26	37.87	.000	-241.28	-136.02

Group	Mean	SD	Std Error of Mean
Vitamin D	223.35	79.75	17.83
Placebo	195.85	55.92	12.50

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	1.25	.271	1.26	38	.214	-16.59	71.59
Equal variances not assumed			1.26	34.05	.215	-16.76	71.76

Group	Mean	SD	Std Error of Mean
Multivitamin	412.00	84.57	18.91
Placebo	195.85	55.92	12.50

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.66	.421	9.53	38	.000	170.25	262.05

Equal variances not assumed		9.53	32.95	.000	170.02	262.28

B_{12}

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	.06	7.20	3.46	1.43
	Intake + Supplement	.06	7.20	3.46	1.43
Multivitamin	Intake Alone	.40	11.20	3.70	2.57
	Intake + Supplements	2.90	13.70	6.20	2.57
Vitamin C	Intake Alone	.80	5.00	3.12	1.26
	Intake + Supplements	.80	5.00	3.12	1.26

ANOVA

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	3.340	2	1.67	.49	.616
	Within groups	194.920	57	3.42		
	Total	198.260	59			
Diet + Supplement	Between Groups	113.740	2	56.87	16.63	.000
	Within Groups	194.920	57	3.42		
	Total	308.660	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	3.46	1.43	0.32
Multivitamin	6.20	2.57	0.58

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	3.78	.059	-4.15	38	.000	-4.07	-1.40
Equal variances not assumed			-4.15	29.74	.000	-4.08	-1.39

Group	Mean	SD	Std Error of Mean
Vitamin D	3.46	1.43	0.32
Placebo	3.12	1.26	0.28

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	.01	.905	.79	38	.432	-0.52	1.20
Equal variances not assumed			.79	37.36	.432	-0.52	1.20

Group	Mean	SD	Std Error of Mean
Multivitamin	6.20	2.57	0.58
Placebo	3.12	1.26	0.28

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	4.07	.051	4.80	38	.000	1.78	4.37
Equal variances not assumed			4.80	27.56	.000	1.76	4.39

Minerals

Calcium

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	293.00	1038.00	702.35	200.57
	Intake + Supplement	293.00	1038.00	702.35	200.57
Multivitamin	Intake Alone	416.00	1201.00	801.50	173.91
	Intake + Supplements	616.00	1401.00	1001.50	173.91
Vitamin C	Intake Alone	502.00	1230.00	811.50	185.50
	Intake + Supplements	502.00	1230.00	811.50	185.50

ANOVA

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	145629.63	2	78814.82	2.08	.134
	Within groups	1992712.55	57	34959.87		
	Total	2138342.18	59			
Diet + Supplement	Between Groups	916696.30	2	458348.15	13.11	.000
	Within Groups	1992712.55	57	34959.87		
	Total	2909408.85	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	702.35	200.57	44.85
Multivitamin	1001.50	173.91	38.89

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.72	.401	-5.04	38	.000	-419.32	-178.98
Equal variances not assumed			-5.04	37.25	.000	-419.40	-178.90

Group	Mean	SD	Std Error of Mean
Vitamin D	702.35	200.57	44.85
Placebo	811.50	185.50	41.48

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.37	.549	-1.79	38	.082	-232.82	14.52
Equal variances not assumed			-1.79	37.78	.082	-232.84	14.54

Group	Mean	SD	Std Error of Mean
Multivitamin	1001.50	173.91	38.89
Placebo	811.50	185.50	41.48

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.05	.832	3.34	38	.002	74.90	305.10
Equal variances not assumed			3.34	37.84	.002	74.88	305.11

Iodine

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	24.00	250.00	100.75	51.19
	Intake + Supplement	24.00	250.00	100.75	51.19
Multivitamin	Intake Alone	21.00	187.00	104.15	44.08
	Intake + Supplements	171.00	337.00	254.15	44.08
Vitamin C	Intake Alone	36.00	148.00	96.20	33.53
	Intake + Supplements	36.00	148.00	96.20	33.53

ANOVA

	Levene Statistic	df1	df2	p
Intake Alone	0.85	2	57	.432
Intake plus supplement	0.85	2	57	.432

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	636.43	2	318.22	0.17	.846
	Within groups	108063.5	57	1895.85		

	Total	108699.9	59			
Diet + Supplement	Between Groups	323336.4	2	161668.2	85.28	.000
	Within Groups	108063.5	57	1895.85		
	Total	431399.9	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	100.75	51.18	11.45
Multivitamin	254.15	44.08	9.86

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.26	.612	-10.16	38	.000	-183.98	-122.82
Equal variances not assumed			-10.16	37.18	.000	-184.00	-122.80

Group	Mean	SD	Std Error of Mean
Vitamin D	100.75	51.19	11.45
Placebo	96.20	33.53	7.50

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper

Equal variances assumed	1.74	.195	0.33	38	.741	-23.15	32.25
Equal variances not assumed			0.33	32.77	.742	-23.30	32.40

Group	Mean	SD	Std Error of Mean
Multivitamin	254.15	44.08	9.86
Placebo	96.20	33.53	7.50

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.69	.411	12.75	38	.000	132.88	183.02
Equal variances not assumed			12.75	35.78	.000	132.82	183.08

Iron

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	6.30	22.40	10.97	3.76
	Intake + Supplement	6.30	22.40	10.97	3.76
Multivitamin	Intake Alone	6.90	18.30	11.61	3.30
	Intake + Supplements	20.90	32.30	25.61	3.30
Vitamin C	Intake Alone	5.90	23.50	11.01	4.83
	Intake + Supplements	5.90	23.50	11.01	4.83

ANOVA

	Sum of Squares	*df*	Mean Square	*F*	*p*

Diet	Between groups	5.14	2	2.57	0.16	.853
	Within groups	917.92	57	16.10		
	Total	923.06	59			
Diet + Supplement	Between Groups	2849.94	2	1424.97	88.49	.000
	Within Groups	917.92	57	16.10		
	Total	3767.86	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	10.97	3.76	0.84
Multivitamin	25.61	3.30	0.74

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.11	.743	-13.09	38	.000	-16.90	-12.38
Equal variances not assumed			-13.09	37.36	.000	-16.90	-12.38

Group	Mean	SD	Std Error of Mean
Vitamin D	10.97	3.76	0.84
Placebo	11.01	4.83	1.08

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.34	.561	-0.03	38	.977	-2.81	2.73
Equal variances not assumed			-0.03	35.85	.977	-2.82	2.74

Group	Mean	SD	Std Error of Mean
Multivitamin	25.61	3.30	0.74
Placebo	11.01	4.83	1.08

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.78	.382	11.17	38	.000	11.95	17.25
Equal variances not assumed			33.55	33.55	.000	11.94	17.26

Magnesium

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	136.00	403.00	247.40	68.54
	Intake + Supplement	136.00	403.00	247.40	68.54
Multivitamin	Intake Alone	188.00	481.00	278.45	64.83
	Intake + Supplements	248.00	541.00	338.45	64.83
Vitamin C	Intake Alone	161.00	422.00	261.80	67.22

	Intake + Supplements	161.00	422.00	261.80	67.22

ANOVA

	Levene Statistic	df1	df2	p
Intake Alone	.253	2	57	.778
Intake plus supplement	.253	2	57	.778

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	9657.90	2	4828.95	1.08	.347
	Within groups	254956.95	57	4472.93		
	Total	264614.85	59			
Diet + Supplement	Between Groups	95819.90	2	47908.95	10.71	.000
	Within Groups	254956.95	57	4472.93		
	Total	350774.85	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	247.40	68.54	15.33
Multivitamin	338.45	64.83	14.50

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.46	.500	-4.32	38	.000	-133.76	-48.34
Equal variances not assumed			-4.32	37.88	.000	-133.76	-48.34

Group	Mean	SD	Std Error of Mean
Vitamin D	247.40	68.54	15.33
Placebo	361.80	67.22	15.03

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.04	.841	-0.67	38	.506	-57.86	29.06
Equal variances not assumed			-0.67	37.99	.506	-57.86	29.06

Group	Mean	SD	Std Error of Mean
Multivitamin	338.45	64.83	14.50
Placebo	261.80	67.22	15.03

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.23	.632	3.67	38	.001	34.38	118.92
Equal variances not assumed			3.67	37.95	.001	34.38	118.92

Selenium

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	14.00	71.00	36.15	13.01
	Intake + Supplement	14.00	71.00	36.15	13.01
Multivitamin	Intake Alone	8.00	90.00	36.15	19.34
	Intake + Supplements	63.00	145.00	91.15	19.34
Vitamin C	Intake Alone	13.00	96.00	38.40	18.78
	Intake + Supplements	13.00	96.00	38.45	18.78

ANOVA

	Levene Statistic	df1	df2	p
Intake Alone	0.61	2	57	.546
Intake plus supplement	0.61	2	57	.546

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	70.53	2	35.28	0.12	.889
	Within groups	17020.05	57	298.60		
	Total	17090.58	59			
Diet + Supplement	Between Groups	38717.20	2	19358.60	64.83	.000
	Within Groups	17020.05	57	298.60		
	Total	55737.25	59			

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	36.15	13.01	2.91
Multivitamin	91.15	19.34	4.32

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	1.21	.278	-10.55	38	.000	-65.55	-44.45
Equal variances not assumed			-4.32	37.88	.000	-65.60	-44.40

Group	Mean	SD	Std Error of Mean
Vitamin D	36.15	13.01	2.91
Placebo	38.45	18.78	4.20

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.87	.358	-0.45	38	.655	-12.64	8.04
Equal variances not assumed			-0.45	33.82	.655	-12.68	8.08

Group	Mean	SD	Std Error of Mean
Multivitamin	91.15	19.34	4.32
Placebo	38.45	18.78	4.20

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.02	.884	8.74	38	.000	40.50	64.90
Equal variances not assumed			8.74	37.97	.000	40.50	64.90

Zinc

Descriptives

Group		Minimum	Maximum	Mean	SD
Vitamin D	Intake Alone	3.30	10.20	6.93	1.86
	Intake + Supplement	3.30	10.20	6.93	1.86
Multivitamin	Intake Alone	5.00	15.20	8.00	2.63
	Intake + Supplements	15.00	25.20	18.00	2.63
Vitamin C	Intake Alone	5.10	14.10	7.68	2.08
	Intake + Supplements	5.10	14.10	7.68	2.08

ANOVA

	Levene Statistic	df1	df2	p
Intake Alone	1.17	2	57	.318
Intake plus supplement	1.17	2	57	.318

		Sum of Squares	*df*	Mean Square	*F*	*p*
Diet	Between groups	11.94	2	5.97	1.22	.303
	Within groups	279.07	57	4.90		
	Total	291.01	59			
Diet + Supplement	Between Groups	1529.94	2	764.97	156.25	.000
	Within Groups	279.07	57	4.90		

Total	1809.03	59

Diet Plus Supplements

Group	Mean	SD	Std Error of Mean
Vitamin D	6.93	1.86	0.41
Multivitamin	18.00	2.63	0.59

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	1.87	.180	-15.38	38	.000	-12.52	-9.61
Equal variances not assumed			-15.38	34.16	.000	-12.53	-9.60

Group	Mean	SD	Std Error of Mean
Vitamin D	6.93	1.86	0.41
Placebo	7.68	2.08	0.47

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	0.00	.965	-1.20	38	.240	-2.01	0.52
Equal variances not assumed			-1.20	37.51	.240	-2.01	0.52

Group	Mean	SD	Std Error of Mean
Multivitamin	18.00	2.63	0.59
Placebo	7.68	2.08	0.67

Independent Samples t-test

	Levene's Test for Equality of Variances		t-test for Equality of Means			95% Confidence Interval of the Difference	
	F	*p*	*t*	*df*	*p*	Lower	Upper
Equal variances assumed	.237	13.76	-3.84	38	.000	8.80	11.84
Equal variances not assumed			13.76	36.01	.000	8.80	11.84

B6: Post-intervention t-tests on cognitive measures

WASI-II

Paired Samples Statistics

Intervention			Mean	N	SD	SE Mean
Vitamin D	Pair 1	WASI_Verbal_T1	106.70	20	7.33	1.64
		WASI_Verbal_T2	108.75	20	7.75	1.73
	Pair 2	WASI_Perceptual_T1	117.10	20	14.18	3.17
		WASI_Perceptual_T2	122.20	20	15.63	3.49
	Pair 3	WASI_FSIQ4_T1	113.15	20	10.41	2.33
		WASI_FSIQ4_T2	116.50	20	11.11	2.49
Multivitamin	Pair 1	WASI_Verbal_T1	105.70	20	9.78	2.19
		WASI_Verbal_T2	106.70	20	8.06	1.80
	Pair 2	WASI_Perceptual_T1	113.55	20	14.39	3.22
		WASI_Perceptual_T2	118.95	20	13.21	2.95
	Pair 3	WASI_FSIQ4_T1	110.40	20	12.07	2.70
		WASI_FSIQ4_T2	114.05	20	10.42	2.33
Vitamin C	Pair 1	WASI_Verbal_T1	109.00	20	11.08	2.48
		WASI_Verbal_T2	109.50	20	9.89	2.21
	Pair 2	WASI_Perceptual_T1	116.45	20	12.71	2.84
		WASI_Perceptual_T2	119.45	20	12.50	2.79
	Pair 3	WASI_FSIQ4_T1	114.15	20	11.16	2.49
		WASI_FSIQ4_T2	116.15	20	10.32	2.31

Paired Samples Correlations

intervention			N	Correlation	*p*
Vitamin D	Pair 1	WASI_Verbal_T1 & WASI_Verbal_T2	20	.85	<.001
	Pair 2	WASI_Perceptual_T1 & WASI_Perceptual_T2	20	.95	<.001
	Pair 3	WASI_FSIQ4_T1 & WASI_FSIQ4_T2	20	.94	<.001
Multivitamin	Pair 1	WASI_Verbal_T1 & WASI_Verbal_T2	20	.76	<.001
	Pair 2	WASI_Perceptual_T1 & WASI_Perceptual_T2	20	.89	<.001
	Pair 3	WASI_FSIQ4_T1 & WASI_FSIQ4_T2	20	.86	<.001
Vitamin C	Pair 1	WASI_Verbal_T1 & WASI_Verbal_T2	20	.87	<.001
	Pair 2	WASI_Perceptual_T1 & WASI_Perceptual_T2	20	.912	<.001
	Pair 3	WASI_FSIQ4_T1 &WASI_FSIQ4_T2	20	.922	<.001

Paired Samples T-Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Intervention			Mean	SD	Std. Error Mean	Lower	Upper	*t*	*df*	*p*
Vitamin D	Pair 1	WASI_Verbal_T1 - WASI_Verbal_T2	-2.05	4.14	0.92	-3.99	-0.11	-2.22	19	.039
	Pair 2	WASI_Perceptual_T1 - WASI_Perceptual_T2	-5.10	4.80	1.07	-7.35	-2.85	-4.75	19	<.001
	Pair 3	WASI_FSIQ4_T1 - WASI_FSIQ4_T2	-3.35	3.79	0.85	-5.12	-1.58	-3.96	19	.001
Multivitamin	Pair 1	WASI_Verbal_T1 - WASI_Verbal_T2	-1.00	6.34	1.42	-3.97	1.97	-0.70	19	.490
	Pair 2	WASI_Perceptual_T1 - WASI_Perceptual_T2	-5.40	6.61	1.48	-8.49	-2.31	-3.65	19	.002

	Pair 3	WASI_FSIQ4_T1 - WASI_FSIQ4_T2	-3.65	6.18	1.38	-6.54	-0.76	-2.64	19	.016
Vitamin C	Pair 1	WASI_Verbal_T1 - WASI_Verbal_T2	-0.50	5.52	1.23	-3.08	2.08	-0.41	19	.690
	Pair 2	WASI_Perceptual_T1 - WASI_Perceptual_T2	-3.00	5.29	1.18	-5.48	-0.52	-2.54	19	.020
	Pair 3	WASI_FSIQ4_T1 - WASI_FSIQ4_T2	-2.00	4.32	0.97	-4.02	0.02	-2.07	19	.052

Digit Span and Wechsler Memory Scale Measures

Paired Samples Statistics

Intervention			Mean	N	SD	SE Mean
Vitamin D	Pair 1	WAIS_DigitSpan_T1	10.85	20	3.03	0.68
		WAIS_DigitSpan_T2	11.75	20	3.18	0.71
	Pair 2	WMS_LM1_T1	11.60	20	2.28	0.51
		WMS_LM1_T2	12.95	20	2.56	0.57
	Pair 3	WMS_LM2_T1	11.35	20	3.13	0.70
		WMS_LM2_T2	13.20	20	3.19	0.71
	Pair 4	WMS_VR1_T1	12.40	20	2.74	0.61
		WMS_VR1_T2	12.85	20	2.16	0.48
	Pair 5	WMS_VR2_T1	11.55	20	3.65	0.82
		WMS_VR2_T2	14.35	20	2.98	0.67
	Pair 6	WMS_SS_T1	11.75	20	3.04	0.68
		WMS_SS_T2	12.80	20	3.05	0.68
Multivitamin	Pair 1	WAIS_DigitSpan_T1	10.15	20	2.96	0.66
		WAIS_DigitSpan_T2	10.60	20	2.35	0.53
	Pair 2	WMS_LM1_T1	10.80	20	2.59	0.58
		WMS_LM1_T2	12.50	20	2.59	0.58
	Pair 3	WMS_LM2_T1	11.00	20	2.64	0.59
		WMS_LM2_T2	13.30	20	2.43	0.54
	Pair 4	WMS_VR1_T1	12.25	20	2.34	0.52
		WMS_VR1_T2	12.00	20	2.18	0.49
	Pair 5	WMS_VR2_T1	10.95	20	2.35	0.53
		WMS_VR2_T2	14.30	20	2.43	0.54
	Pair 6	WMS_SS_T1	11.80	20	3.58	0.80
		WMS_SS_T2	13.65	20	3.13	0.70
Vitamin C	Pair 1	WAIS_DigitSpan_T1	11.50	20	2.21	0.49
		WAIS_DigitSpan_T2	11.45	20	2.96	0.66
	Pair 2	WMS_LM1_T1	11.75	20	2.53	0.57
		WMS_LM1_T2	13.65	20	1.84	0.41
	Pair 3	WMS_LM2_T1	11.45	20	2.61	0.58

	WMS_LM2_T2	14.20	20	2.26	0.51
Pair 4	WMS_VR1_T1	12.30	20	2.87	0.64
	WMS_VR1_T2	13.50	20	2.16	0.48
Pair 5	WMS_VR2_T1	13.05	20	3.25	0.73
	WMS_VR2_T2	15.45	20	2.82	0.63
Pair 6	WMS_SS_T1	12.25	20	2.95	0.66
	WMS_SS_T2	13.75	20	2.79	0.62

Paired Samples Correlations

Intervention			N	Correlation	*p*
Vitamin D	Pair 1	WAIS_DigitSpan_T1 & WAIS_DigitSpan_T2	20	.85	<.001
	Pair 2	WMS_LM1_T1 & WMS_LM1_T2	20	.75	<.001
	Pair 3	WMS_LM2_T1 & WMS_LM2_T2	20	.87	<.001
	Pair 4	WMS_VR1_T1 & WMS_VR1_T2	20	.59	.006
	Pair 5	WMS_VR2_T1 & WMS_VR2_T2	20	.78	<.001
	Pair 6	WMS_SS_T1 & WMS_SS_T2	20	.77	<.001
Multivitamin	Pair 1	WAIS_DigitSpan_T1 & WAIS_DigitSpan_T2	20	.80	<.001
	Pair 2	WMS_LM1_T1 & WMS_LM1_T2	20	.43	.057
	Pair 3	WMS_LM2_T1 & WMS_LM2_T2	20	.38	.100
	Pair 4	WMS_VR1_T1 & WMS_VR1_T2	20	.81	<.001
	Pair 5	WMS_VR2_T1 & WMS_VR2_T2	20	.45	.049
	Pair 6	WMS_SS_T1 & WMS_SS_T2	20	.67	.001
Vitamin C	Pair 1	WAIS_DigitSpan_T1 & WAIS_DigitSpan_T2	20	.78	<.001
	Pair 2	WMS_LM1_T1 & WMS_LM1_T2	20	.54	.013
	Pair 3	WMS_LM2_T1 & WMS_LM2_T2	20	.73	<.001
	Pair 4	WMS_VR1_T1 & WMS_VR1_T2	20	.63	.003

	Pair 5	WMS_VR2_T1 & WMS_VR2_T2	20	.43	.060
	Pair 6	WMS_SS_T1 & WMS_SS_T2	20	.55	.013

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
intervention			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
Vitamin D	Pair 1	WAIS_DigitSpan_T1 - WAIS_DigitSpan_T2	-0.90	1.68	0.38	-1.69	-0.11	-2.39	19	.027
	Pair 2	WMS_LM1_T1 - WMS_LM1_T2	-1.35	1.73	0.39	-2.16	-0.54	-3.50	19	.002
	Pair 3	WMS_LM2_T1 - WMS_LM2_T2	-1.85	1.63	0.36	-2.61	-1.09	-5.07	19	<.001
	Pair 4	WMS_VR1_T1 - WMS_VR1_T2	-0.45	2.28	0.51	-1.52	0.62	-.88	19	.389
	Pair 5	WMS_VR2_T1 - WMS_VR2_T2	-2.80	2.31	0.52	-3.88	-1.72	-5.43	19	<.001
	Pair 6	WMS_SS_T1 - WMS_SS_T2	-1.05	2.06	0.46	-2.02	-0.08	-2.28	19	.035
Multivitamin	Pair 1	WAIS_DigitSpan_T1 - WAIS_DigitSpan_T2	-0.45	1.79	0.40	-1.29	0.38	-1.12	19	.275
	Pair 2	WMS_LM1_T1 - WMS_LM1_T2	-1.70	2.75	0.62	-2.99	-0.41	-2.76	19	.012
	Pair 3	WMS_LM2_T1 - WMS_LM2_T2	-2.30	2.83	0.63	-3.62	-0.98	-3.63	19	.002
	Pair 4	WMS_VR1_T1 - WMS_VR1_T2	0.25	1.41	0.32	-0.41	0.91	0.79	19	.437
	Pair 5	WMS_VR2_T1 - WMS_VR2_T2	-3.35	2.52	0.56	-4.53	-2.17	-5.95	19	<.001
	Pair 6	WMS_SS_T1 - WMS_SS_T2	-1.85	2.76	0.62	-3.14	-0.56	-3.00	19	.007
Vitamin C	Pair 1	WAIS_DigitSpan_T1 - WAIS_DigitSpan_T2	0.05	1.85	0.41	-0.82	0.92	0.12	19	.905
	Pair 2	WMS_LM1_T1 - WMS_LM1_T2	-1.90	2.17	0.49	-2.92	-0.88	-3.91	19	.001

	Pair 3	WMS_LM2_T1 - WMS_LM2_T2	-2.75	1.80	0.40	-3.59	-1.91	-6.82	19	<.001
	Pair 4	WMS_VR1_T1 - WMS_VR1_T2	-1.20	2.26	0.51	-2.26	-0.14	-2.37	19	.028
	Pair 5	WMS_VR2_T1 - WMS_VR2_T2	-2.40	3.27	0.73	-3.93	-0.87	-3.29	19	.004
	Pair 6	WMS_SS_T1 - WMS_SS_T2	-1.50	2.74	0.61	-2.78	-0.22	-2.45	19	.024

Doors and People

Paired Samples Statistics

intervention			Mean	N	S.D	SE Mean
Vitamin D	Pair 1	DP_OverallScore_T1	12.35	20	3.27	0.73
		DP_OverallScore_T2	13.80	20	2.57	0.57
Multivitamin	Pair 1	DP_OverallScore_T1	12.05	20	2.63	0.59
		DP_OverallScore_T2	13.70	20	2.56	0.57
Vitamin C	Pair 1	DP_OverallScore_T1	12.65	20	2.35	0.52
		DP_OverallScore_T2	14.45	20	2.16	0.48

Paired Samples Correlations

Intervention			N	Correlation	*p*
Vitamin D	Pair 1	DP_OverallScore_T1 & DP_OverallScore_T2	20	.76	<.000
Multivitamin	Pair 1	DP_OverallScore_T1 & DP_OverallScore_T2	20	.71	<.000
Vitamin C	Pair 1	DP_OverallScore_T1 & DP_OverallScore_T2	20	.58	.007

Paired Samples T-Test

			Paired Differences							
						95% Confidence Interval of the Difference				
intervention			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
Vitamin D	Pair 1	DP_OverallScore_T1 - DP_OverallScore_T2	-1.45	2.11	0.47	-2.44	-0.46	-3.07	19	.006
Multivitamin	Pair 1	DP_OverallScore_T1 - DP_OverallScore_T2	-1.65	1.98	0.44	-2.58	-0.72	-3.73	19	.001

Placebo (vitamin C)	Pair 1	DP_OverallScore_T1 - DP_OverallScore_T2	-1.80	2.07	0.46	-2.77	-0.83	-3.89	19	.001

D-KEFS Trail Making

Paired Samples Statistics

Intervention			Mean	N	SD	SE Mean
Vitamin D	Pair 1	DKEFS_TrailVisScan_T1	12.60	20	1.60	0.36
		DKEFS_TrailVisScan_T2	13.00	20	1.49	0.33
	Pair 2	DKEFS_TrailNumSeq_T1	11.40	20	2.19	0.49
		DKEFS_TrailNumSeq_T2	12.80	20	1.64	0.37
	Pair 3	DKEFS_TrailLetSeq_T1	12.45	20	1.64	0.37
		DKEFS_TrailLetSeq_T2	12.75	20	1.77	0.40
	Pair 4	DKEFS_TrailSwitch_T1	12.05	20	1.39	0.31
		DKEFS_TrailSwitch_T2	12.40	20	1.10	0.24
	Pair 5	DKEFS_TrailMotor_T1	11.75	20	2.40	0.54
		DKEFS_TrailMotor_T2	12.45	20	0.89	0.20
Multivitamin	Pair 1	DKEFS_TrailVisScan_T1	12.65	20	1.27	0.28
		DKEFS_TrailVisScan_T2	12.15	20	1.46	0.33
	Pair 2	DKEFS_TrailNumSeq_T1	11.80	20	2.33	0.52
		DKEFS_TrailNumSeq_T2	12.20	20	1.70	0.38
	Pair 3	DKEFS_TrailLetSeq_T1	12.65	20	1.87	0.42
		DKEFS_TrailLetSeq_T2	12.45	20	2.04	0.46
	Pair 4	DKEFS_TrailSwitch_T1	11.75	20	1.92	0.43
		DKEFS_TrailSwitch_T2	12.10	20	1.83	0.41
	Pair 5	DKEFS_TrailMotor_T1	11.55	20	1.88	0.42
		DKEFS_TrailMotor_T2	12.05	20	1.47	0.33
Vitamin C	Pair 1	DKEFS_TrailVisScan_T1	12.45	20	1.43	0.32
		DKEFS_TrailVisScan_T2	13.00	20	1.49	0.33
	Pair 2	DKEFS_TrailNumSeq_T1	11.95	20	1.54	0.34
		DKEFS_TrailNumSeq_T2	12.60	20	1.43	0.32
	Pair 3	DKEFS_TrailLetSeq_T1	12.60	20	1.64	0.37
		DKEFS_TrailLetSeq_T2	12.85	20	1.60	0.36
	Pair 4	DKEFS_TrailSwitch_T1	12.40	20	1.31	0.29
		DKEFS_TrailSwitch_T2	12.95	20	1.23	0.28
	Pair 5	DKEFS_TrailMotor_T1	12.20	20	1.20	0.27
		DKEFS_TrailMotor_T2	12.10	20	1.02	0.23

Paired Samples Correlations

Intervention			N	Correlation	*p*
Vitamin D	Pair 1	DKEFS_TrailVisScan_T1 & DKEFS_TrailVisScan_T2	20	.80	<.001
	Pair 2	DKEFS_TrailNumSeq_T1 & DKEFS_TrailNumSeq_T2	20	.46	.040
	Pair 3	DKEFS_TrailLetSeq_T1 & DKEFS_TrailLetSeq_T2	20	.62	.003
	Pair 4	DKEFS_TrailSwitch_T1 & DKEFS_TrailSwitch_T2	20	.78	<.001
	Pair 5	DKEFS_TrailMotor_T1 & DKEFS_TrailMotor_T2	20	.25	.282
Multivitamin	Pair 1	DKEFS_TrailVisScan_T1 & DKEFS_TrailVisScan_T2	20	.51	.021
	Pair 2	DKEFS_TrailNumSeq_T1 & DKEFS_TrailNumSeq_T2	20	.55	.011
	Pair 3	DKEFS_TrailLetSeq_T1 & DKEFS_TrailLetSeq_T2	20	.75	<.001
	Pair 4	DKEFS_TrailSwitch_T1 & DKEFS_TrailSwitch_T2	20	.76	<.001
	Pair 5	DKEFS_TrailMotor_T1 & DKEFS_TrailMotor_T2	20	.62	.004
Placebo (vitamin C)	Pair 1	DKEFS_TrailVisScan_T1 & DKEFS_TrailVisScan_T2	20	.49	.027
	Pair 2	DKEFS_TrailNumSeq_T1 & DKEFS_TrailNumSeq_T2	20	.18	.443
	Pair 3	DKEFS_TrailLetSeq_T1 & DKEFS_TrailLetSeq_T2	20	.32	.172
	Pair 4	DKEFS_TrailSwitch_T1 & DKEFS_TrailSwitch_T2	20	.76	<.001
	Pair 5	DKEFS_TrailMotor_T1 & DKEFS_TrailMotor_T2	20	.54	.013

Paired Samples T-Test

	Paired Differences						
				95% Confidence Interval of the Difference			
	Mean	SD	SE Mean	Lower	Upper	*df*	*p*

Vitamin D	Pair 1	DKEFS Trail Visual Scanning T1 - DKEFS Trail Visual Scanning_T2	-0.40	0.99	0.22	-0.87	0.07	-1.80	19	.088
	Pair 2	DKEFS Trail Number Sequencing T1 – DKEFS Trail Number Sequencing_T2	-1.40	2.04	0.46	-2.35	-0.45	-3.07	19	.006
	Pair 3	DKEFS Trail Letter Sequencing T1 – DKEFS Trail Letter Sequencing T2	-0.30	1.49	0.33	-1.00	0.40	-0.90	19	.379
	Pair 4	DKEFS Trail Switching T1 – DKEFS Trail Switching _T2	-0.35	0.88	0.20	-0.76	0.06	-1.79	19	.090
	Pair 5	DKEFS Trail Motor Speed T1 – DKEFS Trail Motor Speed T2	-0.70	2.34	0.52	-1.80	0.40	-1.34	19	.197
Multivitamin	Pair 1	DKEFS Trail Visual Scanning T1 – DKEFS Trail Visual Scanning T2	0.50	1.36	0.30	-0.14	1.14	1.65	19	.116
	Pair 2	DKEFS Trail Number Sequencing T1 – DKEFS Trail Number Sequencing T2	-0.40	1.98	0.44	-1.33	0.53	-0.90	19	.379
	Pair 3	DKEFS Trail Letter Sequencing T1 – DKEFS Trail Letter Sequencing T2	0.20	1.40	0.31	-0.45	0.85	0.64	19	.530
	Pair 4	DKEFS Trail Switching T1 – DKEFS Trail Switching T2	-0.35	1.31	0.29	-0.96	0.26	-1.20	19	.246
	Pair 5	DKEFS Trail Motor Speed T1 – DKEFS Trail Motor Speed T2	-0.50	1.50	0.34	-1.20	0.20	-1.49	19	.154

Vitamin C	Pair 1	DKEFS_Trail Visual Scanning T1 – DKEFS Trail Visual Scanning T2	-0.55	1.47	0.33	-1.24	0.14	-1.68	19	.110
	Pair 2	DKEFS Trail Number Sequencing T1 – DKEFS Trail Number Sequencing T2	-0.65	1.90	0.42	-1.54	0.24	-1.53	19	.142
	Pair 3	DKEFS Trail Letter Sequencing T1 – DKEFS Trail Letter Sequencing T2	-0.25	1.89	0.42	-1.13	0.63	-0.59	19	.561
	Pair 4	DKEFS Trail Switching T1 – DKEFS Trail Switching T2	-0.55	0.89	0.20	-0.97	-0.13	-2.77	19	.012
	Pair 5	DKEFS Trail Motor Speed T1 – DKEFS Trail Motor Speed T2	0.10	1.07	0.24	-0.40	0.60	.42	19	.681

D-KEFS Design Fluency

Paired Samples Statistics

Intervention			Mean	N	SD	SE Mean
Vitamin D	Pair 1	DKEFS_Design_Filled_T1	7.55	20	1.50	0.34
		DKEFS_Design_Filled_T2	8.00	20	1.92	0.43
	Pair 2	DKEFS_Design_Empty_T1	7.15	20	2.08	0.47
		DKEFS_Design_Empty_T2	7.80	20	2.09	0.47
	Pair 3	DKEFS_Design_Switch_T1	10.00	20	3.03	0.68
		DKEFS_Design_Switch_T2	10.65	20	3.10	0.69
	Pair 4	DKEFS_DesignTotCorr_T1	8.25	20	2.51	0.56
		DKEFS_DesignTotCorr_T2	9.05	20	2.80	0.63
Multivitamin	Pair 1	DKEFS_Design_Filled_T1	7.35	20	1.57	0.35
		DKEFS_Design_Filled_T2	7.65	20	1.79	0.40
	Pair 2	DKEFS_Design_Empty_T1	6.85	20	1.23	0.27
		DKEFS_Design_Empty_T2	7.95	20	1.85	0.41
	Pair 3	DKEFS_Design_Switch_T1	10.05	20	1.96	0.44
		DKEFS_Design_Switch_T2	11.20	20	2.33	0.52
	Pair 4	DKEFS_DesignTotCorr_T1	7.90	20	1.55	0.35

		DKEFS_DesignTotCorr_T2	9.45	20	2.31	0.52
Vitamin C	Pair 1	DKEFS_Design_Filled_T1	7.15	20	1.27	0.28
		DKEFS_Design_Filled_T2	8.05	20	1.47	0.33
	Pair 2	DKEFS_Design_Empty_T1	7.40	20	1.60	0.36
		DKEFS_Design_Empty_T2	8.00	20	1.41	0.32
	Pair 3	DKEFS_Design_Switch_T1	10.65	20	1.50	0.33
		DKEFS_Design_Switch_T2	11.35	20	2.23	0.50
	Pair 4	DKEFS_DesignTotCorr_T1	8.35	20	1.39	0.31
		DKEFS_DesignTotCorr_T2	9.35	20	1.57	0.35

Paired Samples Correlations

Intervention			N	Correlation	*p*
Vitamin D	Pair 1	DKEFS_Design_Filled_T1 & DKEFS_Design_Filled_T2	20	.69	.001
	Pair 2	DKEFS_Design_Empty_T1 & DKEFS_Design_Empty_T2	20	.67	.001
	Pair 3	DKEFS_Design_Switch_T1 & DKEFS_Design_Switch_T2	20	.83	<.001
	Pair 4	DKEFS_DesignTotCorr_T1 & DKEFS_DesignTotCorr_T2	20	.85	<.001
Multivitamin	Pair 1	DKEFS_Design_Filled_T1 & DKEFS_Design_Filled_T2	20	.72	<.001
	Pair 2	DKEFS_Design_Empty_T1 & DKEFS_Design_Empty_T2	20	.60	.005
	Pair 3	DKEFS_Design_Switch_T1 & DKEFS_Design_Switch_T2	20	.27	.242
	Pair 4	DKEFS_DesignTotCorr_T1 & DKEFS_DesignTotCorr_T2	20	.62	.004
Vitamin C	Pair 1	DKEFS_Design_Filled_T1 & DKEFS_Design_Filled_T2	20	.56	.010
	Pair 2	DKEFS_Design_Empty_T1 & DKEFS_Design_Empty_T2	20	.56	.011
	Pair 3	DKEFS_Design_Switch_T1 & DKEFS_Design_Switch_T2	20	.45	.047
	Pair 4	DKEFS_DesignTotCorr_T1 & DKEFS_DesignTotCorr_T2	20	.55	.013

Paired Samples T-Test

		Paired Differences							
					95% Confidence Interval of the Difference				
Intervention		Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*

Vitamin D	Pair 1	DKEFS_Design_Filled_T1 - DKEFS_Design_Filled_T2	-0.45	1.39	0.31	-1.10	0.20	-1.44	19	.165
	Pair 2	DKEFS_Design_Empty_T1 - DKEFS_Design_Empty_T2	-0.65	1.69	0.38	-1.44	0.14	-1.72	19	.103
	Pair 3	DKEFS_Design_Switch_T1 - DKEFS_Design_Switch_T2	-0.65	1.79	0.40	-1.49	0.19	-1.63	19	.120
	Pair 4	DKEFS_Design Total Correct_T1 - DKEFS_Design Total Correct_T2	-0.80	1.47	0.33	-1.49	-0.11	-2.43	19	.025
Multivitamin	Pair 1	DKEFS_Design_Filled_T1 - DKEFS_Design_Filled_T2	-0.30	1.26	0.28	-0.89	0.29	-1.06	19	.301
	Pair 2	DKEFS_Design_Empty_T1 - DKEFS_Design_Empty_T2	-1.10	1.48	0.33	-1.79	-0.41	-3.32	19	.004
	Pair 3	DKEFS_Design_Switch_T1 - DKEFS_Design_Switch_T2	-1.15	2.60	0.58	-2.37	0.07	-1.98	19	.063
	Pair 4	DKEFS_Design Total Correct_T1 - DKEFS_Design Total Correct_T2	-1.55	1.82	0.41	-2.40	-0.70	-3.81	19	.001
Vitamin C	Pair 1	DKEFS_Design_Filled_T1 - DKEFS_Design_Filled_T2	-0.90	1.29	0.29	-1.50	-0.29	-3.11	19	.006
	Pair 2	DKEFS_Design_Empty_T1 - DKEFS_Design_Empty_T2	-0.60	1.43	0.32	-1.27	0.07	-1.88	19	.076
	Pair 3	DKEFS_Design_Switch_T1 - DKEFS_Design_Switch_T2	-0.70	2.05	0.46	-1.66	0.26	-1.52	19	.144

	Pair 4	DKEFS_Design Total Correct_T1 - DKEFS_Design Total Correct_T2	-1.00	1.41	0.32	-1.66	-0.34	-3.16	19	.005

D-KEFS Verbal Fluency

Paired Samples Statistics

Intervention			Mean	N	SD	SE Mean
Vitamin D	Pair 1	DKEFS_VerbalLetter_T1	13.10	20	2.55	0.57
		DKEFS_VerbalLetter_T2	13.75	20	2.61	0.58
	Pair 2	DKEFS_Verbal Cat_T1	14.40	20	3.07	0.69
		DKEFS_Verbal Cat_T2	16.45	20	3.56	0.80
	Pair 3	DKEFS Verbal Switching _T1	14.85	20	3.18	0.71
		DKEFS Verbal Switching_T2	14.20	20	3.09	0.69
Multivitamin	Pair 1	DKEFS_VerbalLetter_T1	11.90	20	3.67	0.82
		DKEFS_VerbalLetter_T2	12.25	20	3.63	0.81
	Pair 2	DKEFS_Verbal Cat_T1	12.80	20	3.86	0.86
		DKEFS_Verbal Cat_T2	13.75	20	4.28	0.96
	Pair 3	DKEFS Verbal Switching T1	12.85	20	3.22	0.72
		DKEFS Verbal Switching_T2	13.05	20	3.33	0.75
Vitamin C	Pair 1	DKEFS_VerbalLetter_T1	12.65	20	3.47	0.78
		DKEFS_VerbalLetter_T2	13.05	20	3.46	0.77
	Pair 2	DKEFS_VerbalCat_T1	15.25	20	2.69	0.60
		DKEFS_VerbalCat_T2	16.15	20	2.80	0.63
	Pair 3	DKEFS Verbal SwitchingT1	14.75	20	2.99	0.67
		DKEFS Verbal Switching T2	15.30	20	2.72	0.61

Paired Samples Correlations

Intervention			N	Correlation	*p*
Vitamin D	Pair 1	DKEFS_VerbalLetter_T1 & DKEFS_VerbalLetter_T2	20	.56	.011
	Pair 2	DKEFS_VerbalCat_T1 & DKEFS_VerbalCat_T2	20	.36	.121
	Pair 3	DKEFS Verbal Switching_T1 & DKEFS Verbal Switching_T2	20	.49	.028

Multivitamin	Pair 1	DKEFS_VerbalLetter_T1 & DKEFS_VerbalLetter_T2	20	.77	<.001
	Pair 2	DKEFS_VerbalCat_T1 & DKEFS_VerbalCat_T2	20	.52	.019
	Pair 3	DKEFS Verbal Switching T1 & DKEFS Verbal Switching_T2	20	.76	<.001
Vitamin C	Pair 1	DKEFS_VerbalLetter_T1 & DKEFS_VerbalLetter_T2	20	.82	<.001
	Pair 2	DKEFS_VerbalCat_T1 & DKEFS_VerbalCat_T2	20	.53	.017
	Pair 3	DKEFS Verbal Switching _T1 & DKEFS Verbal Switching_T2	20	.44	0.54

Paired Samples T-Test

			Paired Differences							
						95% Confidence Interval of the Difference				
intervention			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
Vitamin D	Pair 1	DKEFS_Verbal Letters T1 – DKEFS Verbal Letters_T2	-0.65	2.43	0.54	-1.79	0.49	-1.19	19	.247
	Pair 2	DKEFS_Verbal Categories T1 – DKEFS Verbal Categories_T2	-2.05	3.78	0.84	-3.82	-0.28	-2.43	19	.025
	Pair 3	DKEFS Verbal Switch T1 – DKEFS Verbal Switching T2	0.65	3.17	0.71	-0.83	2.13	0.92	19	.370
Multivitamin	Pair 1	DKEFS_VerbalLett_T1 - DKEFS_VerbalLett_T2	-0.35	2.50	0.56	-1.52	0.82	-0.63	19	.538
	Pair 2	DKEFS_VerbalCat_T1 - DKEFS_VerbalCat_T2	-0.95	4.01	0.90	-2.82	0.92	-1.06	19	.302
	Pair 3	DKEFS Verbal Switching _T1 – DKEFS Verbal Switching_T2	-0.20	2.28	0.51	-1.27	0.87	-0.39	19	.700

Vitamin C	Pair 1	DKEFS_VerbalLett_T1 - DKEFS_VerbalLett_T2	-0.40	2.09	0.47	-1.38	0.58	-0.86	19	.402
	Pair 2	DKEFS_VerbalCat_T1 - DKEFS_VerbalCat_T2	-0.90	2.67	0.60	-2.15	0.35	-1.51	19	.149
	Pair 3	DKEFS Verbal Switching T1 – DKEFS Verbal Switching T2	-0.55	3.03	0.68	-1.97	0.87	-0.81	19	.428

D-KEFS Tower

Paired Samples Statistics

Intervention			Mean	N	SD	SE Mean
Vitamin D	Pair 1	DKEFS_TowerTotScore_T1	12.50	20	2.74	0.61
		DKEFS_TowerTotScore_T2	13.45	20	2.24	0.50
	Pair 2	DKEFS_TowerMean1stMoveT1	11.50	20	1.36	0.30
		DKEFS_TowerMean1stMove_T2	11.90	20	1.74	0.39
	Pair 3	DKES_TowerTimeperMove_T1	11.15	20	1.14	0.25
		DKES_TowerTimeperMove_T2	11.60	20	1.39	0.31
	Pair 4	DKEFS_TowerMoveAcc_T1	11.00	20	1.30	0.29
		DKEFS_TowerMoveAcc_T2	10.70	20	1.81	0.40
Multivitamin	Pair 1	DKEFS_TowerTotScore_T1	12.30	20	2.56	0.57
		DKEFS_TowerTotScore_T2	12.50	20	1.85	0.41
	Pair 2	DKEFS_TowerMean1stMoveT1	10.95	20	2.37	0.53
		DKEFS_TowerMean1stMove_T2	11.95	20	1.50	0.34
	Pair 3	DKES_TowerTimeperMove_T1	11.00	20	1.72	0.38
		DKES_TowerTimeperMove_T2	11.35	20	1.73	0.39
	Pair 4	DKEFS_TowerMoveAcc_T1	10.50	20	1.73	0.39
		DKEFS_TowerMoveAcc_T2	10.35	20	1.31	0.29
Vitamin C	Pair 1	DKEFS_TowerTotScore_T1	12.75	20	2.17	0.49
		DKEFS_TowerTotScore_T2	12.50	20	1.85	0.41
	Pair 2	DKEFS_TowerMean1stMoveT1	11.70	20	2.11	0.47
		DKEFS_TowerMean1stMove_T2	12.35	20	1.95	0.44
	Pair 3	DKES_TowerTimeperMove_T1	10.90	20	1.33	0.30
		DKES_TowerTimeperMove_T2	11.95	20	1.39	0.31
	Pair 4	DKEFS_TowerMoveAcc_T1	10.40	20	1.60	0.36
		DKEFS_TowerMoveAcc_T2	10.55	20	1.47	0.33

Paired Samples Correlations

Intervention	N	Correlation	*p*

Vitamin D	Pair 1	DKEFS Tower Total Score_T1 & DKEFS_Tower Total Score_T2	20	.39	.089
	Pair 2	DKEFS_Tower Mean 1st Move T1 & DKEFS_Tower Mean 1st Move_T2	20	.31	.182
	Pair 3	DKES_Tower Time per Move_T1 & DKES_Tower Time per Move_T2	20	.71	.001
	Pair 4	DKEFS_Tower Move Accuracy T1 & DKEFS_Tower Move Accuracy_T2	20	.25	.295
Multivitamin	Pair 1	DKEFS_Tower Total Score_T1 & DKEFS_Tower Total Score_T2	20	.36	.123
	Pair 2	DKEFS_Tower Mean 1st MoveT1 & DKEFS_Tower Mean 1st Move_T2	20	.80	.000
	Pair 3	DKES_Tower Time per Move_T1 & DKES_Tower Time per Move_T2	20	.71	.000
	Pair 4	DKEFS_Tower Move Accuracy_T1 & DKEFS_Tower Move Accuracy_T2	20	.20	.404
Vitamin C	Pair 1	DKEFS_Tower Total Score_T1 & DKEFS_Tower Total Score_T2	20	.35	.134
	Pair 2	DKEFS_Tower Mean 1st Move T1 & DKEFS_Tower Mean 1st Move_T2	20	.82	.000
	Pair 3	DKES_Tower Time per Move_T1 & DKES_Tower Time per Move_T2	20	.71	.001

Pair 4	DKEFS_Tower Move Accuracy_T1 & DKEFS_Tower Move Accuracy_T2	20	.33	.160

Paired Samples T-Test

			Paired Differences							
						95% Confidence Interval of the Difference				
intervention			Mean	SD	Std. Error Mean	Lower	Upper	*t*	*df*	*p*
Vitamin D	Pair 1	DKEFS_Tower Total Score_T1 - DKEFS_Tower Total Score_T2	-0.95	2.78	0.62	-2.25	0.35	-1.53	19	.143
	Pair 2	DKEFS_Tower Mean 1st Move T1 - DKEFS_Tower Mean 1st Move_T2	-0.40	1.85	0.41	-1.26	0.46	-0.97	19	.345
	Pair 3	DKES_Tower Time per Move_T1 - DKES_Tower Time per Move_T2	-0.45	1.00	0.22	-0.92	0.02	-2.02	19	.058
	Pair 4	DKEFS_Tower Move Accuracy_T1 - DKEFS_Tower Move Accuracy_T2	0.30	1.95	0.44	-0.61	1.21	0.69	19	.500
Multivitamin	Pair 1	DKEFS_Tower Total Score_T1 - DKEFS_Tower Total Score_T2	-0.20	2.57	0.57	-1.40	1.00	-0.35	19	.731
	Pair 2	DKEFS_Tower Mean 1st Move T1 - DKEFS_Tower Mean 1st Move_T2	-1.00	1.49	0.33	-1.70	-0.30	-3.01	19	.007
	Pair 3	DKES_Tower Time per Move_T1 - DKES_Tower Time per Move_T2	-0.35	1.31	0.29	-0.96	0.26	-1.20	19	.246

	Pair 4	DKEFS_Tower Move Accuracy_T1 - DKEFS_Tower Move Accuracy_T2	0.15	1.95	0.44	-0.76	1.06	0.34	19	.735
Vitamin C	Pair 1	DKEFS_Tower Total Score_T1 - DKEFS_Tower Total Score_T2	0.25	2.31	0.52	-0.83	1.33	0.48	19	.635
	Pair 2	DKEFS_Tower Mean 1st MoveT1 - DKEFS_Tower Mean 1st Move_T2	-0.65	1.23	0.27	-1.22	-0.08	-2.37	19	.028
	Pair 3	DKES Tower Time per Move_T1 – DKES Tower Time per Move_T2	-1.05	1.05	0.23	-1.54	-0.56	-4.47	19	<.001
	Pair 4	DKEFS Tower Move Accuracy T1 – DKEFS Tower Move Accuracy_T2	-0.15	1.79	0.40	-0.99	0.69	-0.38	19	.711

PANAS and Symbol Search

Paired Samples Statistics

Intervention			Mean	N	SD	SE Mean
Vitamin D	Pair 1	PANAS_PA_T1	33.60	20	7.35	1.64
		PANAS_PA_T2	32.65	20	7.81	1.75
	Pair 2	PANAS_NA_T1	19.50	20	6.42	1.44
		PANAS_NA_T2	16.70	20	6.52	1.46
	Pair 3	WAIS_SymbolSearch_T1	12.75	20	3.52	0.79
		WAIS_SymbolSearch_T2	13.95	20	3.14	0.70
Multivitamin	Pair 1	PANAS_PA_T1	36.30	20	6.14	1.37
		PANAS_PA_T2	35.00	20	6.74	1.51
	Pair 2	PANAS_NA_T1	17.45	20	5.42	1.21
		PANAS_NA_T2	20.25	20	8.16	1.83
	Pair 3	WAIS_Symbol Search_T1	12.05	20	2.67	0.60
		WAIS_Symbol Search_T2	13.40	20	2.37	0.53
Vitamin C	Pair 1	PANAS_PA_T1	35.50	20	5.49	1.23

	PANAS_PA_T2	33.40	20	6.72	1.50
Pair 2	PANAS_NA_T1	17.65	20	6.38	1.43
	PANAS_NA_T2	17.80	20	6.72	1.50
Pair 3	WAIS_Symbol Search_T1	13.60	20	2.04	0.46
	WAIS_Symbol Search_T2	14.95	20	2.33	0.52

Paired Samples Correlations

Intervention			N	Correlation	*p*
Vitamin D	Pair 1	PANAS_PA_T1 & PANAS_PA_T2	20	.60	.006
	Pair 2	PANAS_NA_T1 & PANAS_NA_T2	20	.22	.346
	Pair 3	WAIS Symbol Search_T1 & WAIS Symbol Search_T2	20	.89	<.000
Multivitamin	Pair 1	PANAS_PA_T1 & PANAS_PA_T2	20	.67	.001
	Pair 2	PANAS_NA_T1 & PANAS_NA_T2	20	.56	.010
	Pair 3	WAIS Symbol Search T1 & WAIS Symbol Search T2	20	.72	<.000
Vitamin C	Pair 1	PANAS_PA_T1 & PANAS_PA_T2	20	.63	.003
	Pair 2	PANAS_NA_T1 & PANAS_NA_T2	20	.56	.010
	Pair 3	WAIS Symbol Search T1 & WAIS SymbolSearch T2	20	.57	.008

Paired Samples T-Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Intervention			Mean	SD	SE Mean	Lower	Upper	t	df	*p*
Vitamin D	Pair 1	PANAS_PA_T1 - PANAS_PA_T2	0.95	6.83	1.53	-2.25	4.15	1.62	19	.541
	Pair 2	PANAS_NA_T1 - PANAS_NA_T2	2.80	8.07	1.80	-0.98	6.58	1.55	19	.137
	Pair 3	WAIS Symbol Search_T1 – WAIS Symbol Search_T2	-1.20	1.64	0.37	-1.97	-0.43	-3.27	19	.004

Multivitamin	Pair 1	PANAS_PA_T1 - PANAS_PA_T2	1.30	5.28	1.18	-1.17	3.77	1.10	19	.285
	Pair 2	PANAS_NA_T1 - PANAS_NA_T2	-2.80	6.80	1.52	-5.98	0.38	-1.84	19	.081
	Pair 3	WAIS Symbol Search_T1 – WAIS Symbol Search_T2	-1.35	1.90	0.42	-2.24	-0.46	-3.18	19	.005
Vitamin C	Pair 1	PANAS_PA_T1 - PANAS_PA_T2	2.10	5.37	1.20	-0.41	4.61	1.75	19	.096
	Pair 2	PANAS_NA_T1 - PANAS_NA_T2	-0.15	6.15	1.38	-3.03	2.73	-0.11	19	.914
	Pair 3	WAIS Symbol Search_T1 – WAIS Symbol Search_T2	-1.35	2.03	0.45	-2.30	-0.40	-2.97	19	.008

SRT – Outliers Out

Paired Samples Statistics

Intervention			Mean	N	SD	SE Mean
Vitamin D	Pair 1	SRTLearning_T1	82.12	19	38.12	8.75
		SRTLearning_T2	90.33	19	62.52	14.34
Multivitamin	Pair 1	SRTLearning_T1	81.14	18	31.87	7.51
		SRTLearning_T2	113.61	18	35.96	8.47
Vitamin C	Pair 1	SRTLearning_T1	92.17	19	39.98	9.17
		SRTLearning_T2	100.36	19	39.22	9.00

Paired Samples Correlations

Intervention			N	Correlation	*p*
Vitamin D	Pair 1	SRTLearning_T1 & SRTLearning_T2	19	.21	.388
Multivitamin	Pair 1	SRTLearning_T1 & SRTLearning_T2	18	.59	.010
Vitamin C	Pair 1	SRTLearning_T1 & SRTLearning_T2	19	.03	.913

Paired Samples Test

Intervention	Paired Differences	*t*	*df*	*p*

						95% Confidence Interval of the Difference				
			Mean	SD	SE Mean	Lower	Upper			
Vitamin D	Pair 1	SRTLearning_T1 - SRTLearning_T2	-8.21	66.03	15.15	-40.03	23.62	-0.54	18	.595
Multivitamin	Pair 1	SRTLearning_T1 - SRTLearning_T2	-32.47	30.98	7.30	-47.88	-17.06	-4.45	17	<.001
Vitamin C	Pair 1	SRTLearning_T1 - SRTLearning_T2	-8.19	55.25	12.67	-34.82	18.44	-0.65	18	.526

SRT – Outliers In

Paired Samples Statistics

Intervention			Mean	N	SD	SE Mean
Vitamin D	Pair 1	SRTLearning_T1	79.52	20	38.90	8.70
		SRTLearning_T2	84.84	20	65.61	14.67
Multivitamin	Pair 1	SRTLearning_T1	64.74	20	63.25	14.14
		SRTLearning_T2	102.46	20	73.65	16.47
Vitamin C	Pair 1	SRTLearning_T1	89.22	20	41.08	9.18
		SRTLearning_T2	95.08	20	44.87	10.03

Paired Samples Correlations

Intervention			N	Correlation	*p*
Vitamin D	Pair 1	SRTLearning_T1 & SRTLearning_T2	20	.30	.202
Multivitamin	Pair 1	SRTLearning_T1 & SRTLearning_T2	20	.78	<.001
Vitamin C	Pair 1	SRTLearning_T1 & SRTLearning_T2	20	.19	.422

Paired Samples T-Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Intervention			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
Vitamin D	Pair 1	SRTLearning_T1 - SRTLearning_T2	-5.32	65.55	14.66	-36.00	25.35	-0.36	19	.720

Multivitamin	Pair 1	SRTLearning_T1 - SRTLearning_T2	-37.72	46.48	10.39	-59.47	-15.97	-3.63	19	.002
Vitamin C	Pair 1	SRTLearning_T1 - SRTLearning_T2	-5.86	54.78	12.25	-31.50	19.77	-0.48	19	.638

Reading the Mind in the Eyes and Movie for the Assessment of Social Cognition

Paired Samples Statistics

Intervention			Mean	N	SD	SE Mean
Vitamin D	Pair 1	RME_T1	27.95	20	2.50	0.56
		RME_T2	29.25	20	2.83	0.63
	Pair 2	MASCCorrect_T1	36.10	20	2.86	0.64
		MASCCorrect_T2	38.10	20	2.61	0.58
Multivitamin	Pair 1	RME_T1	27.20	20	3.97	0.89
		RME_T2	27.90	20	2.43	0.54
	Pair 2	MASCCorrect_T1	36.00	20	3.55	0.79
		MASCCorrect_T2	37.50	20	3.69	0.83
Vitamin C	Pair 1	RME_T1	27.65	20	3.39	0.76
		RME_T2	27.75	20	3.48	0.78
	Pair 2	MASCCorrect_T1	36.25	20	3.61	0.81
		MASCCorrect_T2	38.35	20	3.95	0.88

Paired Samples Correlations

Intervention			N	Correlation	*p*
Vitamin D	Pair 1	RME_T1 & RME_T2	20	.53	.016
	Pair 2	MASCCorrect_T1 & MASCCorrect_T2	20	.69	.001
Multivitamin	Pair 1	RME_T1 & RME_T2	20	.64	.003
	Pair 2	MASCCorrect_T1 & MASCCorrect_T2	20	.75	.000
Vitamin C	Pair 1	RME_T1 & RME_T2	20	.74	.000
	Pair 2	MASCCorrect_T1 & MASCCorrect_T2	20	.80	.000

Paired Samples Test

Intervention	Paired Differences	*t*	*df*	*p*

				95% Confidence Interval of the Difference						
		Mean	SD	SE Mean	Lower	Upper				
Vitamin D	Pair 1	RME_T1 - RME_T2	-1.30	2.60	0.58	-2.52	-0.08	-2.24	19	.037
	Pair 2	MASCCorrect_T1 - MASCCorrect_T2	-2.00	2.18	0.49	-3.02	-0.98	-4.11	19	.001
Multivitamin	Pair 1	RME_T1 - RME_T2	-0.70	3.06	0.68	-2.13	0.73	-1.02	19	.320
	Pair 2	MASCCorrect_T1 - MASCCorrect_T2	-1.50	2.54	0.57	-2.69	-0.31	-2.64	19	.016
Vitamin C	Pair 1	RME_T1 - RME_T2	-0.10	2.49	0.56	-1.26	1.07	-0.18	19	.859
	Pair 2	MASCCorrect_T1 - MASCCorrect_T2	-2.10	2.43	0.54	-3.24	-0.96	-3.87	19	.001

B7: Non-parametric analyses

Intelligence, Working Memory, and Processing Speed

Test Measure	Group	Baseline median	Follow up median	Z	p	r
WASI Verbal Comp	Vit D	107.00	109.50	-1.99	.047	0.26
	Multivitamin	107.50	109.50	-0.79	.431	0.10
	Placebo	111.50	111.50	-0.59	.558	0.08
WASI Percept. Reasoning	Vit D	117.50	122.50	-3.21	.001	0.41
	Multivitamin	111.00	118.50	-3.03	.002	0.39
	Placebo	117.00	119.00	-2.04	.042	0.26
WASI FSIQ	Vit D	113.00	116.50	-3.08	.002	0.40
	Multivitamin	108.00	115.00	-2.22	.027	0.29
	Placebo	114.50	118.50	-2.22	.027	0.29
WAIS Digit Span	Vit D	10.50	11.00	-2.29	.022	0.30
	Multivitamin	9.00	11.00	-1.18	.238	0.15
	Placebo	12.00	11.00	-0.02	.981	<0.01

Symbol Search	Vit D	13.50	14.00	-2.81	.005	0.36
	Multivitamin	12.50	14.00	-2.81	.005	0.36
	Placebo	13.00	15.50	-2.61	.009	0.34

WMS Measures

Test Measure	Group	Baseline median	Followup median	Z	p	r
LM1	Vit D	11.50	13.00	-2.78	.004	0.36
	Multivitamin	11.00	13.00	-2.56	.008	0.34
	Placebo	11.00	14.50	-2.96	.002	0.38
LM2	Vit D	12.00	14.00	-3.45	<.001	0.45
	Multivitamin	11.00	13.00	-3.30	<.001	0.43
	Placebo	11.50	14.00	-3.71	<.001	0.48
VR1	Vit D	13.00	13.00	-0.91	.392	0.11
VR1	Multivitamin	13.00	12.50	-0.79	.498	0.10
	Placebo	12.00	14.00	-2.29	.020	0.30
VR2	Vit D	11.00	14.50	-3.53	<.001	0.46
VR2	Multivitamin	11.00	14.00	-3.82	<.001	0.49
	Placebo	13.50	16.00	-2.73	.004	0.35

Symbol Span and Doors Overall Score

Test Measure	Group	Baseline median	Followup median	Z	p	r
WAIS Symbol Span	Vit D	12.00	13.50	-1.91	.029	0.25
	Multivitamin	12.00	14.00	-2.80	.004	0.36
	Placebo	12.00	14.00	-2.12	.033	0.27
Doors Overall Score	Vit D	12.00	14.00	-2.69	.007	0.34
	Multivitamin	13.00	14.00	-3.06	.002	0.39
	Placebo	13.00	14.00	-3.14	.002	0.41

DKEFS Verbal Fluency

Test Measure	Group	Baseline median	Followup median	Z	p	r
Phonemic	Vit D	13.50	13.50	-1.13	.257	0.15
	Multivitamin	12.00	12.00	-0.38	.702	0.05
	Placebo	11.50	13.50	-0.72	.469	0.13
Semantic	Vit D	15.00	17.50	-2.14	.033	0.28
	Multivitamin	12.00	14.50	-0.68	.505	0.09
	Placebo	15.00	16.50	-1.54	.130	0.20

Semantic Switching	Vit D	15.00	14.00	-0.98	.327	0.13
	Multivitamin	12.50	12.00	-0.37	.710	0.05

DKEFS Trail Making

Test Measure	Group	Baseline median	Followup median	Z	p	r
Visual Scanning	Vit D	13.00	13.00	-1.63	.137	0.21
	Multivitamin	13.00	12.50	-1.67	.111	0.22
	Placebo	13.00	13.00	-1.60	.137	0.21
Number Sequencing	Vit D	12.00	13.00	-2.57	.008	0.33
	Multivitamin	12.00	12.50	-0.75	.479	0.10
	Placebo	12.00	12.50	-1.36	.191	0.18
Letter Sequencing	Vit D	13.00	13.00	-0.88	.400	0.11
	Multivitamin	13.00	13.00	-0.49	.646	0.06
	Placebo	13.00	13.50	-0.67	.535	0.09
Switching	Vit D	12.00	12.50	-1.73	.083	0.22
	Multivitamin	12.00	12.00	-1.09	.276	0.14
	Placebo	13.00	13.00	-2.50	.012	0.32
Motor Speed	Vitamin D	12.00	12.50	-1.03	.408	0.13
	Multivitamin	12.00	12.00	-1.51	.201	0.19
	Placebo	12.00	12.00	-0.24	1.00	0.03

D-KEFS Design Fluency

Test Measure	Group	Baseline median	Followup median	Z	p	r
Empty	Vit D	7.00	8.00	-1.62	.112	0.21
	Multivitamin	7.00	7.00	-2.68	.006	0.35
	Placebo	7.00	8.00	-1.72	.100	0.22
Filled	Vit D	8.00	8.00	-1.27	.237	0.16
	Multivitamin	7.00	8.00	-1.20	.259	0.15
	Placebo	7.00	8.00	-2.69	.007	0.35
Switching	Vit D	10.00	10.50	-1.49	.136	0.19
	Multivitamin	10.00	10.50	-1.98	.048	0.26
	Placebo	10.00	12.00	-1.27	.204	0.16
Total Correct	Vit D	8.00	9.00	-2.17	.030	0.28
	Multivitamin	8.00	9.00	-3.11	.002	0.40
	Placebo	8.00	10.00	-2.66	.008	0.34

DKEFS Tower

Test Measure	Group	Baseline median	Followup median	Z	p	r
Total Achievement	Vit D	11.00	13.50	-1.38	.174	0.22
	Multivitamin	12.50	12.50	-0.66	.519	0.11
	Placebo	12.50	13.00	-0.12	.932	0.02
Mean 1st Move	Vit D	12.00	12.50	-0.92	.382	0.15
	Multivitamin	12.00	12.00	-2.62	.008	0.42
	Placebo	12.00	13.00	-2.10	.044	0.33
Time/Move	Vit D	11.00	12.00	-1.90	.073	0.30
	Multivitamin	11.00	12.00	-1.27	.233	0.20
	Placebo	11.00	12.00	-3.21	.001	0.51
Tower Move Accuracy	Vit D	11.00	11.00	-0.48	.634	0.06
	Multivitamin	11.00	10.50	-1.28	.200	0.17
	Placebo	11.00	11.00	-0.32	.750	0.04

Serial Reaction Time task

Test Measure	Group	Baseline median	Followup median	Z	p	r
SRT Explicit	Vit D	10.00	12.50	-0.94	.363	0.12
	Multivitamin	10.00	17.00	-2.97	.002	0.38
	Placebo	10.00	12.50	-2.97	.002	0.38
SRT Implicit	Vit D	73.40	86.90	-0.15	.898	0.02
	Multivitamin	72.33	114.53	-3.25	<.001	0.42
	Placebo	91.28	90.73	-0.26	.812	0.03

PANAS

Test Measure	Group	Baseline median	Followup median	Z	p	r
Positive Affect	Vit D	35.00	34.50	-1.20	.241	0.15
	Multivitamin	36.00	35.50	-0.83	.422	0.11
	Placebo	35.50	34.50	-1.72	.088	0.22
Negative Affect	Vit D	18.00	15.50	-1.83	.071	0.24
	Multivitamin	15.50	18.50	-1.79	.075	0.23
	Placebo	16.00	16.00	-0.34	.749	0.04

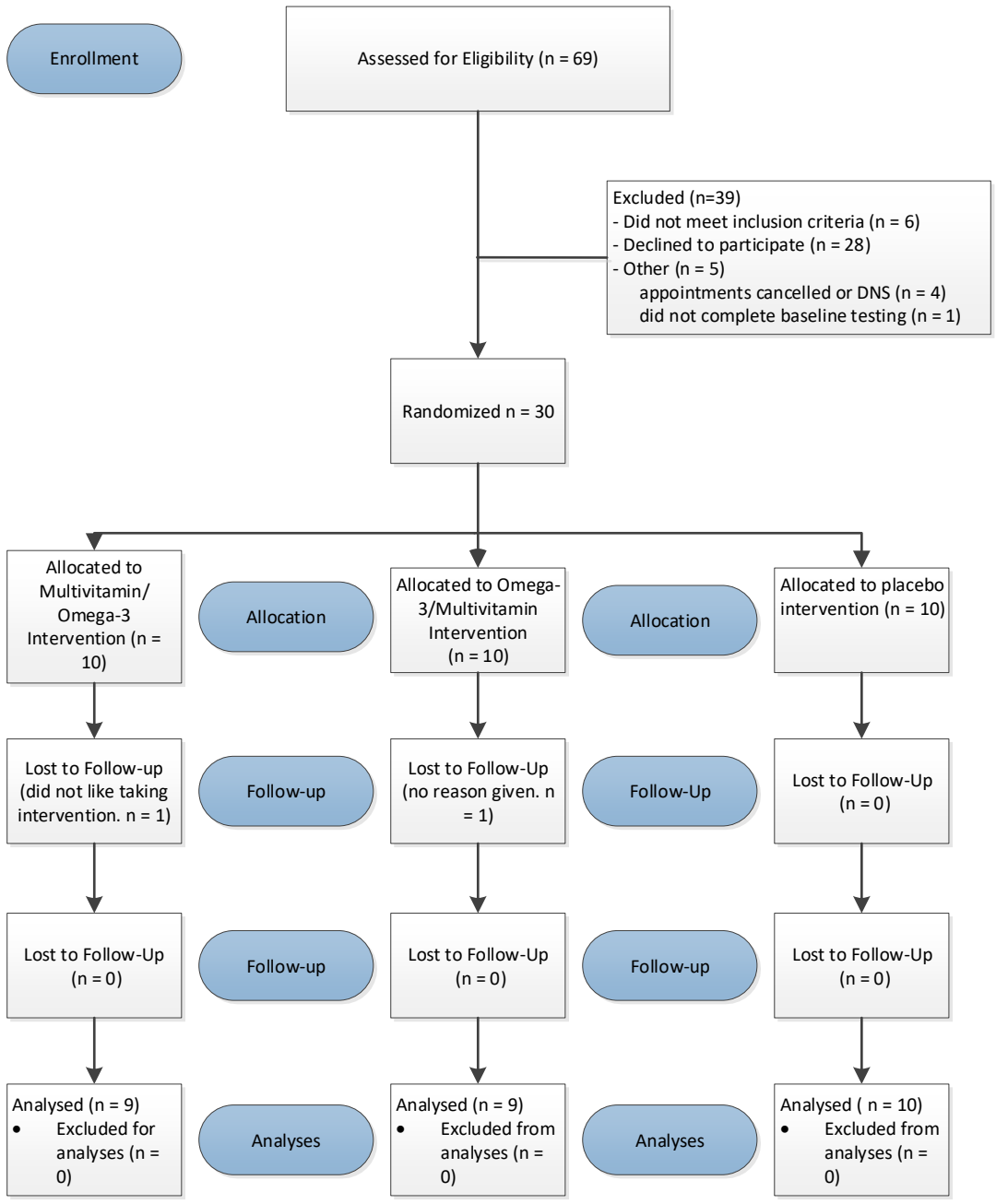
Social Cognition Measures

Test Measure	Group	Baseline median	Followup median	Z	p	r
MASC	Vit D	35.00	38.00	-3.00	.002	0.39

	Multivitamin	37.00	37.50	-2.33	.019	0.30
	Placebo	36.00	39.00	-3.21	.001	0.41
RME	Vit D	28.00	29.00	-2.06	.039	0.27
	Multivitamin	29.00	28.00	-1.32	.197	0.17
	Placebo	29.00	28.00	-0.24	.824	0.03

Appendix C

C.1 Consort Diagram



C.2: Supplement Composition

Omega-3

Piping Rock Triple Strength Omega-3 oil gel capsule (1360mg)	
Eicosapentaenoic acid (EPA)	580mg
Docosahexaenoic acid (DHA)	320mg

Multivitamin

Swisse Women's 50+ Ultivite

Vitamins		Minerals		Additional Extracts	
Vit. A	800µg	Magnesium	57mg	Ubidecareone	1mg
Thiamine	25mg	Selenium	100µg	Blueberry Extract	100mg
Riboflavin	25mg	Calcium	160mg	Cranberry Dry Extract	800mg
Niacin	20mg	Iron	4.2mg	Grape Seed Extract	25g
Pantothenic Acid	25mg	Zinc	10mg	Green Tea Dry Extract	20mg
B_6	9.5mg			Turmeric Dry Extract	100mg
Biotin	450µg			Carotenoids	1.2mg
Folate	400µg			Lutein	1mg
B_{12}	120µg			Zeaxanthin	50µg
Vitamin C	80mg			Flavonoid Complex	1mg
Vitamin D	10µg			Hesperidin	0.88mg
Vitamin E	18mg			Lycopene	120µg
Vitamin K	80µg			Phospatidylserine	1mg

Placebo

400mg sucrose encapsulated in vegetable cellulose and water

C.3 Participant Materials

C.3.1 Participant Information

IRAS Number: 157987

Sheffield Hallam University

Rebecca Denniss
Sheffield Hallam University
Department of Psychology, Sociology and Politics
Rm 1.05, Heart of Campus Building,
Collegiate Crescent Campus
Sheffield S10 2 BP

Telephone: 0114 225 3417
Email: r.denniss@shu.ac.uk

Micronutrient Intervention Effects on Cognitive Outcomes in Post-Acute Traumatic Brain Injury

Hello, I am conducting this study as part of my doctoral research. This is a voluntary study, you are not obliged to take part and you may refuse to take part at any point during the research.
This sheet outlines why the research is being conducted and what you, as a participant, would be required to do. If you have any questions, or you do not fully understand something, feel free to call or e-mail me at any point.

What is this study about?
Research has suggested that certain vitamins, minerals and oils may help people who have had a head injury to think, remember and process information.

To investigate this we are going to compare the task performance of people taking one of three different tablets. These tablets will be a multivitamin, omega-3 fish oil or a tablet that contains sucrose that has no effects (a placebo). All of the supplements are over the

counter formulations and taking one of these tablets a day, combined with normal diet, will not exceed upper intake limits for any micronutrient.

Do I have to take part?

This study is voluntary and you decide whether you want to take part in the research. If you do decide to participate then you will be asked to sign a written consent form to show that you are fully informed and willing to take part. For this study, you **must not** take any other dietary supplement (e.g. vitamins, minerals) apart from what you have been prescribed by your doctor. Your GP will be informed of your participation in the study. If you do take any additional over-the-counter supplements this **must** be disclosed to the researcher, particularly as additional supplements may result in **risk to your health**.

Please be aware that if you do participate you are able to stop taking part in the research at any time without question. You are also able to withdraw any of your results up to two weeks after the final testing session. It will not be possible to withdraw results after two weeks as your data will have been put together with the other participants and analysed. If after reading this sheet you do not want to take part in the research then that is fine, no questions will be asked this will not affect you medical or rehabilitation care in any way.

What will I have to do if I say yes?

If you would like to take part you may be asked to do the following:

- Complete a set of baseline tasks. These would be completed over a three sessions within a one week period, with the length of the session and rest breaks during the sessions determined by you (each session being approximately two hours long). Tasks would be to measure your general intelligence levels, memory and problem solving abilities.
- Take one of three tablets (either a multivitamin, an omega-3 fish oil or a placebo containing sucrose once a day for 8 weeks.
- During these eight weeks you would need to complete two 3-day food diaries. The food diaries will require you to note everything that you eat and drink over each of the three day periods, being as accurate as you can. You will be contacted by the researcher each time you need to complete a diary

- After eight weeks you would complete some of the same sort of tasks as you completed before you took the tablet. This time it would be two test sessions, approximately two hours in length.
- You would then be asked to avoid taking any supplements for the next six weeks.
- After the six weeks you would be asked to take one of three tablets (again a multivitamin, an omega-3 fish oil or a sucrose placebo) for another eight weeks and also complete two more 3-day food diaries. I would contact you to ask you to fill in each food diary.
- Finally you would complete some of the tasks you have completed earlier in the study again (again two test sessions approximately two hours long). This would be the end of your involvement in the study.

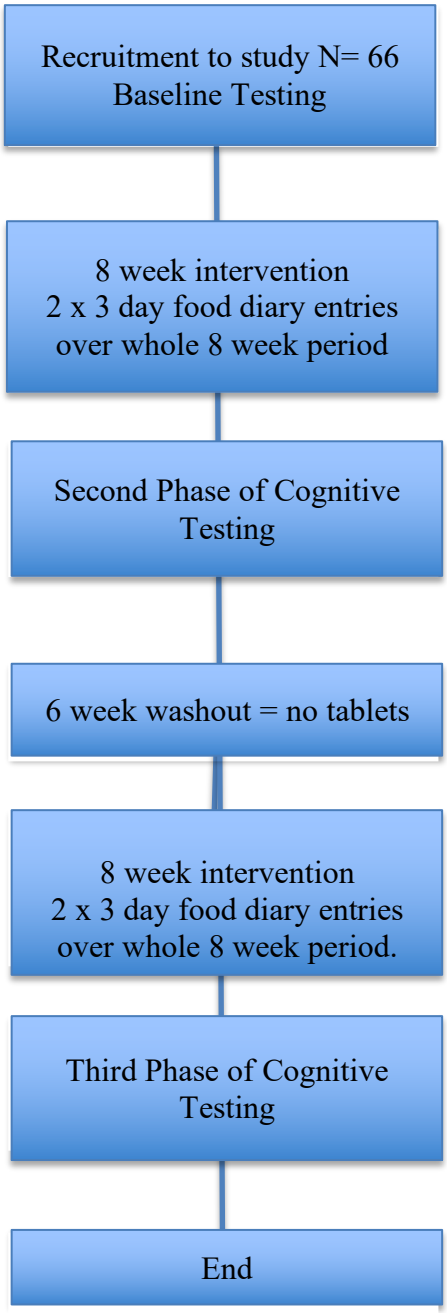
If you say yes to being involved in this research we will ask you to give your contact details on the consent form. These details will only be used to remind you to take your supplements, fill in your food diaries and make appointments for test sessions. Consent forms with your name and contact details on will be kept in a separate locked cabinet to your test forms and will be destroyed following completion of the study. If you are currently taking any non-prescription vitamin or mineral supplements you will be asked to stop taking them six weeks before you can start the study.

In addition, if you consent to being involved in this study the research team will ask to see your medical notes. This is for the purpose of making note of details of your head injury, for example how long you were unconscious for, how long you were in hospital and which areas of your brain appeared to be damaged on scans. This information will be kept confidential.

All test sessions would take place either at the hospital, rehabilitation centre or Sheffield Hallam University. During the second and third sets of sessions you will do the same tasks, or similar ones. Full instructions on how to fill in the food diary will be given to you by the researcher and will also be written in the food diary booklet. You will be reminded by email, telephone or text message each day to complete your food diary and take your supplements. The multivitamin used in the study is an over-the-counter product that contains a number of different nutrients (e.g. B vitamins, iron etc), the omega-3 fish oil tablet is also a one-a-day over the counter product and the placebo has no micronutrient content. The supplements will be allocated in a ‘double-blind’ way; neither the researcher or you will know which tablets you get at each of the two time points. This is to ensure that the researcher has no unintended bias when administering or scoring the

tasks (so as not to influence the results). You will not know which group you are in, this is so we can tell if people automatically get better at these tasks when they think they are taking vitamins or fish oils or when they are actually taking supplements. If you are in the placebo group at any point during the study you will be offered the active supplement or nearest equivalent.

Study Design



Following completion of the study you may be asked if you would mind being interviewed about your experiences of being in the study. This would be a very short interview lasting no more than 15 minutes.

Who is the Sheffield Hallam research team?

There are two researchers involved in this Sheffield Hallam research. As previously stated this research is being conducted by Rebecca Denniss. Rebecca is a Doctoral Researcher with an MSc in Cognitive Neuroscience and full training and experience in the correct administration of psychological tests. Overseeing this research is:

Dr. Lynne Barker, Reader in Cognitive Neuroscience, email: l.barker@shu.ac.uk

Telephone Number: 0114 225 5379.

Where will all of this take place?

Research will take place either on the Sheffield Hallam University Collegiate campus in the specially designed psychology research labs, or the researcher can travel to the rehabilitation centre, hospital ward for testing or participants home for testing. In recognition of the extended nature of the study you will be given a £10 high street voucher following completion of each set of test sessions (to a maximum of £30).

How long will the study take?

From when you begin the study you will be involved for a maximum of 8 months. You will be tested at three time points across the length of the study; once when you begin to see how you are doing, again after the first eight weeks and then finally after another fourteen weeks. Each testing session will last for approximately 2 hours with rest breaks determined by you.

What will be done with my results?

Your test results will only be seen by the researchers and clinicians involved in your care (clinicians involved with your care will only see your results with your permission). All of your results will be made anonymous, this means that your information will be given a code and this code will be used on all data associated with you; your name will not appear anywhere on your task materials or in the results. As the researcher will need to contact you over the course of the study, information linking your name and contact details with this code will be kept in paper form and stored in a locked cabinet. Only the researcher carrying out the tests and contacting you will have the cabinet key. This information will be shredded following completion of the research. All data collected will from you will be stored in a locked filing cabinet within a restricted access building or encrypted and stored on a password protected PC. Your anonymous data will be kept on a database so that other researchers can refer to it. Your results will be added to other participant's results and the researcher will look for patterns within these. The overall result of the research will form part of a doctoral thesis and may be published in a scientific journal. If you would like to receive copies of any publications arising from this research you may ask for them from the researchers involved.

If you decide that you are happy for clinicians (e.g. psychologists) involved in your care to see your test results then your data will not be anonymous for this purpose (although your name will never appear on these forms). Clinician's access will be restricted; they will have to ask to see specific test results that relate to your on-going rehabilitation. Following a request to see your test results the researcher will use the separate file containing personal information to link to your test papers. Once the clinician has looked at the requested papers they will be returned to the University for secure storage. At all other times your data will remain anonymous.

Is this study safe?

Yes. This research has been reviewed and approved by the Faculty Research Ethics Committee (FREC) at Sheffield Hallam University and the NHS Research Ethics Committee. None of the tablets are predicted to have any negative effects; the micronutrient supplements are all over-the-counter preparations and there are no reported negative consequences reported from taking these levels of supplements. We wish to make you aware that there is some evidence that moderate to heavy levels of smoking (more than 10 cigarettes a day) in combination with taking beta-carotene (vitamin A) at levels twenty times the level you will take in this study (over several years) carries an increased risk of lung cancer. Contrary to this there is evidence that beta-carotene in the smaller doses you may be taking in this study may be beneficial following head injury.

Should you experience any negative effects related to taking the tablets (for example prolonged numbness or pain in hands or feet, prolonged facial flushing [feeling hot] or extended period of upset stomach) you should discontinue taking the supplement and contact the researcher (Rebecca Denniss) immediately. In the unlikely event that you experience a serious event directly related to your involvement in the study, Sheffield Hallam University has full insurance to cover any compensation.

Pregnant or breast-feeding women should not take part in this study.

Individuals with diabetes or clinically low blood pressure should not take part in this study.

What are the advantages of taking part?

You will receive an evaluation how you did on the tests across the time period of the research and we are happy to provide a breakdown of scores. You mind find this useful when planning your future rehabilitation. Findings of this research may also expand knowledge of how nutrition affects thinking, memory and processing information following a head injury.

What are the disadvantages of taking part?

There are no foreseeable risks to this research and it is not expected that any of the tasks should cause you any discomfort or distress. If you experience any adverse reactions to the supplement or are unhappy completing the tasks you are entitled to discontinue your participation in the study. Test sessions may be quite long (up to two hours); to make this experience as comfortable as possible for you, you will be able to take breaks during test sessions whenever you need them, for whatever reason.

Can I know my results?

You can request a feedback document that will tell you how well you did on the tasks. You won't be able to have the document straight away during your participation in the study as this may affect how you do the tasks. Your feedback will be given to you in person or over the telephone to allow you to ask questions, once you have completed the study. We will not be able to tell you if you have done in relation to other people, as we are not allowed to discuss other people's results.

When can I ask questions?

You are free to ask any questions at any point during the research. If you have any questions now please feel free to ask. If you think of any questions after you leave here today please feel free to contact me.

PLEASE REMEMBER THAT ALL RESULTS WILL STAY CONFIDENTIAL AND WILL BE MADE ANONYMOUS. YOU ARE FREE TO WITHDRAW FROM THIS STUDY AT ANY TIME DURING THE RESEARCH.

Thank you for taking the time to read this.

The University undertakes research as part of its function for the community under its legal status. Data protection allows us to use personal data for research with appropriate safeguards in place under the legal basis of public tasks that are in the public interest. A full statement of your rights can be found at https://www.shu.ac.uk/about-this-website/privacy-policy/privacy-notices/privacy-notice-for-research. However, all University research is reviewed to ensure that participants are treated appropriately and their rights respected. This study was approved by Sheffield Hallam University Research Ethics Committee (authorisation number: 333DEN). Further information can be found at https://www.shu.ac.uk/research/ethics-integrity-and-practice.

Rebecca Denniss (Doctoral Researcher),
Department of Psychology, Heart of the Campus Building,
Sheffield Hallam University, Sheffield. S10 2BP
Email: r.denniss@shu.ac.uk. Telephone 0114 225 3417

If you wish to query this further and do not wish to speak to the researcher please contact:

Dr Lynne Barker, Reader in Cognitive Neuroscience, Department of Psychology, Heart of the Campus Building, Sheffield Hallam University, Sheffield. S10 2BP.
Tel: 0114 225 5379. email: l.barker@shu.ac.uk

If at any time during the study you wish to talk to someone outside the research team about any matter related to your involvement please contact the **Patient Advice and Liason Service** at one of the below addresses:

33 Love Street
Sheffield
S3 8NW
Tel: 0114 2718956

Northern General Hospital
Herries Road
Sheffield
S5 7AU
Tel: 0114 2712400

Tickhill Road Hospital
Weston Road
Tickhill Road, Balby,
Doncaster
DN4 8QN
Tel: 0800 0154334

You should contact the Data Protection Officer if:	**You should contact the Head of Research Ethics (Professor Ann Macaskill) if**
• you have a query about how your data is used by the University • you would like to report a data security breach (e.g. if you think your personal data has been lost or disclosed inappropriately) • you would like to complain about how the University has used your personal data DPO@shu.ac.uk	• you have concerns with how the research was undertaken or how you were treated a.macaskill@shu.ac.uk
Postal address: Sheffield Hallam University, Howard Street, Sheffield S1 1WBT Telephone: 0114 225 5555	

C.3.2 Consent Form

Sheffield Hallam University

Rebecca Denniss
Sheffield Hallam University
Department of Psychology, Sociology and Politics
Rm 1.05, Heart of Campus Building,
Collegiate Crescent Campus
Sheffield S10 2 BP

Telephone: 0114 225 3417
Email: r.denniss@shu.ac.uk

IRAS ID: 157987

Participant Identification Number:

CONSENT FORM

Title of Project: Micronutrient Intervention Effects on Cognitive Outcomes in Post-Acute Traumatic Brain Injury

Please initial box

1. I have read and understood the participant information sheet (version 7) and understand what will be required of me in the study. ☐

2. I consent to medical records being accessed by the research team. ☐

3. All of my questions have been answered sufficiently and I am aware I can ask more questions at any time. ☐

4. I understand that this research is voluntary and that I am free to withdraw from the research at any point during the testing phase. I am aware that I can withdraw my results up to two weeks after final testing without question or any negative consequences. ☐

5. I understand that all my results will be made anonymous by associating it with a code, not personal information, and will stay confidential and secure throughout the research process. ☐

6. I understand that if I am pregnant, breastfeeding, diabetic or have clinically low blood pressure I should not take part in the study. ☐

7. I understand the risks as presented of the link between high doses of beta-carotene (vitamin A) intake over a long period of time and lung cancer associated with smoking. ☐

8. I know how to get in contact with the researcher if I have any questions, concerns or wish to withdraw. ☐

9. I consent to the researcher getting in contact with me via telephone, text message or email (my choice) to remind me to fill in a food diary and to take my tablet. ☐

10. I consent to take part in the research ☐

Name (Printed) _____ Date _____
Signature _____ Mobile Number _____
Email Address
_____

11. I am happy/not happy for my test scores to be made available for clinicians involved in my care to aid in rehabilitation plans.
Name (Printed) _____ Date _____
Signature _____

Name of person taking consent:_____
Signature: _____ Date: _____

If you would like to be contacted about published results and where you can find them then please indicate here

If you have any questions about the research and you do not wish to discuss them with the researcher then please contact:
Dr Lynne Barker, Reader in Cognitive Neuroscience,
Dept., of Psychology, Sociology and Politics,

Heart of Campus Building,

Sheffield Hallam University

Sheffield S10 2BP,

Telephone +44 (0)114 225 5379

Email: L.barker@shu.ac.uk

C.3.3 Debrief

Sheffield Hallam University

Rebecca Denniss
Sheffield Hallam University, Department of Psychology,
Heart of Campus Building, Collegiate Campus,
Sheffield Hallam University, Sheffield. S10 2LD
Telephone: 0114 225 5580
Email: r.denniss@shu.ac.uk

Micronutrient Intervention Effects on Cognitive Outcomes in Post-Acute Traumatic Brain Injury

Thank you for participating in this research. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information.

The purpose of this research is to investigate whether vitamin supplements can improve an individual's ability to process certain kinds of information following a head injury. You were allocated to the _____ condition for the first 8 weeks and the _____condition for the second 8 weeks. It was necessary that both you and the person administering the tests were unaware of the tablets you were taking at what time to ensure that there was no bias in the results, either from your expectations or from the expectations of the experimenter. This form of study is known as a double-blind randomised trial.

During this research you initially completed a number of tasks to test general levels of cognitive ability, memory capability and problem solving ability. You were then asked to take two tablets once a day for 6 months in total and keep a food diary. You have then completed a number of the same kinds of tasks as you did in the first session on two other occasions. This was to compare changes in test scores between two different groups at different time points.

All information provided by you will remain confidential and will be stored anonymously in accordance with the Data Protection Act 1998. Only members of the research team will have access to your data. Hard copies of data will be stored in locked cabinet in a key-card only building. Data transferred onto a computer will be password protected and stored on Sheffield Hallam University's secure network.

The results from the analysis of this research will be written up as part of my doctoral thesis and may also be submitted to an academic journal for publication. Results from this study will also be used to inform further research into nutrition and cognition in people with neurological conditions.
If you have any concerns about the experiment, the research or the researcher and you do not wish to discuss them with the researcher then please contact:
Dr Lynne Barker, Reader in Cognitive Neuroscience
Department of Psychology,
Heart of Campus Building,
Collegiate Campus,
Sheffield Hallam University,
Sheffield
S10 2LD
Telephone Number: 0114 225 5379
email: l.barker@shu.ac.uk

Appendix D: Chapter 6 SPSS Outputs

Overall Descriptive Statistics

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Time since injury at recruitment into the study in months	30	24.00	3.00	27.00	12.70	7.10
Education	30	5.00	.00	5.00	1.87	1.25
Age	30	51.00	19.00	70.00	41.83	16.03
Valid N (listwise)	30					

Breakdown by category

Gender

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Female	9	30.0	30.0	30.0
	Male	21	70.0	70.0	100.0
	Total	30	100.0	100.0	

Education

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	GCSE or Equivalent	2	6.70	6.70	6.70
	A level or training to 18	15	50.00	50.00	56.70
	HND HNC or equivalent	1	3.30	3.30	60.00

	Undergraduate degree	10	33.30	33.30	93.30
	Masters degree	1	3.30	3.30	96.70
	PhD	1	3.30	3.30	100.00
	Total	30	100.0	100.0	

Living Arrangements

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Alone	4	13.30	13.30	13.30
	With partner/family	26	86.70	86.70	100.00
	Total	30	100.00	100.000	

Cause_of_Injury

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Motor Vehicle Accident	6	20.00	20.00	20.00
	Hit by Motor Vehicle	4	13.30	13.30	33.30
	Cycling Accident	3	10.00	10.00	43.30
	Horse Riding Accident	1	3.30	3.30	46.70
	Trip or Fall	12	40.00	40.00	86.70
	Assault	1	3.30	3.30	90.00
	Accident at Work	2	6.70	6.70	96.70
	Sporting Injury	1	3.30	3.30	100.00
	Total	30	100.00	100.00	

Descriptive statistics of IQ measures

		TOPF_Est_IQ_B	WASI_FSIQ4_B
N	Valid	29	30
	Missing	1	0
Mean		104.31	101.37
Median		103.00	104.00
Std. Deviation		9.41	11.46
Minimum		87.00	76.00
Maximum		121.00	116.00

Appendix E : Chapter 7 SPSS Outputs

E.1 Demographic Descriptives

Time Since injury

Group		Statistic	Std. Error
MO	Mean	11.30	2.17
	Median	9.50	
	Std. Deviation	8.86	
	Minimum	3.00	
	Maximum	24.00	
	Interquartile Range	11.50	
	Skewness	.57	.69
	Kurtosis	-0.67	1.33
OM	Mean	15.00	1.98
	Median	14.50	
	Std. Deviation	6.27	
	Minimum	6.00	
	Maximum	24.00	
	Interquartile Range	10.75	
	Skewness	.03	.69
	Kurtosis	-1.18	1.33
Placebo	Mean	11.80	2.59
	Median	9.00	
	Std. Deviation	8.19	
	Minimum	4.00	
	Maximum	27.00	
	Interquartile Range	13.25	

	Skewness	1.05	.69
	Kurtosis	-.19	1.33
Age Group			
MO	Mean	36.60	5.86
	Median	28.00	
	Std. Deviation	18.54	
	Minimum	19.00	
	Maximum	69.00	
	Interquartile Range	33.50	
	Skewness	.63	.69
	Kurtosis	-1.30	1.33
OM	Mean	46.10	4.05
	Median	48.50	
	Std. Deviation	12.81	
	Minimum	22.00	
	Maximum	61.00	
	Interquartile Range	19.75	
	Skewness	-.76	.69
	Kurtosis	-.32	1.33
placebo	Mean	42.80	5.18
	Median	42.00	
	Std. Deviation	16.39	
	Minimum	19.00	
	Maximum	70.00	
	Interquartile Range	27.00	
	Skewness	.172	.69
	Kurtosis	1.08	1.33

ANOVA Time since injury

Levene's Test

F	df1	df2	*p*
.33	2	27	.719

Source	Type III Sum of Squares	*df*	Mean Square	*F*	*p*	η_p^2
Corrected Model	80.60	2	40.30	0.79	.465	.06
Intercept	4838.70	1	4838.70	94.55	<.001	.78

Overall Group	80.60	2	40.30	0.79	.465	.06
Error	1381.70	27	51.17			
Total	6301.00	30				
Corrected Total	1462.30	29				

ANOVA Age

F	df1	df2	*p*
1.74	2	27	.194

Source	Type III Sum of Squares	df	Mean Square	*F*	*p*	η_p^2
Corrected Model	465.27	2	232.63	0.90	.419	.06
Intercept	52500.83	1	52500.83	202.88	<.001	.88
Overall Group	465.27	2	232.63	0.90	.419	.06
Error	6986.90	27	258.77			
Total	59953.00	30				
Corrected Total	7452.17	29				

ANOVA TOPF Est Intelligence

Levene's Test

F	df1	df2	Sig.
2.17	2	26	.134

Source	Type III Sum of Squares	df	Mean Square	F	*p*	η_p^2
Corrected Model	10.82	2	5.41	.06	.945	.004
Intercept	314922.72	1	314922.71	3315.80	.000	.99
Group_Period1	10.82	2	5.41	.06	.945	.004
Error	2469.39	26	94.976			
Total	318019.00	29				
Corrected Total	2480.21	28				

ANOVA WASI FSIQ

Levene's Test

F	df1	df2	Sig.
.80	2	27	.461

Source	Type III Sum of Squares	df	Mean Square	F	p	η_p^2
Corrected Model	141.27	2	70.63	.52	.600	.04
Intercept	308256.03	1	308256.03	2269.25	<.001	.99
Group_Period1	141.27	2	70.63	.52	.600	.04
Error	3667.70	27	135.84			
Total	312065.00	30				
Corrected Total	3808.97	29				

E.2 Behavioural Data Descriptives

Behavioural measures descriptive data for each intervention. Participants took one intervention for 8 weeks, had a 6 week washout, and then took the other intervention. Participants allocated the placebo also took the placebo. Intervention OM = omega-3 taken for the first 8 weeks and multivitamin taken for the second 8 weeks. Intervention MO = multivitamin taken for the first 8 weeks and omega-3 taken for the second 8 weeks. Participants taking the placebo took this for both periods. Dotted line denotes washout period of 6 weeks.

	Intervention OM			Intervention MO			Placebo		
Cognitive Measure	Baseline Mean (SD) (N = 10 Males = 5) [Range]	T1 Assessment after omega-3 Mean (SD) (N = 9 Males = 4) [Range]	T2 Assessment test after multivitamin Mean (SD) (N = 9 Males = 4) [Range]	Baseline Mean (SD) N = 10, Males = 8 [Range]	T1 Assessment test after multivitamin Mean (SD) N = 9 Males = 8 [Range]	T2 Assessment test after omega-3. Mean (SD) N = 9 Males = 8 [Range]	Baseline Mean (SD) N = 10 Males = 8 [Range]	T1 Assessment after placebo condition Mean (SD) N = 10 Males = 8 [Range]	T2 Assessment testing after the 2nd placebo condition Mean (SD) N = 10 Males = 8 [Range]
IQ Measures									
Test of Pre-morbid Function Est. IQ	103.50 (10.14) [87 - 121]			104.30 (11.82) [87 – 121]			105.11 (6.03) [97 – 116]		
WASI-II Full Scale IQ	103.38 (6.95) [92 - 111]			98.30 (12.48) [83 – 115]			105.78 (9.38) [84 – 114]		
Activities of Daily Living									
Nottingham Extended Activities of Daily Living	50.17 (12.82) [39]	50.11 (14.50) [44]	53.11 (9.91) [30]	53.67 (7.21) [21]	52.67 (9.91) [25]	51.44 (12.41) [40]	48.90 (17.48) [53]	51.10 (19.40) [54]	50.20 (17.74) [54]
Mood State									

PANAS Positive Affect	28.22 (8.87) [28]	33.44 (7.09) [23]	28.22 (6.74) [25]	28.67 (11.91) [33]	32.11 (10.84) [35]	29.33 (10.57) [34]	30.90 (8.72) [32]	31.90 (7.26) [26]	30.50 (8.09) [24]
PANAS Negative Affect	24.00 (10.56) [35]	20.56 (10.33) [34]	25.11 (8.65) [27]	20.89 (7.24) [22]	23.72 (9.33) [28]	22.06 (9.94) [28]	19.30 (5.19) [18]	18.90 (7.56) [24]	18.60 (5.52) [20]
Processing Speed									
WAIS-III Symbol Search	9.00 (1.73) [4]	10.11 (3.89) [12]	10.33 (4.50) [14]	8.89 (1.62) [5]	11.00 (3.24) [9]	11.44 (3.32) [12]	8.60 (3.31) [11]	9.90 (4.75) [17]	10.10 (5.61) [18]
Memory									
WAIS-III Digit Span Overall Score	7.56 (2.46) [7]	8.33 (3.08) [8]	8.44 (3.43) [11]	10.22 (2.73) [8]	11.00 (2.69) [9]	11.55 (3.09) [8]	10.50 (2.95) [9]	10.30 (2.67) [9]	11.80 (2.86) [9]
WMS-IV VPA: Verbal Memory Immediate Recall	8.22 (1.56) [5]	10.33 (3.00) [8]	10.11 (3.25) [9]	8.78 (3.35) [9]	10.44 (4.03) [14]	12.00 (3.64) [12]	8.40 (3.27) [9]	10.20 (4.57) [14]	11.90 (4.56) [14]
WMS-IV VPA: Verbal Memory Delayed Recall	8.00 (2.55) [9.00]	10.11 (4.01) [12]	9.44 (3.47) [10]	8.89 (4.04) [11]	10.67 (4.03) [12]	11.44 (3.17) [9]	9.50 (3.57) [10]	10.40 (4.38) [14]	11.10 (3.60) [10]
Doors Visual Recognition	8.22 (3.80) [12]	9.89 (5.04) [14]	10.11 (5.80) [17]	9.78 (2.99) [9]	10.67 (4.36) [15]	11.75 (4.71) [14]	9.60 (2.76) [9]	9.90 (3.18) [9]	10.89 (2.20) [6]
ROCFT – Copy (perceptual organisation)	35.22 (0.83) [2]	34.78 (1.30) [4]	34.78 (1.20) [3]	34.56 (1.59) [5]	34.39 (2.23) [5.50]	34.67 (1.73) [4]	32.50 (6.19) [20]	32.20 (7.97) [26]	32.60 (5.12) [17.50]
ROCFT Immediate Visual Recall	23.72 (5.47) [18]	24.50 (6.54) [21]	23.33 (7.34) [20]	24.56 (5.80) [15.50]	25.67 (9.51) [24]	27.83 (5.90) [17.50]	22.65 (9.43) [32]	25.55 (8.44) [31]	26.40 (9.50) [31.50]
ROCFT Delayed Visual Recall	22.94 (6.78) [20]	23.50 (6.97) [25]	24.56 (6.86) [22.50]	22.72 (7.74) [22]	25.72 (9.15) [24]	28.94 (6.14) [19.50]	21.00 (8.80) [28.50]	24.35 (8.71) [31]	25.15 (9.62) [33]

Executive Function									
DKEFS Trail Making Visual Scanning	7.44 (4.61) [12]	9.00 (5.07) [13]	9.22 (4.89) [12]	9.56 (2.83) [7]	10.56 (2.96) [9]	11.56 (1.68) [5]	8.70 (4.69) [13]	8.40 (5.21) [13]	8.90 (4.63) [13]
DKEFS Trail Making Number Sequencing	9.67 (4.24) [13]	9.00 (5.52) [13]	9.78 (4.82) [14]	9.44 (2.74) [8]	12.33 (2.06) [6]	11.78 (2.59) [7]	10.00 (4.37) [14]	10.30 (4.30) [14]	10.70 (4.00) [14]
DKEFS Trail Making Letter Sequencing	8.89 (4.62) [11]	10.67 (4.74) [13]	11.11 (4.04) [12]	10.67 (2.74) [8]	11.00 (3.12) [10]	12.78 (1.30) [4]	9.70 (4.69) [14]	9.90 (3.54) [13]	11.00 (4.22) [14]
DKEFS Trail Making Number/Letter Switching	10.44 (3.13) [10]	10.67 (3.20) [9]	10.67 (3.50) [8]	10.33 (2.96) [8]	11.22 (2.77) [7]	12.33 (2.00) [6]	10.10 (4.07) [13]	10.40 (3.95) [14]	10.90 (3.93) [14]
DKEFS Trail Making Motor Speed	9.00 (4.06) [12]	9.33 (4.27) [11]	9.89 (4.37) [12]	11.33 (1.50) [5]	12.11 (0.93) [3]	12.00 (0.78) [2]	10.10 (3.41) [12]	9.70 (3.56) [11]	10.20 (3.49) [12]
DKEFS Verbal Fluency: Phonemic Fluency	9.56 (2.65) [9]	9.78 (3.35) [11]	9.56 (3.40) [11]	11.67 (4.61) [13]	12.11 (5.37) [15]	12.44 (5.20) [14]	10.70 (3.23) [11]	10.70 (3.27) [10]	12.20 (3.29) [10]
DKEFS Verbal Fluency: Semantic Fluency	10.33 (3.43) [11]	10.56 (6.35) [18]	10.33 (5.20) [16]	11.33 (4.36) [15]	11.67 (5.07) [15]	13.00 (5.09) [16]	11.90 (4.95) [17]	10.60 (6.26) [18]	11.90 (3.98) [13]
DKEFS Verbal Fluency: Semantic Switching	11.33 (1.00) [3]	10.56 (2.79) [10]	10.11 (3.37) [10]	10.89 (3.62) [12]	9.33 (3.54) [11]	12.78 (4.21) [14]	11.40 (4.09) [14]	11.30 (4.32) [15]	12.80 (2.65) [9]
DKEFS Colour Word Naming	7.56 (4.16) [12]	8.11 (4.43) [13]	8.75 (3.73) [13]	8.44 (2.30) [7]	10.11 (2.93) [11]	9.78 (3.60) [13]	7.90 (4.51) [14]	8.40 (4.84) [14]	8.80 (4.52) [13]
DKEFS Colour Word Reading	7.89 (4.28) [12]	8.78 (4.63) [13]	9.00 (3.93) [12]	10.00 (2.18) [6]	10.44 (2.13) [6]	10.44 (3.32) [12]	9.67 (3.39) [10]	10.22 (4.49) [14]	10.22 (3.80) [11]

DKEFS Colour Word Inhibition	8.11 (4.23) [12]	10.62 (4.31) [13]	10.63 (4.17) [13]	9.44 (3.24) [11]	11.78 (1.56) [5]	11.22 (3.19) [11]	10.33 (4.00) [14]	10.56 (4.95) [15]	10.56 (3.36) [10]
DKEFS Colour Word Inhibition Switching	8.00 (4.53) [12]	10.50 (4.04) [12]	10.37 (4.45) [13]	9.56 (4.10) [13]	11.44 (2.46) [6]	11.44 (3.21) [9]	9.67 (4.47) [12]	9.44 (5.46) [14]	11.44 (3.13) [9]
Learning									
SRT Explicit Learning	3.36 (3.06) [8.5]	7.03 (3.85) [11]	6.57 (5.16) [16]	7.33 (4.00) [13]	8.83 (5.32) [17]	10.50 (6.07) [19]	6.50 (3.72) [13]	8.65 (4.61) [12.50]	8.33 (4.64) [15]
SRT Implicit Learning	34.51 (44.69) [128]	38.90 (48.50) [155]	44.16 (36.87) [106.55]	76.57 (90.43) [278.90]	21.76 (79.37) [220.95]	60.68 (40.81) [127.75]	28.64 (66.21) [199.15]	79.82 (137.80) [429.15]	129.24 (171.58) [552.35]
Social Cognition									
Reading the Mind in the Eyes	24.67 (3.94) [11]	22.78 (5.43) [18]	23.22 (5.76) [18]	23.22 (4.27) [11]	24.22 (5.70) [17]	25.00 (5.01) [14]	23.30 (5.89) [18]	24.30 (6.06) [17]	23.78 (5.19) [14]

DKEFS = Delis-Kaplan Executive Function System
PANAS = Positive and Negative Affect Schedule
ROCFT = Rey-Osterreith Complex Figure Test
SRT = Serial Reaction Time
WAIS-IV = Weschler Adult Intelligence Scale
WASI-II = Weschler Abbreviated Scale of Intelligence
WMS-IV VPA = Weschler Memory Scale Verbal Paired Associates

E3 Baseline behavioural MANOVAs

Memory

Box's Test	
Box's M	138.47
F	1.42
df1	56
df2	1747.35
p.	.024

Effect		Value	F	Hyp. df	Error df	*p.*	η_p^2
Group	Pillai's Trace	.54	1.06	14.00	40.00	.424	.270
	Wilks' Lambda	.50	1.12	14.00	38.00	.371	.293
	Hotelling's Trace	.92	1.18	14.00	36.00	.331	.315
	Roy's Largest Root	.82	2.34	7.00	20.00	.064	.451

Trail Making

Box's Test	
Box's M	44.31
F	1.03
df1	30
df2	1937.23
p.	.418

Effect		Value	F	Hypo. df	Error df	Sig.	η_p^2
Group	Pillai's Trace	.54	1.64	10.00	44.00	.126	.27
	Wilks' Lambda	.48	1.88	10.00	42.00	.077	.31
	Hotelling's Trace	1.05	2.10	10.00	40.00	.048	.34
	Roy's Largest Root	1.00	4.41	5.00	22.00	.006	.50

Verbal Fluency

Box's Test	
Box's M	23.79
F	1.63
df1	12
df2	2951.75
p.	.077

Effect		Value	F	Hyp. df	Error df	p.	η_p^2
Group	Pillai's Trace	.13	.53	6.00	48.00	.780	.06
	Wilks' Lambda	.88	.52	6.00	46.00	.791	.06
	Hotelling's Trace	.14	.51	6.00	44.00	.801	.06
	Roy's Largest Root	.12	.93	3.00	24.00	.440	.105

Colour word interference test

Box's Test	
Box's M	31.09
F	1.17
df1	20
df2	2067.59
p.	.27

Effect		Value	F	Hypo. df	Error df	p.	η_p^2
Group	Pillai's Trace	.17	.50	8.00	44.00	.850	.08
	Wilks' Lambda	.84	.48	8.00	42.00	.862	.08
	Hotelling's Trace	.19	.46	8.00	40.00	.874	.09
	Roy's Largest Root	.14	.77	4.00	22.00	.559	.12

Processing Speed and Learning

Box's Test	
Box's M	13.89
F	.93
df1	12
df2	1998.69
p.	.520

Effect		Value	F	Hyp. df	Error df	p.	η_p^2
Group	Pillai's Trace	.28	1.20	6.00	44.00	.325	.14
	Wilks' Lambda	.74	1.16	6.00	42.00	.345	.14
	Hotelling's Trace	.34	1.12	6.00	40.00	.367	.14
	Roy's Largest Root	.24	1.79	3.00	22.00	.179	.20

ADL, Mood State and Social Cognition

Box's Test	
Box's M	27.88
F	1.06
df1	20
df2	2192.57
p.	.386

Effect		Value	F	Hypothesis df	Error df	p.	η_p^2
Group	Pillai's Trace	.16	.50	8.00	46.00	.847	.081
	Wilks' Lambda	.85	.48	8.00	44.00	.862	.081
	Hotelling's Trace	.18	.46	8.00	42.00	.876	.081
	Roy's Largest Root	.10	.60	4.00	23.00	.668	.094

E.4 Food diary Analyses

T-tests – Difference to RDA intervention period 1

Vitamin A

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	t	df	p
OM	Pair 1	Vit A - RDA	-112.22	219.62	73.21	-281.04	56.60	-1.53	8	.164
	Pair 2	Supp.+Diet - RDA	-112.22	219.62	73.21	-281.04	56.60	-1.53	8	.164
MO	Pair 1	Vit A - RDA	-187.38	540.71	191.17	-639.42	264.67	-0.98	7	.360
	Pair 2	Supp.+Diet1 – RDA	612.63	540.71	191.17	160.58	1064.67	3.21	7	.015
Placebo	Pair 1	Vit A1 - RDA	-55.20	328.58	103.91	-290.25	179.85	-0.53	9	.608
	Pair 2	Supp.+Diet1 - RDA	-55.20	328.58	103.91	-290.25	179.85	-0.53	9	.608

Vitamin C

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	t	df	p
MO	Pair 1	Vitamin C – RDA	-21.65	38.34	13.56	-53.70	10.40	-1.60	7	.154
	Pair 2	Diet+Supp - RDA	143.65	38.34	13.56	111.60	175.70	10.60	7	<.001
OM	Pair 1	VitaminC1 - RDA	-1.41	46.30	15.43	-37.00	34.17	-.091	8	.929
	Pair 2	Diet+Supp - RDA	-1.41	46.30	15.43	-37.00	34.17	-.091	8	.929
Placebo	Pair 1	VitaminC1 - RDA	-18.80	56.41	17.84	-59.22	21.48	-1.06	9	.318
	Pair 2	Diet+Supp - RDA	-18.87	56.41	17.84	-59.22	21.48	-1.06	9	.318

Vitamin D

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Vitamin D – RDA	-12.27	1.45	.51	-13.48	-11.05	-23.94	7	<.001
	Pair 2	Diet+Supp - RDA	-2.27	1.45	.51	-3.48	-1.05	-4.42	7	.003
OM	Pair 1	Vitamin D – RDA	-11.76	1.90	.63	-13.21	-10.30	-18.60	8	<.001
	Pair 2	Diet+Supp - RDA	-11.76	1.90	.63	-13.21	-10.30	-18.60	8	<.001
Placebo	Pair 1	Vitamin D – RDA	-12.55	1.41	.45	-13.56	-11.55	-28.16	9	<.001
	Pair 2	Diet+Supp - RDA	-12.55	1.41	.45	-13.56	-11.55	-28.16	9	<.001

Vitamin K

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Vitamin K – RDA	-79.59	23.50	8.31	-99.23	-59.94	-9.58	7	<.001
	Pair 2	Diet+Supp – RDA	0.41	23.50	8.31	-19.23	20.06	0.05	7	.962
OM	Pair 1	Vitamin K – RDA	-33.20	78.23	26.08	-93.33	26.93	-1.27	8	.239
	Pair 2	Diet+Supp – RDA	-33.20	78.23	26.08	-93.33	26.93	-1.27	8	.239
Placebo	Pair 1	Vitamin K – RDA	-55.23	59.86	18.93	-98.05	-12.41	-2.92	9	.017
	Pair 2	Diet+Supp – RDA	-55.23	59.86	18.93	-98.05	-12.41	-2.92	9	.017

Thiamin

Paired Samples Test

Group			Paired Differences					*t*	*df*	*p*
			Mean	SD	SE Mean	95% Confidence Interval of the Difference Lower	Upper			
MO	Pair 1	Thiamin1 - RDA	0.39	0.53	0.19	-0.05	0.83	2.11	7	.072
	Pair 2	Diet+Supp – RDA	25.39	0.53	0.19	24.95	25.83	136.36	7	<.001
OM	Pair 1	Thiamin – RDA	0.34	0.29	0.10	0.12	0.57	3.54	8	.008
	Pair 2	Diet+Supp – RDA	0.34	0.29	0.10	0.12	0.57	3.54	8	.008
Placebo	Pair 1	Thiamin – RDA	0.39	0.63	0.20	-0.06	0.84	1.94	9	.084
	Pair 2	Diet+Supp - RDA	0.39	0.63	0.20	-0.06	0.84	1.94	9	.084

Riboflavin

Paired Samples Test

Group			Paired Differences					*t*	*df*	*p*
			Mean	SD	SE Mean	95% Confidence Interval of the Difference Lower	Upper			
MO	Pair 1	Riboflavin - RDA	0.70	0.63	0.22	0.17	1.23	3.14	7	.016
	Pair 2	Diet+Supp – RDA	25.70	0.63	0.22	25.17	26.23	115.35	7	<.001
OM	Pair 1	Riboflavin – RDA	0.50	0.49	0.16	0.12	0.87	3.07	8	.015
	Pair 2	Diet+Supp – RDA	0.50	0.49	0.16	0.12	0.87	3.07	8	.015
Placebo	Pair 1	Riboflavin – RDA	0.73	0.73	0.23	0.21	1.25	3.16	9	.012
	Pair 2	Diet+Supp - RDA	0.73	0.73	0.23	0.21	1.25	3.16	9	.012

Niacin

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group_Period1			Mean	SD	SE Mean	Lower	Upper	t	df	p
MO	Pair 1	Niacin - RDA	24.88	8.10	2.87	18.10	31.65	8.68	7	<.001
	Pair 2	Diet+Supp – RDA	44.88	8.10	2.87	38.10	51.65	15.66	7	<.001
OM	Pair 1	Niacin - RDA	19.58	5.14	1.71	15.63	23.53	11.43	8	<.001
	Pair 2	Diet+Supp – RDA	19.58	5.14	1.71	15.63	23.53	11.43	8	<.001
Placebo	Pair 1	Niacin - RDA	20.17	14.71	4.65	9.64	30.70	4.34	9	.002
	Pair 2	DietSupp - RDA	20.17	14.71	4.65	9.64	30.70	4.34	9	.002

Pantothenic Acid

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group_Period1			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Pantothenic Acid - RDA	0.76	1.53	0.54	-0.52	2.04	1.41	7	.202
	Pair 2	Diet+Supp – RDA	25.76	1.53	0.54	24.48	27.04	47.61	7	<.001
OM	Pair 1	Pantothenic Acid - RDA	0.53	1.22	0.41	-0.40	1.47	1.32	8	.225
	Pair 2	Diet+Supp – RDA	0.53	1.22	0.41	-0.40	1.47	1.32	8	.225
Placebo	Pair 1	Pantothenic Acid - RDA	0.69	2.27	0.72	-0.94	2.32	0.96	9	.362
	Pair 2	Diet+Supp - RDA	0.69	2.27	0.72	-0.94	2.32	0.96	9	.362

B6

Paired Samples Test

			Paired Differences							
					SE Mea	95% Confidence Interval of the Difference				
Group			Mean	SD	n	Lower	Upper	t	df	p
MO	Pair 1	B6 - RDA	0.63	0.45	0.16	0.25	1.00	3.93	7	.006
	Pair 2	Diet+Supp – RDA	10.13	0.45	0.16	9.75	10.50	63.70	7	.000
OM	Pair 1	B6 - RDA	0.43	0.57	0.19	-0.002	0.87	2.30	8	.051
	Pair 2	Diet+Supp – RDA	0.43	0.57	0.19	-0.002	0.87	2.30	8	.051
Placebo	Pair 1	B6 - RDA	0.54	0.63	0.20	0.09	0.99	2.74	9	.023
	Pair 2	Diet+Supp - RDA	0.54	0.63	0.20	0.09	0.99	2.74	9	.023

Biotin

Paired Samples Test

			Paired Differences							
					SE	95% Confidence Interval of the Difference				
Group			Mean	SD	Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Biotin - RDA	6.24	11.67	4.12	-3.52	15.99	1.51	7	.174
	Pair 2	Diet+Supp – RDA	456.24	11.67	4.12	446.48	465.99	110.60	7	<.001
OM	Pair 1	Biotin1 - RDA	11.77	10.62	3.54	3.60	19.93	3.32	8	.010
	Pair 2	Diet+Supp – RDA	11.77	10.62	3.54	3.60	19.93	3.32	8	.010
Placebo	Pair 1	Biotin - RDA	4.21	17.61	5.57	-8.39	16.81	.76	9	.469
	Pair 2	Diet+Supp - RDA	4.21	17.61	5.57	-8.39	16.81	.76	9	.469

Folate

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	t	df	p
MO	Pair 1	Folates - RDA	-153.75	91.25	32.26	-230.03	-77.47	-4.77	7	.002
	Pair 2	Diet+Supp – RDA	246.25	91.22	32.26	169.97	322.53	7.63	7	<.001
OM	Pair 1	Folates - RDA	-160.44	61.91	20.64	-208.03	-112.86	-7.78	8	<.001
	Pair 2	Diet+Supp – RDA	-160.44	61.91	20.64	-208.03	-112.86	-7.78	8	<.001
Placebo	Pair 1	Folates - RDA	-160.10	98.32	31.09	-230.43	-89.77	-5.15	9	.001
	Pair 2	Diet+Supp - RDA	-160.10	98.32	31.09	-230.43	-89.77	-5.15	9	.001

B12

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	t	df	p
MO	Pair 1	B12 - RDA	2.94	1.76	0.62	1.47	4.41	4.72	7	.002
	Pair 2	Diet+Supp - RDA	122.94	1.76	0.62	121.47	124.41	197.50	7	<.001
OM	Pair 1	B12 - RDA	2.66	2.08	0.69	1.06	4.25	3.83	8	.005
	Pair 2	Diet+Supp – RDA	2.66	2.08	0.69	1.06	4.25	3.83	8	.005
Placebo	Pair 1	B12 - RDA	2.68	1.84	0.58	1.37	3.99	4.61	9	.001
	Pair 2	Diet+Supp - RDA	2.68	1.84	0.58	1.37	3.99	4.61	9	.001

Calcium

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	t	df	p
MO	Pair 1	Calcium – RDA	-54.50	239.80	84.78	-254.98	145.98	-0.64	7	.541
	Pair 2	Diet+Supp – RDA	105.50	239.80	84.78	-94.98	305.98	1.24	7	.253
OM	Pair 1	Calcium – RDA	-209.56	292.75	97.58	-434.58	15.47	-2.15	8	.064
	Pair 2	Diet+Supp – RDA	-209.56	292.75	97.58	-434.58	15.47	-2.15	8	.064
Placebo	Pair 1	Calcium – RDA	-156.60	250.22	79.13	-335.60	22.40	-1.98	9	.079
	Pair 2	Diet+Supp - RDA	-156.60	250.22	79.13	-335.60	22.40	-1.98	9	.079

Iodine

Paired Samples Test[a]

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	SD	SE Mean	Lower	Upper	t	df	p
MO	Iodine – RDA	-9.25	45.99	16.26	-47.70	29.20	-0.57	7	.587
OM	Iodine – RDA	-7.78	43.32	14.44	-41.08	25.52	-0.54	8	.605
Placebo	Iodine - RDA	-19.44	42.00	13.28	-49.49	10.61	-1.46	9	.177

Iron

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	t	df	p
MO	Pair 1	Iron - RDA	0.50	3.65	1.29	-2.55	3.55	0.39	7	.710
	Pair 2	Diet+Supp – RDA	4.70	3.65	1.29	1.65	7.75	3.64	7	.008
OM	Pair 1	Iron - RDA	-4.41	6.43	2.14	-9.35	0.53	-2.06	8	.074
	Pair 2	Diet+Supp – RDA	-4.41	6.43	2.14	-9.35	0.53	-2.06	8	.074
Placebo	Pair 1	Iron - RDA	0.70	6.20	1.96	-3.73	5.13	0.36	9	.729
	Pair 2	Diet+Supp - RDA	0.70	6.20	1.96	-3.73	5.13	0.36	9	.729

Magnesium

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	t	df	p
MO	Pair 1	Magnesium – RDA	-186.80	115.50	40.84	-283.36	-90.23	-4.57	7	.003
	Pair 2	Diet+Supp – RDA	-129.80	115.50	40.84	-226.36	-33.23	-3.18	7	.016
OM	Pair 1	Magnesium – RDA	-96.11	56.91	18.97	-139.86	-52.37	-5.0	8	.001
	Pair 2	Diet+Supp – RDA	-96.11	56.91	18.97	-139.86	-52.37	-5.07	8	.001
Placebo	Pair 1	Magnesium – RDA	-138.50	127.54	40.33	-229.74	-47.26	-3.43	9	.007
	Pair 2	Diet+Supp - RDA	-138.50	127.54	40.33	-229.74	-47.26	-3.43	9	.007

Selenium

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	t	df	p
MO	Pair 1	Selenium – RDA	-3.91	14.64	5.18	-16.15	8.32	-0.76	7	.474
	Pair 2	Diet+Supp – RDA	96.09	14.64	5.18	83.85	108.32	18.57	7	<.000
OM	Pair 1	Selenium – RDA	-6.32	13.73	4.58	-16.88	4.23	-1.38	8	.205
	Pair 2	Diet+Supp – RDA	-6.32	13.73	4.58	-16.88	4.23	-1.38	8	.205
Placebo	Pair 1	Selenium – RDA	-13.71	16.78	5.31	-25.71	-1.71	-2.58	9	.030
	Pair 2	Diet+Supp - RDA	-13.71	16.78	5.31	-25.71	-1.71	-2.58	9	.030

Zinc

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	t	df	p
MO	Pair 1	Zinc - RDA	-1.05	2.17	0.77	-2.87	0.77	-1.37	7	.214
	Pair 2	Diet+Supp – RDA	8.95	2.17	0.77	7.13	10.77	11.64	7	<.001
OM	Pair 1	Zinc - RDA	-1.79	1.59	0.53	-3.01	-0.57	-3.38	8	.010
	Pair 2	Diet+Supp – RDA	-1.79	1.59	0.53	-3.01	-0.57	-3.38	8	.010
Placebo	Pair 1	Zinc - RDA	-1.56	3.32	1.05	-3.93	0.81	-1.49	9	.171
	Pair 2	Diet+Supp - RDA	-1.56	3.32	1.05	-3.93	0.81	-1.49	9	.171

Omega-3

Paired Samples Test

Group			Paired Differences					t	df	p
			Mean	SD	SE Mean	95% Confidence Interval of the Difference Lower	Upper			
MO	Pair 1	Omega3 – RDA	-0.48	0.66	0.23	-1.03	0.07	-2.07	7	.078
	Pair 2	Diet+Supp – RDA	-0.48	0.66	0.23	-1.03	0.07	-2.07	7	.078
OM	Pair 1	Omega3 – RDA	-0.22	0.75	0.25	-0.79	0.36	-0.86	8	.413
	Pair 2	Diet+Supp – RDA	899.78	0.75	0.25	899.21	900.36	3608.28	8	<.001
Placebo	Pair 1	Omega3 – RDA	-0.21	1.31	0.41	-1.15	0.72	-0.52	9	.617
	Pair 2	Diet+Supp - RDA	-0.21	1.31	0.41	-1.15	0.72	-0.52	9	.617

E.5 MANOVAs of micronutrients from diet plus supplements intervention period 1

B vitamins

Box's Test

Box's M	71.57
F	.93
df1	36
df2	945.54
p.	.594

Effect		Value	F	Hyp. df	Error df	p.	η_p^2
Group	Pillai's Trace	1.11	2.83	16.00	36.00	.005	.56
	Wilks' Lambda	.00	125.77	16.00	34.00	<.001	.98
	Hotelling's Trace	3210.12	3210.12	16.00	32.00	<.001	1.00
	Roy's Largest Root	3210.00	7222.49	8.00	18.00	<.001	1.00

Follow up between-subject ANOVAs

Levene's Test

	F	df1	df2	p.
B1	1.80	2	24	.188
B2	5.26	2	24	.013
B3	1.66	2	24	.211
B5	5.00	2	24	.015
B6	0.58	2	24	.566
B7	1.70	2	24	.205
B9	1.46	2	24	.252
B12	0.28	2	24	.760

Source	DV	Type III Sum of Squares	df	Mean Square	F	p.	η_p^2
Overall Group	B1	3532.84	2,24	1766.42	6812.77	<.001	1.00
	B2	2776.41	2,24	1388.20	67.26	<.001	0.85
	B3	3516.11	2,24	1758.05	16.11	<.001	0.57
	B5	3560.05	2,24	1780.03	571.68	<.001	0.98
	B6	522.67	2,24	261.34	836.67	<.001	0.99
	B7	1132420.72	2,24	566210.36	2925.01	<.001	1.00
	B9	930313.45	2,24	465156.73	63.45	<.001	0.84
	B12	81430.63	2,24	40715.32	11278.88	<.001	1.00

Fat soluble vitamins and vitamin C

Box's Test

Box's M	34.33
F	.78
df1	30
df2	1689.65
p.	.796

Effect		Value	*F*	Hypo. df	Error df	*p.*	η_p^2
Group	Pillai's Trace	1.02	4.36	10.00	42.00	<.001	.51
	Wilks' Lambda	.05	13.42	10.00	40.00	<.001	.77
	Hotelling's Trace	16.61	31.56	10.00	38.00	<.001	.89
	Roy's Largest Root	16.53	69.42	5.00	21.00	<.001	.94

Levene's Test

	F	df1	df2	*p.*
A	1.60	2	24	.222
C	1.35	2	24	.280
D	.29	2	24	.754
E	.17	2	24	.844
K	1.07	2	24	.359

Tests of Between-Subjects Effects

Source	DV	Type III Sum of Squares	df	Mean Square	*F*	*p.*	η_p^2
Group	A	3189951.04	2,24	1594975.52	12.06	<.001	0.50
	C	141059.03	2,24	70529.51	33.51	<.001	0.74
	D	555.92	2,24	277.96	108.74	<.001	0.90
	E	1675.42	2,24	837.71	75.13	<.001	0.86
	K	16134.15	2,24	8067.07	2.75	.084	0.19

Minerals and Omega-3

Box's Test

Box's M	78.51
F	1.15
df1	42
df2	1585.24
p.	.235

Effect		Value	F	Hyp. df	Error df	p.	η_p^2
Group	Pillai's Trace	1.41	8.04	12.00	40.00	<.001	0.71
	Wilks' Lambda	.02	21.40	12.00	38.00	<.001	0.87
	Hotelling's Trace	33.27	49.91	12.00	36.00	<.001	0.94
	Roy's Largest Root	32.47	108.25	6.00	20.00	<.001	0.97

Levene's Test

	F	df1	df2	p.
Calcium	0.06	2	24	.940
Iron	2.51	2	24	.103
Mg	1.05	2	24	.367
Se	0.10	2	24	.910
Zn	4.12	2	24	.029
Omega-3	1.47	2	24	.250

Between subjects ANOVAs

Source	DV	Type III Sum of Squares	df	Mean Square	F	p.	η_p^2
Group	Calcium	477585.90	2,24	238792.95	3.47	.047	.22
	Iron	100.94	2,24	50.47	5.17	.014	.30
	Mg	1167.21	2,24	583.60	.07	.937	.01
	Se	63869.24	2,24	31934.62	138.29	.000	.92
	Zn	733.01	2,24	366.50	67.55	.000	.85
	Omega-3	4.73	2,24	2.37	2.71	.087	.18

E.6 T-tests looking at difference between groups (Diet plus Supplement)

Omega-3

	Overall Group	N	Mean	SD	SE Mean
Omega-3 Diet Plus	OM	9	901.11	0.7	0.24
Supp	MO	8	0.99	0.69	0.24

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	*p*	*t*	df	*p*	Mean Diff	SE Diff	Lower	Upper
Omega-3 Diet Plus Supp	Equal variances assumed	0.28	.606	2646.32	15	<.001	900.11	.34	899.39	900.84
	Equal variances not assumed			2652.93	14.89	<.001	900.11	.34	899.39	900.84

Group Statistics

	Group	N	Mean	SD	SE Mean
Omega-3 Diet Plus Supp	OM	9	901.11	0.71	0.24
	Placebo	10	1.29	1.23	0.39

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	*p*	*t*	df	*p*	Mean Diff	SE Diff	Lower	Upper
Omega-3 Diet Plus Supp	Equal variances assumed	1.40	.253	1922.21	17	<.001	899.82	0.47	898.83	900.81
	Equal variances not assumed			1976.04	14.68	<.001	899.82	0.46	898.85	900.79

Group Statistics

	Overall_Group	N	Mean	SD	SE Mean
Omega-3 Diet Plus Supp	MO	8	0.99	0.69	0.24
	Placebo	10	1.29	1.23	0.39

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	*p*	*t*	df	*p*	Mean Diff.	SE Diff	Lower	Upper
Omega-3 Diet Pus Supp	Equal variances assumed	1.88	.190	-0.60	16	.555	-0.29	0.49	-1.33	0.74
	Equal variances not assumed			-0.64	14.53	.531	-0.29	0.46	-1.27	0.68

E.7 T-tests – Difference to RDA intervention period 2

Vitamin A

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
OM	Pair 1	Vitamin A - RDA	-145.13	411.58	145.52	-489.22	198.97	-1.00	7	.352
	Pair 2	Supp.+Diet - RDA	654.88	411.58	145.52	310.78	998.97	4.50	7	.003
MO	Pair 1	Vitamin A - RDA	-293.00	181.30	64.10	-444.57	-141.43	-4.57	7	.003
Placebo	Pair 2	Supp.+Diet2 - RDA	-293.00	181.30	64.10	-444.57	-141.43	-4.57	7	.003

	Pair 1	VitaminA2 - RDA	-141.00	431.58	136.48	-449.74	167.74	-1.03	9	.329
	Pair 2	Supp.+Diet2 - RDA	-141.00	431.58	136.48	-449.74	167.74	-1.03	9	.329

Vitamin C

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Vitamin C – RDA	-24.53	62.32	22.03	-76.63	27.58	-1.11	7	.302
	Pair 2	Diet+Supp – RDA	-24.53	62.32	22.03	-76.63	27.58	-1.11	7	.302
OM	Pair 1	VitaminC – RDA	-7.54	46.40	16.41	-46.33	31.26	-0.46	7	.660
	Pair 2	Diet+Supp. – RDA	157.76	46.40	16.41	118.97	196.56	9.62	7	<.001
Placebo	Pair 1	Vitamin C – RDA	1.39	79.55	25.15	-55.51	58.29	0.06	9	.957
	Pair 2	Diet+Supp. - RDA	1.39	79.55	25.15	-55.51	58.29	0.06	9	.957

Vitamin D

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Vitamin D – RDA	-13.05	1.14	0.40	-14.01	-12.09	-32.23	7	<.001
	Pair 2	Diet+Supp – RDA	-13.05	1.14	0.40	-14.01	-12.09	-32.23	7	<.001
OM	Pair 1	Vitamin D – RDA	-12.86	0.53	0.19	-13.31	-12.42	-68.08	7	<.001
	Pair 2	Diet+Supp – RDA	-2.86	0.53	0.19	-3.31	-2.42	-15.15	7	<.001

Placebo	Pair 1	Vitamin D – RDA	-13.08	0.71	0.23	-13.59	-12.57	-57.88	9	<.001
	Pair 2	Diet+Supp - RDA	-13.08	0.71	0.23	-13.59	-12.57	-57.88	9	<.001

Vitamin K

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Vitamin K – RDA	-82.28	43.02	15.21	-118.24	-46.31	-5.41	7	.001
	Pair 2	Diet+Supp – RDA	-82.28	43.02	15.21	-118.24	-46.31	-5.41	7	.001
OM	Pair 1	Vitamin K – RDA	-71.49	23.42	8.28	-91.07	-51.91	-8.63	7	<.001
	Pair 2	Diet+Supp – RDA	8.51	23.42	8.28	-11.07	28.09	1.03	7	.338
Placebo	Pair 1	Vitamin K – RDA	-56.34	91.24	28.85	-121.61	8.93	-1.95	9	.083
	Pair 2	Diet+Supp - RDA	-56.34	91.24	28.85	-121.61	8.93	-1.95	9	.083

Thiamin

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Thiamin – RDA	0.03	0.28	0.10	-0.21	0.27	0.31	7	.765
	Pair 2	Diet+Supp – RDA	0.03	0.28	0.10	-0.21	0.27	0.31	7	.765
OM	Pair 1	Thiamin – RDA	0.16	0.26	0.09	-0.06	0.38	1.69	7	.135

	Pair 2	Diet+Supp – RDA	25.16	0.26	0.09	24.94	25.38	269.90	7	<.001
Placebo	Pair 1	Thiamin – RDA	0.28	0.61	0.19	-0.16	0.72	1.46	9	.178
	Pair 2	Diet+Supp - RDA	0.28	0.61	0.19	-0.16	0.72	1.46	9	.118

Riboflavin

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Riboflavin – RDA	0.49	0.43	0.15	0.13	0.85	3.21	7	.015
	Pair 2	Diet+Supp – RDA	0.49	0.43	0.15	0.13	0.85	3.21	7	.015
OM	Pair 1	Riboflavin – RDA	0.39	0.36	0.13	0.09	0.69	3.08	7	.018
	Pair 2	Diet+Supp – RDA	25.39	0.36	0.13	25.09	25.69	201.52	7	<.001
Placebo	Pair 1	Riboflavin – RDA	0.62	0.68	0.22	0.13	1.11	2.86	9	.019
	Pair 2	Diet+Supp - RDA	0.62	0.68	0.22	0.13	1.11	2.86	9	.019

Niacin

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Niacin - RDA	16.81	9.38	3.32	8.97	24.65	5.07	7	.001
	Pair 2	Diet+Supp – RDA	16.81	9.38	3.32	8.97	24.65	5.07	7	.001

OM	Pair 1	Niacin - RDA	18.03	6.05	2.14	12.97	23.08	8.43	7	<.001
	Pair 2	Diet+Supp - RDA	38.03	6.05	2.14	32.97	43.08	17.79	7	<.001
Placebo	Pair 1	Niacin - RDA	16.85	8.56	2.71	10.73	22.97	6.22	9	<.001
	Pair 1	Diet+Supp - RDA	16.85	8.56	2.71	10.73	22.97	6.22	9	<.001

Pantothenic Acid

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Pantothenic Acid - RDA	-0.30	0.90	0.32	-1.05	0.45	-0.94	7	.378
	Pair 2	Diet+Supp – RDA	-0.30	0.90	0.32	-1.05	0.45	-0.94	7	.378
OM	Pair 1	Pantothenic Acid - RDA	-0.15	1.12	0.40	-1.08	0.78	-0.38	7	.715
	Pair 2	Diet+Supp – RDA	24.85	1.12	0.40	23.92	25.78	62.90	7	<.001
Placebo	Pair 1	Pantothenic Acid - RDA	0.62	2.20	0.70	-0.95	2.19	0.89	9	.396
	Pair 2	Diet+Supp - RDA	0.62	2.20	0.70	-0.95	2.19	0.89	9	.396

B6

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	B6 - RDA	0.34	0.33	0.11	0.07	0.61	2.94	7	.022

	Pair 2	Diet+Supp – RDA	0.34	0.33	0.11	0.07	0.61	2.94	7	.022
OM	Pair 1	B6 - RDA	0.13	0.47	0.17	-0.26	0.53	0.79	7	.454
	Pair 2	Diet+Supp – RDA	9.63	0.47	0.17	9.24	10.03	57.59	7	<.001
Placebo	Pair 1	B6 - RDA	0.29	0.65	0.21	-0.18	0.75	1.41	9	.193
	Pair 2	Diet+Supp - RDA	0.29	0.65	0.21	-0.18	0.75	1.41	9	.193

Biotin

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Biotin - RDA	1.00	12.56	4.44	-9.50	11.50	0.23	7	.828
	Pair 2	Diet+Supp – RDA	1.00	12.56	4.44	-9.50	11.50	1.51	7	.828
OM	Pair 1	Biotin - RDA	8.09	13.19	4.66	-2.94	19.11	1.73	7	.126
	Pair 2	Diet+Supp – RDA	458.09	13.19	4.66	447.06	469.11	118.73	7	<.001
Placebo	Pair 1	Biotin - RDA	3.60	18.06	5.71	-9.32	16.52	0.63	9	.544
	Pair 2	Diet+Supp - RDA	3.60	18.06	5.71	-9.32	16.52	0.76	9	.544

Folate

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Folates - RDA	-214.13	39.42	13.94	-247.08	-181.17	-15.36	7	<.001
	Pair 2	Diet+Supp – RDA	-214.13	39.42	13.94	-247.08	-181.17	-15.36	7	<.001
OM	Pair 1	Folates - RDA	-154.63	111.55	39.44	-247.88	-61.37	-3.92	7	.006
	Pair 2	Diet+Supp – RDA	245.38	111.55	39.44	152.12	338.63	6.22	7	<.001
Placebo	Pair 1	Folates - RDA	-172.80	111.46	35.25	-252.53	-93.07	-4.90	9	.001
	Pair 2	Diet+Supp - RDA	-172.80	111.46	35.25	-252.53	-93.07	-4.90	9	.001

B12

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	B12 - RDA	2.63	2.09	0.74	0.88	4.37	3.56	7	.009
	Pair 2	Diet+Supp - RDA	2.63	2.09	0.74	0.88	4.37	3.56	7	.009
OM	Pair 1	B12 - RDA	1.71	1.31	0.46	0.62	2.81	3.70	7	.008
	Pair 2	Diet+Supp - RDA	121.71	1.31	0.46	120.62	122.81	262.62	7	<.001
Placebo	Pair 1	B12 - RDA	1.76	1.77	0.56	0.49	3.03	3.14	9	.012

	Pair 2	Diet+Supp - RDA	1.76	1.77	0.56	0.49	3.03	3.14	9	.012

Calcium

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Calcium – RDA	-245.63	281.22	99.43	-480.73	-10.52	-2.47	7	.043
	Pair 2	Diet+Supp – RDA	-245.63	281.22	99.43	-480.73	-10.52	-2.47	7	.043
OM	Pair 1	Calcium – RDA	-266.63	161.60	57.13	-401.72	-131.53	-4.67	7	.002
	Pair 2	Diet+Supp – RDA	-106.63	161.60	57.13	-241.72	28.47	-1.87	7	.104
Placebo	Pair 1	Calcium – RDA	-172.60	321.63	101.71	-402.68	57.48	-1.70	9	.124
	Pair 2	Diet+Supp - RDA	-172.60	321.63	101.71	-402.68	57.48	-1.70	9	.124

Iodine

Paired Samples Test[a]

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Iodine – RDA	-46.59	56.47	19.97	-93.80	0.62	-2.33	7	.052
OM	Iodine – RDA	-37.75	66.70	23.58	-93.51	18.01	-1.60	7	.153
Placebo	Iodine - RDA	-45.02	50.09	15.84	-80.85	-9.19	-2.84	9	.019

Iron

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Iron - RDA	0.06	4.23	1.50	-3.48	3.60	0.04	7	.968
	Pair 2	Diet+Supp – RDA	0.06	4.23	1.50	-3.48	3.60	0.04	7	.968
OM	Pair 1	Iron - RDA	-3.49	7.00	2.47	-9.34	2.36	-1.41	7	.201
	Pair 2	Diet+Supp – RDA	0.71	7.00	2.47	-5.14	6.56	0.29	7	.782
Placebo	Pair 1	Iron - RDA	-0.02	6.40	2.02	-4.60	4.56	-0.01	9	.992
	Pair 2	Diet+Supp - RDA	-0.02	6.40	2.02	-4.60	4.56	-0.01	9	.992

Magnesium

Paired Samples Test

			Paired Differences							
						95% Confidence Interval of the Difference				
Group			Mean	SD	SE Mean	Lower	Upper	*t*	*df*	*p*
MO	Pair 1	Magnesium – RDA	-176.88	66.04	23.35	-232.09	-121.66	-7.58	7	<.001
	Pair 2	Diet+Supp – RDA	-176.88	66.04	23.35	-232.09	-121.66	-7.58	7	<.001
OM	Pair 1	Magnesium – RDA	-110.00	61.93	21.89	-161.77	-58.23	-5.02	7	.002
	Pair 2	Diet+Supp – RDA	-53.00	61.93	21.89	-104.77	-1.23	-2.42	7	.046
Placebo	Pair 1	Magnesium – RDA	-131.00	137.24	43.40	-229.17	-32.83	-3.02	9	.015
	Pair 2	Diet+Supp - RDA	-131.00	137.24	43.40	-229.17	-32.83	-3.02	9	.015

Selenium

Paired Samples Test

Group			Paired Differences					*t*	*df*	*p*
						95% Confidence Interval of the Difference				
			Mean	SD	SE Mean	Lower	Upper			
MO	Pair 1	Selenium - RDA	-12.00	14.96	5.29	-24.50	0.50	-2.27	7	.058
	Pair 2	DietSupp - RDA	-12.00	14.96	5.29	-24.50	0.50	-2.27	7	.058
OM	Pair 1	Selenium - RDA	-9.40	13.04	4.61	-20.30	1.50	-2.04	7	.081
	Pair 2	Diet+Supp - RDA	90.60	13.04	4.61	79.70	101.50	19.66	7	<.001
Placebo	Pair 1	Selenium - RDA	-21.42	10.46	3.31	-28.90	-13.94	-6.48	9	<.001
	Pair 2	Diet+Supp - RDA	-21.42	10.46	3.31	-28.90	-13.94	-6.48	9	<.001

Zinc

Paired Samples Test

Group			Paired Differences					*t*	*df*	*p*
						95% Confidence Interval of the Difference				
			Mean	SD	SE Mean	Lower	Upper			
MO	Pair 1	Zinc - RDA	-1.66	3.02	1.07	-4.18	0.86	-1.56	7	.163
	Pair 2	Diet+Supp – RDA	-1.66	3.02	1.07	-4.18	0.86	-1.56	7	.163
OM	Pair 1	Zinc - RDA	-1.91	1.43	0.51	-3.11	-0.71	-3.77	7	.007
	Pair 2	Diet+Supp – RDA	8.09	1.43	0.51	6.89	9.29	15.96	7	<.001
Placebo	Pair 1	Zinc - RDA	-2.22	3.29	1.04	-4.57	0.13	-2.14	9	.061
	Pair 2	Diet+Supp - RDA	-2.22	3.29	1.04	-4.57	0.13	-2.14	9	.061

Post-hoc t-test: Omega-3

Paired Samples Test

Group			Paired Differences					*t*	*df*	*p*
			Mean	SD	SE Mean	95% Confidence Interval of the Difference Lower	Upper			
MO	Pair 1	Omega3 – RDA	-0.74	0.36	0.13	-1.04	-0.43	-5.74	7	.001
	Pair 2	Diet+Supp – RDA	-0.74	0.36	0.13	-1.04	-0.43	-5.74	7	.001
OM	Pair 1	Omega3 – RDA	-0.63	0.48	0.17	-1.02	-0.23	-3.70	7	.008
	Pair 2	DietSupp – RDA	899.38	0.48	0.17	898.98	899.77	5326.44	7	<.001
Placebo	Pair 1	Omega3 – RDA	-0.57	1.12	0.35	-1.36	0.23	-1.60	9	.144
	Pair 2	DietSupp - RDA	-0.57	1.12	0.35	-1.36	0.23	-1.60	9	.144

E.8 MANOVAs of micronutrients from diet plus supplements intervention period 2

B vitamins

Multivariate Tests

Effect		Value	*F*	Hyp. df	Error df	*p.*	η_p^2
Group	Pillai's Trace	1.34	4.32	16	34	<.001	0.67
	Wilks' Lambda	<.001	127.20	16	32	<.001	0.99
	Hotelling's Trace	2752.03	2580.03	16	30	<.001	1.00
	Roy's Largest Root	2751.51	5846.97	8	1	<.001	1.00

Levene's Test

	F	df1	df2	*p*
B1 Diet Plus Supp	5.49	2	23	.011
B2 Diet Plus Supp	2.67	2	23	.091
B3 Diet Plus Supp	0.72	2	23	.496
B5 Diet Plus Supp	0.57	2	23	.572
B6 Diet Plus Supp	3.55	2	23	.045
B7 Diet Plus Supp	1.55	2	23	.234
B9 Diet Plus Supp	2.87	2	23	.077
B12 Diet Plus Supp	0.76	2	23	.477

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	*F*	*p*	η_p^2
Group	B1 Diet + Supp	3448.82	2	1724.41	8653.93	<.001	1.00
	B2 Diet + Supp	3413.40	2	1706.70	6121.27	<.001	1.00
	B3 Diet + Supp	2487.26	2	1243.63	18.68	<.001	0.62
	B5 Diet + Supp	35.11	2	17.56	0.12	.888	0.01
	B6 Diet + Supp	481.30	2	240.65	907.63	<.001	0.99
	B7 Diet + Supp	1150408.40	2	575204.20	2884.21	<.001	1.00
	B9 Diet + Supp	1063047.04	2	531523.52	58.27	<.001	0.84
	B12 Diet + Supp	79184.05	2	39592.03	12871.32	<.001	1.00

Fat-soluble vitamins and vitamin C

Box's Test

Box's M	60.22
F	1.34
df1	30
df2	1525.00
p.	.106

Multivariate Tests

Effect		Value	*F*	Hyp. df	Error df	*p*	η_p^2
Group	Pillai's Trace	1.06	4.55	10	40	<.001	.532
	Wilks' Lambda	0.02	23.13	10	38	<.001	.859
	Hotelling's Trace	45.01	81.02	10	36	<.001	.957
	Roy's Largest Root	44.92	179.67	5	20	<.001	.978

Levene's Test

	F	df1	df2	*p*
A Supp + Diet	1.86	2	23	.178
C_Diet + Supp	0.50	2	23	.613
D_Diet + Supp	4.77	2	23	.018
E_Supp + Diet	1.53	2	23	.238
K_Diet + Supp	1.74	2	23	.199

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	*F*	*p.*	η_p^2
Group	A Sup + Diet	3599414.24	2	1799707.12	14.02	<.001	0.55
	C Diet + Supp	149684.65	2	74842.33	19.60	<.001	0.63
	D Diet + Supp	576.63	2	288.32	420.45	<.001	0.97
	E Supp + Diet	2174.36	2	1087.18	150.92	<.001	0.93
	K Diet + Supp	26896.78	2	13448.39	3.50	.05	0.23

Mineral and Omega-3

Box's Test

Box's M	98.06
F	1.39
df1	42
df2	1431.11
p	.050

Multivariate Tests[a]

Effect		Value	*F*	Hypo. df	Error df	*p*	η_p^2
Group	Pillai's Trace	1.95	123.22	12	38	<.001	0.98
	Wilks' Lambda	<.001	12758.63	12	36	<.001	1.00
	Hotelling's Trace	906812.92	1284651.64	12	34	<.001	1.00
	Roy's Largest Root	906793.97	2871514.23	6	19	<.001	1.00

Levene's Test

	F	df1	df2	*p.*
Calcium Diet + Supp	1.46	2	23	.253
Iron Diet + Supp	1.97	2	23	.163
Mg Diet + Supp	1.70	2	23	.206
Se Diet + Supp	0.57	2	23	.575
Zn Diet + Supp	3.01	2	23	.069
Omega-3 Diet + Supp	1.34	2	23	.281

Tests of Between-Subjects Effects

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	*F*	*p.*	η_p^2
Group	Calcium Diet + Supp	77360.47	2	38680.23	.53	.594	0.04
	Iron Diet + Supp	91.89	2	45.95	3.99	.033	0.26
	Mg Diet + Supp	29985.09	2	14992.54	1.68	.209	0.13
	Se Diet + Supp	64795.77	2	32397.88	199.28	<.001	0.95
	Zn Diet + Supp	457.31	2	228.66	29.33	<.001	0.72
	Omega3 Diet + Supp	4485140.56	2	2242570.28	4660349.44	<.001	1.00

E.9 Post-hoc t-tests

Group Statistics

	Group	N	Mean	SD	SE Mean
B1 Diet+ Supp	OM	8	26.31	0.30	0.11
	MO	8	1.22	0.30	0.11
B2 Diet + Supp	OM	8	26.49	0.36	0.13
	MO	8	1.59	0.43	0.15
B3 Diet + Supp	OM	8	54.03	6.05	2.14
	MO	8	32.81	9.38	3.32
B5 Diet + Supp	OM	8	29.85	1.12	0.40
	MO	8	4.70	0.90	0.32
B6 Diet + Supp	OM	8	10.93	0.47	0.17
	MO	8	1.64	0.32	0.11
B7 Diet + Supp	OM	8	490.86	10.98	3.88
	MO	8	36.24	11.67	4.12
B9 Diet + Supp	OM	8	645.38	111.55	39.44
	MO	8	185.88	39.42	13.94
B12 Diet+ Supp	OM	8	124.11	1.31	0.46
	MO	8	5.03	2.09	0.74
Calcium Diet+ Supp	OM	8	893.38	161.60	57.13

	MO	8	754.38	281.22	99.43
Iron Diet + Supp	OM	8	13.71	2.20	0.78
	MO	8	9.31	2.50	0.88
Mg Diet + Supp	OM	8	317.00	89.80	31.75
	MO	8	230.63	61.30	21.67
Se Diet + Supp	OM	8	145.60	13.04	4.61
	MO	8	43.00	14.96	5.29
Zn Diet + Supp	OM	8	17.59	1.77	0.63
	MO	8	8.96	3.24	1.15
Omega-3 Diet + Supp	OM	8	0.73	0.33	0.12
	MO	8	1.64	0.46	0.16

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	*p*	*t*	df	*p*	Mean Diff	SE Diff	Lower	Upper
B1 Diet + Supp	Equal variances assumed	<0.01	.954	167.24	14	<.001	25.09	0.15	24.77	25.41
	Equal variances not assumed			167.24	14.00	<.001	25.09	0.15	24.77	25.41
B2 Diet + Supp	Equal variances assumed	0.05	.823	125.70	14	<.001	24.90	0.20	24.47	25.32
	Equal variances not assumed			125.70	13.51	<.001	24.90	0.20	24.47	25.32
B3 Diet + Supp	Equal variances assumed	1.81	.200	5.38	14	<.001	21.21	3.94	12.75	29.67
	Equal variances not assumed			5.38	11.96	<.001	21.21	3.94	12.61	29.81

B5 Diet + Supp	Equal variances assumed	0.83	.378	49.56	14	<.001	25.15	0.51	24.06	26.24
	Equal variances not assumed			49.56	13.40	<.001	25.15	0.51	24.06	26.24
B6 Diet + Supp	Equal variances assumed	2.16	.163	45.812	14	<.001	9.30	0.20	8.86	9.74
	Equal variances not assumed			45.81	12.40	<.001	9.30	0.20	8.86	9.74
B7 Diet + Supp	Equal variances assumed	0.02	.900	80.263	14	<.001	454.63	5.66	442.48	466.7
	Equal variances not assumed			80.263	13.94	<.001	454.63	5.66	442.48	466.78
B9 Diet + Supp	Equal variances assumed	1.57	.231	10.985	14	<.001	459.50	41.83	369.79	549.21
	Equal variances not assumed			10.985	8.72	<.001	459.50	41.83	364.41	554.59
B12 Diet + Supp	Equal variances assumed	1.15	.302	136.693	14	<.001	119.09	0.87	117.22	120.96
	Equal variances not assumed			136.693	11.78	<.001	119.09	0.87	117.19	120.99
Calcium Diet + Supp	Equal variances assumed	1.74	.209	1.212	14	.246	139.00	114.67	-106.95	384.95
	Equal variances not assumed			1.212	11.17	.250	139.0	114.67	-112.93	390.93
Iron Diet + Supp	Equal variances assumed	<.001	1.000	3.742	14	.002	4.40	1.18	1.88	6.93

	Equal variances not assumed			3.742	13.77	.002	4.40	1.18	1.87	6.93
Mg Diet + Supp	Equal variances assumed	1.32	.270	2.247	14	.041	86.38	38.44	3.93	168.82
	Equal variances not assumed			2.247	12.36	.044	86.38	38.44	2.89	169.86
Se Diet + Supp	Equal variances assumed	0.47	.505	14.627	14	<.001	102.60	7.01	87.56	117.64
	Equal variances not assumed			14.627	13.74	<.001	102.60	7.01	87.53	117.67
Zn Diet + Supp	Equal variances assumed	3.83	.071	6.605	14	<.001	8.63	1.31	5.82	11.43
	Equal variances not assumed			6.605	10.83	<.001	8.63	1.31	5.75	11.50
Omega-3 Diet + Supp	Equal variances assumed	1.67	.217	-4.60	14	<.001	-0.92	0.20	-1.34	-0.49
	Equal variances not assumed			4.60	12.71	<.001	-0.92	0.20	-1.35	-0.48

Group Statistics

	OverallGroup	N	Mean	SD	SE Mean
B1 Diet + Supp	OM	8	26.31	0.30	0.11
	Placebo	10	1.46	0.61	0.19
B2 Diet + Supp	OM	8	26.49	0.36	0.13
	Placebo	10	1.72	0.68	0.22
B3 Diet + Supp	OM	8	54.03	6.05	2.14
	Placebo	10	32.85	8.56	2.71
B5 Diet + Supp	OM	8	29.85	1.12	0.40
	Placebo	10	5.62	2.20	0.70
B6 Diet + Supp	OM	8	10.93	0.47	0.17

	Placebo	10	1.59	0.65	0.21
B7 Diet + Supp	OM	8	490.86	10.98	3.88
	Placebo	10	34.21	17.61	5.57
B9 Diet + Supp	OM	8	645.38	111.55	39.44
	Placebo	10	227.20	111.46	35.25
B12 Diet Plus	OM	8	124.11	1.31	0.46
Supp	Placebo	10	4.16	1.77	0.56
Calcium Diet +	OM	8	893.38	161.60	57.13
Supp	Placebo	10	827.40	321.63	101.71
Iron Diet + Supp	OM	8	13.71	2.20	0.78
	Placebo	10	9.98	4.56	1.44
Mg Diet + Supp	OM	8	317.00	89.80	31.75
	Placebo	10	269.00	116.95	36.98
Se Diet + Supp	OM	8	145.60	13.03	4.61
	Placebo	10	33.58	10.46	3.31
Zn Diet + Supp	OM	8	17.59	1.77	0.63
	Placebo	10	8.18	3.05	0.97
Omega-3 Diet +	OM	8	0.73	0.33	0.12
Supp	Placebo	10	0.94	0.99	0.31

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	*p.*	*t*	df	*p*	Mean Diff	SE Diff	Lower	Upper
B1 Diet + Supp	Equal variances assumed	6.57	.021	105.24	16	<.001	24.84	0.24	24.34	25.34
	Equal variances not assumed			112.98	13.74	<.001	24.84	0.22	24.37	25.32
B2 Diet + Supp	Equal variances assumed	3.73	.071	92.45	16	<.001	24.77	0.27	24.20	25.34

	Equal variances not assumed			98.91	14.06	<.001	24.77	0.25	24.23	25.31
B3 Diet + Supp	Equal variances assumed	0.53	.477	5.90	16	<.001	21.18	3.59	13.57	28.78
	Equal variances not assumed			6.14	15.82	<.001	21.18	3.45	13.86	28.49
B5 Diet + Supp	Equal variances assumed	2.30	.149	28.27	16	<.001	24.23	0.86	22.41	26.05
	Equal variances not assumed			30.30	13.89	<.001	24.23	0.80	22.51	25.95
B6 Diet + Supp	Equal variances assumed	1.56	.230	34.03	16	<.001	9.34	0.27	8.7	9.93
	Equal variances not assumed			35.29	15.91	<.001	9.34	0.26	8.78	9.91
B7 Diet + Supp	Equal variances assumed	2.19	.159	63.88	16	<.001	456.65	7.15	441.50	471.81
	Equal variances not assumed			67.28	15.24	<.001	456.65	6.79	442.21	471.10
B9 Diet + Supp	Equal variances assumed	0.68	.423	7.91	16	<.001	418.18	52.89	306.06	530.29
	Equal variances not assumed			7.91	15.14	<.001	418.18	52.89	305.52	530.83
B12 Diet + Supp	Equal variances assumed	1.70	.210	159.39	16	<.001	119.95	0.75	118.36	121.55
	Equal variances not assumed			164.98	15.94	<.001	119.95	0.73	118.41	121.49

Calcium Diet + Supp	Equal variances assumed	3.06	.099	0.53	16	.605	65.98	125.15	-199.33	331.28
	Equal variances not assumed			0.57	13.81	.581	65.98	116.66	-184.55	316.50
Iron Diet + Supp	Equal variances assumed	2.44	.138	2.12	16	.050	3.73	1.76	-0.01	7.47
	Equal variances not assumed			2.28	13.51	.040	3.73	1.64	0.21	7.26
Mg Diet + Supp	Equal variances assumed	0.57	.462	0.96	16	.354	48.00	50.25	-58.52	154.52
	Equal variances not assumed			0.99	15.99	.339	48.00	48.74	-55.33	151.33
Se Diet + Supp	Equal variances assumed	0.03	.862	20.26	16	<.001	112.02	5.53	100.30	123.74
	Equal variances not assumed			19.75	13.32	<.001	112.02	5.67	99.80	124.24
Zn Diet + Supp	Equal variances assumed	6.05	.026	7.72	16	<.001	9.41	1.22	6.82	11.99
	Equal variances not assumed			8.18	14.79	<.001	9.41	1.15	6.95	11.86
Omega-3 Diet +Supp	Equal variances assumed	1.86	.191	-0.57	16	.576	-0.21	0.37	-0.99	0.57
	Equal variances not assumed			-0.63	11.37	.542	-0.21	0.33	-0.94	0.52

Group Statistics

	Group	N	Mean	SD	SE Mean

B1 Diet + Supp	MO	8	1.22	0.30	0.11
	Placebo	10	1.46	0.61	0.19
B2 Diet + Supp	MO	8	1.59	0.43	0.15
	Placebo	10	1.72	0.68	0.22
B3 Diet + Supp	MO	8	32.81	9.34	3.32
	Placebo	10	32.85	8.56	2.71
B5 Diet + Supp	MO	8	4.70	0.90	0.32
	Placebo	10	5.62	2.20	0.70
B6 Diet + Supp	MO	8	1.64	0.32	0.11
	Placebo	10	1.59	0.65	0.21
B7 Diet + Supp	MO	8	36.24	11.67	4.12
	Placebo	10	34.21	17.61	5.57
B9 Diet + Supp	MO	8	185.88	39.42	13.94
	Placebo	10	227.20	111.46	35.25
B12 Diet + Supp	MO	8	5.03	2.09	0.74
	Placebo	10	4.16	1.77	0.56
Calcium Diet + Supp	MO	8	754.38	281.22	99.43
	Placebo	10	827.40	321.63	101.71
Iron Diet + Supp	MO	8	9.31	2.50	0.88
	Placebo	10	9.98	4.56	1.44
Mg Diet + Supp	MO	8	230.63	61.30	21.67
	Placebo	10	269.00	116.95	36.98
Se Diet + Supp	MO	8	43.00	14.96	5.29
	Placebo	10	33.58	10.456	3.31
Zn Diet + Supp	MO	8	8.96	3.24	1.15
	Placebo	10	8.18	3.05	0.97
Omega-3 Diet + Supp	MO	8	1.64	0.46	0.16
	Placebo	10	0.94	0.99	0.31

Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means						
								95% Confidence Interval of the Difference	
	F	*p.*	*t*	df	*p.*	Mean Diff	SE Diff	Lower	Upper

B1 Diet + Supp	Equal variances assumed	6.82	.019	-1.04	16	.315	-0.24	0.24	-0.74	0.25
	Equal variances not assumed			-1.12	13.63	.284	-0.24	0.22	-0.72	0.23
B2 Diet + Supp	Equal variances assumed	3.12	.096	-0.46	16	.653	-0.13	0.28	-0.72	0.46
	Equal variances not assumed			-0.48	15.32	.637	-0.13	0.26	-0.69	0.44
B3 Diet + Supp	Equal variances assumed	0.25	.626	-0.01	16	.993	-0.04	4.23	-9.01	8.94
	Equal variances not assumed			-0.01	14.45	.993	-0.04	4.28	-9.19	9.12
B5 Diet + Supp	Equal variances assumed	3.80	.069	-1.11	16	.285	-0.92	0.83	-2.68	0.84
	Equal variances not assumed			-1.20	12.47	.251	-0.92	0.76	-2.58	0.74
B6 Diet + Supp	Equal variances assumed	6.45	.022	0.19	16	.850	0.05	0.25	-0.49	0.58
	Equal variances not assumed			0.21	13.78	.840	0.05	0.24	-0.46	0.55
B7 Diet + Supp	Equal variances assumed	1.79	.200	0.28	16	.783	2.03	7.26	-13.35	17.41
	Equal variances not assumed			0.29	15.56	.774	2.03	6.93	-12.70	16.75
B9 Diet + Supp	Equal variances assumed	12.16	.003	-1.00	16	.335	-41.33	41.54	-129.38	46.72

	Equal variances not assumed			-1.09	11.67	.298	-41.33	37.90	-124.17	41.52
B12 Diet + Supp	Equal variances assumed	0.04	.849	0.95	16	.355	0.87	0.91	-1.06	2.79
	Equal variances not assumed			0.93	13.83	.366	0.87	0.93	-1.12	2.85
Calcium Diet + Supp	Equal variances assumed	0.21	.657	-0.51	16	.620	-73.03	144.49	-379.33	233.28
	Equal variances not assumed			-0.51	15.83	.615	-73.03	142.23	-374.80	228.75
Iron Diet + Supp	Equal variances assumed	2.17	.160	-0.37	16	.716	-0.67	1.80	-4.49	3.15
	Equal variances not assumed			-0.40	14.41	.699	-0.67	1.69	-4.29	2.95
Mg Diet + Supp	Equal variances assumed	3.18	.093	-0.84	16	.415	-38.38	45.84	-135.55	58.80
	Equal variances not assumed			-0.90	14.10	.386	-38.38	42.87	-130.25	53.50
Se Diet + Supp	Equal variances assumed	1.34	.264	1.57	16	.135	9.42	5.99	-3.27	22.11
	Equal variances not assumed			1.51	12.10	.157	9.42	6.24	-4.16	23.00
Zn Diet + Supp	Equal variances assumed	<0.01	.968	0.53	16	.606	0.78	1.50	-2.37	3.94
	Equal variances not assumed			0.52	14.70	.609	0.78	1.50	-2.42	3.98

Omega-3 + Plus Supp	Equal variances assumed	0.81	.382	1.85	16	.083	0.71	0.38	-0.10	1.51
	Equal variances not assumed			2.00	13.22	.067	0.71	0.35	-0.06	1.47

E.9 Analyses of Cross-Over Effects

Memory

Box's Test

Box's M	96.32
F	1.16
df1	36
df2	861.40
p.	.240

Multivariate Tests

Effect		Value	*F*	Hy. df	Error df	*p.*	η_p^2
Group	Pillai's Trace	0.59	0.88	16.00	34.00	.591	.294
	Wilks' Lambda	0.47	0.91	16.00	32.00	.569	.312
	Hotelling's Trace	0.98	0.92	16.00	30.00	.556	.329
	Roy's Largest Root	0.83	1.76	8.00	17.00	.157	.452

Trail Making

Box's Test

Box's M	80.27
F	1.87
df1	30
df2	1937.23
p.	.003

Multivariate Tests

Effect		Value	*F*	Hyp. df	Error df	*p.*	η_p^2
Group	Pillai's Trace	0.36	0.96	10.00	44.00	.492	.179
	Wilks' Lambda	0.66	0.96	10.00	42.00	.493	.186
	Hotelling's Trace	0.48	0.95	10.00	40.00	.496	.193
	Roy's Largest Root	0.40	1.76	5.00	22.00	.163	.285

Verbal Fluency

Box's Test

Box's M	15.47
F	1.06
df1	12
df2	2951.75
p.	.391

Multivariate Tests

Effect		Value	F	Hyp. df	Error df	p.	η_p^2
Group	Pillai's Trace	0.19	0.83	6.00	48.00	.549	.09
	Wilks' Lambda	0.82	0.80	6.00	46.00	.574	.10
	Hotelling's Trace	0.21	0.77	6.00	44.00	.600	.10
	Roy's Largest Root	0.12	0.99	3.00	24.00	.413	.11

Colour Word Interference Test

Box's Test

Box's M	30.94
F	1.14
df1	20
df2	1839.86
p.	.297

Multivariate Tests

Effect		Value	*F*	Hyp. df	Error df	*p.*	η_p^2
Group	Pillai's Trace	.079	0.22	8.00	42.00	.986	.04
	Wilks' Lambda	.922	0.21	8.00	40.00	.988	.04
	Hotelling's Trace	.084	0.20	8.00	38.00	.989	.04
	Roy's Largest Root	.066	0.35	4.00	21.00	.844	.06

Symbol Search and SRT

Box's Test

Box's M	39.68
F	2.59
df1	12
df2	1900.85
p.	.002

Multivariate Tests

Effect		Value	*F*	Hyp. df	Error df	*p.*	η_p^2
Group	Pillai's Trace	0.29	1.15	6.00	40.00	.352	.15
	Wilks' Lambda	0.72	1.13	6.00	38.00	.366	.15
	Hotelling's Trace	0.37	1.10	6.00	36.00	.383	.16
	Roy's Largest Root	0.29	1.95	3.00	20.00	.153	.23

PANAS, NEADL and RME

Box's Test

Box's M	32.66
F	1.21
df1	20
df2	1839.86
p.	.239

Multivariate Tests

Effect		Value	*F*	Hyp. df	Error df	*p.*	η_p^2
Group	Pillai's Trace	0.09	0.25	8.00	42.00	.977	.05
	Wilks' Lambda	0.91	0.25	8.00	40.00	.979	.05
	Hotelling's Trace	0.10	0.24	8.00	38.00	.981	.05
	Roy's Largest Root	0.09	0.48	4.00	21.00	.753	.08

t-tests

Group Statistics

	Group	N	Mean	SD	SE Mean
NEADL	OM	9	103.22	22.72	7.57
	MO	9	104.11	19.86	6.62
PANAS PA	OM	9	61.67	11.61	3.87
	MO	9	61.44	21.08	7.03
PANAS NA	OM	9	45.67	17.69	5.90
	MO	9	45.78	18.46	6.15
Digit Span	OM	9	16.78	6.32	2.11
	MO	9	22.56	5.59	1.86
Symbol Search	OM	9	20.44	8.31	2.77
	MO	9	22.44	6.29	2.10
VPA Immediate Recall	OM	9	20.44	5.77	1.92
	MO	9	22.44	7.63	2.54
VPA Delayed Recall	OM	9	19.56	7.20	2.40
	MO	9	22.11	7.06	2.35
VPA Recognition	OM	9	73.22	8.26	2.75
	MO	9	77.11	4.43	1.48
Doors	OM	9	20.00	10.68	3.56
	MO	8	22.13	9.01	3.19
TMT Visual Scanning	OM	9	18.22	9.90	3.30
	MO	9	22.11	4.51	1.50
TMT Number Sequencing	OM	9	18.78	9.95	3.32
	MO	9	24.11	4.31	1.44
TMT Letter Sequencing	OM	9	21.78	8.42	2.81
	MO	9	23.78	4.32	1.44
TMT Switching	OM	9	21.33	6.32	2.11
	MO	9	23.56	4.67	1.56
TMT Motor Speed	OM	9	19.22	8.56	2.85
	MO	9	24.22	1.56	0.52
Verbal Fluency Letters	OM	9	19.33	6.40	2.13
	MO	9	24.56	10.17	3.39
Verbal Fluency Categories	OM	9	20.89	11.20	3.73
	MO	9	24.67	10.00	3.33
Verbal Fluency Switching	OM	9	20.67	5.94	1.98
	MO	9	22.11	6.97	2.32
CWIT Naming	OM	8	17.75	7.44	2.63
	MO	9	19.89	6.47	2.16
CWIT Reading	OM	8	18.75	7.65	2.70
	MO	9	20.89	5.18	1.73
CWIT Inhibition	OM	8	21.25	8.45	2.99
	MO	9	23.00	4.72	1.57
CWIT Switching	OM	8	20.88	8.34	2.95
	MO	9	22.89	5.46	1.82
ROCFT Copy	OM	9	69.56	1.81	0.60
	MO	9	69.06	3.34	1.11
ROCFT Immediate Recall	OM	9	47.83	13.16	4.39
	MO	9	53.50	14.88	4.96
ROCFT Delayed Recall	OM	9	48.06	13.00	4.33

	MO	9	54.67	15.07	5.02
RME	OM	9	46.00	10.83	3.61
	MO	8	48.38	9.64	3.41
SRT Explicit	OM	7	13.60	7.60	2.87
	MO	8	17.81	7.03	2.49
SRT Implicit	OM	7	83.06	70.63	26.70
	MO	8	69.83	61.23	21.65

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	*p.*	*t*	df	*p.* (2-tailed)	Mean Diff	SE Diff	Lower	Upper
NEADL	Equal variances assumed	0.11	.740	-0.09	16	.931	-0.89	10.06	-22.21	20.44
	Equal variances not assumed			-0.09	15.72	.931	-0.89	10.06	-22.25	20.47
PANAS PA	Equal variances assumed	3.16	.094	0.03	16	.978	0.22	8.02	-16.78	17.23
	Equal variances not assumed			0.03	12.44	.978	0.22	8.02	-17.19	17.63
PANAS NA	Equal variances assumed	0.13	.727	-0.01	16	.990	-0.11	8.52	-18.18	17.96
	Equal variances not assumed			-0.01	15.97	.990	-0.11	8.52	-18.18	17.96
Digit Span	Equal variances assumed	0.68	.420	-2.05	16	.057	-5.78	2.81	-11.74	0.19
	Equal variances not assumed			-2.05	15.77	.057	-5.78	2.81	-11.745	0.19
Symbol Search	Equal variances assumed	0.54	.471	-0.58	16	.573	-2.00	3.47	-9.36	5.36
	Equal variances not assumed			-0.58	14.90	.573	-2.00	3.47	-9.41	5.41
VPA Immediate Recall	Equal variances assumed	0.21	.651	-0.63	16	.539	-2.000	3.19	-8.76	4.76
	Equal variances not assumed			-0.63	14.89	.540	-2.00	3.19	-8.80	4.80

VPA Delayed Recall	Equal variances assumed	0.25	.626	-0.76	16	.458	-2.56	3.36	-9.68	4.57
	Equal variances not assumed			-0.76	15.99	.458	-2.56	3.36	-9.68	4.57
VPA Recognition	Equal variances assumed	1.72	.209	-1.25	16	.231	-3.889	3.12	-10.51	2.73
	Equal variances not assumed			-1.25	12.25	.236	-3.89	3.12	-10.68	2.90
Doors	Equal variances assumed	0.58	.457	-0.44	15	.666	-2.13	4.83	-12.42	8.17
	Equal variances not assumed			-0.45	14.97	.663	-2.13	4.78	-12.31	8.06
TMT Visual Scanning	Equal variances assumed	6.36	.023	-1.07	16	.299	-3.89	3.63	-11.58	3.80
	Equal variances not assumed			-1.07	11.19	.306	-3.89	3.63	-11.85	4.07
TMT Number Sequencing	Equal variances assumed	10.21	.006	-1.48	16	.159	-5.33	3.61	-12.99	2.33
	Equal variances not assumed			-1.48	10.91	.168	-5.33	3.61	-13.30	2.63
TMT Letter Sequencing	Equal variances assumed	3.07	.099	-0.63	16	.535	-2.00	3.16	-8.69	4.69
	Equal variances not assumed			-0.63	11.94	.538	-2.00	3.16	-8.88	4.88
TMT Switching	Equal variances assumed	1.31	.269	-0.85	16	.409	-2.22	2.62	-7.78	3.33
	Equal variances not assumed			-0.85	14.72	.410	-2.22	2.62	-7.82	3.37
TMT Motor Speed	Equal variances assumed	9.98	.006	-1.73	16	.104	-5.00	2.90	-11.15	1.15
	Equal variances not assumed			-1.73	8.53	.121	-5.00	2.90	-11.61	1.61
Verbal Fluency Letters	Equal variances assumed	3.85	.067	-1.30	16	.211	-5.22	4.01	-13.72	3.27
	Equal variances not assumed			-1.30	13.48	.214	-5.22	4.01	-13.85	3.40

Verbal Fluency Categories	Equal variances assumed	0.23	.640	-0.76	16	.461	-3.78	5.00	-14.39	6.83
	Equal variances not assumed			-0.76	15.80	.461	-3.78	5.00	-14.40	6.84
Verbal Fluency Switching	Equal variances assumed	<0.01	.991	-0.47	16	.642	-1.44	3.05	-7.92	5.03
	Equal variances not assumed			-0.47	15.60	.643	-1.44	3.05	-7.93	5.04
CWIT Naming	Equal variances assumed	0.04	.841	-0.63	15	.535	-2.14	3.37	-9.33	5.05
	Equal variances not assumed			-0.63	14.03	.540	-2.14	3.40	-9.43	5.16
CWIT Reading	Equal variances assumed	0.48	.497	-0.68	15	.505	-2.14	3.14	-8.82	4.54
	Equal variances not assumed			-0.67	12.11	.518	-2.14	3.21	-9.12	4.85
CWIT Inhibition	Equal variances assumed	1.27	.277	-0.54	15	.600	-1.75	3.27	-8.71	5.21
	Equal variances not assumed			-.52	10.70	.615	-1.75	3.38	-9.20	5.70
CWIT Inhibition Switching	Equal variances assumed	0.35	.562	-0.60	15	.560	-2.01	3.38	-9.22	5.19
	Equal variances not assumed			-0.58	11.85	.572	-2.01	3.47	-9.58	5.55
ROCFT Copy	Equal variances assumed	5.44	.033	0.40	16	.698	0.50	1.27	-2.18	3.18
	Equal variances not assumed			0.40	12.33	.700	0.50	1.27	-2.25	3.25
ROCFT Immediate Recall	Equal variances assumed	0.44	.516	-0.87	16	.405	-5.67	6.62	-19.70	8.37
	Equal variances not assumed			-0.87	15.76	.405	-5.67	6.62	-19.72	8.39
ROCFT Delayed Recall	Equal variances assumed	0.33	.577	-1.00	16	.334	-6.61	6.63	-20.68	7.45
	Equal variances not assumed			-1.00	15.66	.334	-6.61	6.63	-20.70	7.48

RME	Equal variances assumed	<0.01	.999	-0.48	15	.642	-2.38	5.00	-13.03	8.28
	Equal variances not assumed			-0.48	15.00	.639	-2.38	5.00	-12.95	8.20
SRT Explicit	Equal variances assumed	0.05	.830	-1.12	13	.285	-4.21	3.78	-12.37	3.95
	Equal variances not assumed			-1.11	12.39	.289	-4.21	3.80	-12.46	4.04
SRT Implicit	Equal variances assumed	0.01	.933	0.39	13	.704	13.23	34.02	-60.27	86.72
	Equal variances not assumed			0.39	12.03	.707	13.23	34.37	-61.64	88.09

OM vs Placebo

	Group	N	Mean	SD
NEADL	OM	9	103.22	22.72
	Placebo	10	101.30	36.84
PANAS PA	OM	9	61.67	11.69
	Placebo	10	62.40	14.76
PANAS NA	OM	9	45.67	17.69
	Placebo	10	37.50	11.97
Digit Span	OM	9	16.78	6.32
	Placebo	10	22.10	5.30
Symbol Search	OM	9	20.44	8.31
	Placebo	10	20.00	10.19
VPA Immediate Recall	OM	9	20.44	5.77
	Placebo	10	22.10	8.82
VPA Delayed Recall	OM	9	19.56	7.20
	Placebo	10	21.50	7.95
Doors	OM	9	20.00	10.68
	Placebo	9	20.44	4.13
TMT Visual Scanning	OM	9	18.22	9.90
	Placebo	10	17.30	9.43
TMT Number Sequencing	OM	9	18.78	9.95
	Placebo	10	21.00	8.16
TMT Letter Sequencing	OM	9	21.78	8.42
	Placebo	10	20.90	7.61
TMT Switching	OM	9	21.33	6.32
	Placebo	10	21.30	7.84
TMT Motor Speed	OM	9	19.22	8.56
	Placebo	10	19.90	6.89
Verbal Fluency Letters	OM	9	19.33	6.40
	Placebo	10	22.90	6.38
Verbal Fluency Categories	OM	9	20.89	11.20
	Placebo	10	22.50	9.90

Verbal Fluency Switching	OM	9	20.67	5.94
	Placebo	10	24.10	6.87
CWIT Naming	OM	8	17.75	7.44
	Placebo	10	17.20	9.28
CWIT Reading	OM	8	18.75	7.65
	Placebo	9	20.44	8.23
CWIT Inhibition	OM	8	21.25	8.45
	Placebo	9	21.11	8.05
CWIT Switching	OM	8	20.88	8.34
	Placebo	9	20.89	8.48
ROCFT Copy	OM	9	69.56	1.81
	Placebo	10	64.80	13.03
ROCFT Immediate Recall	OM	9	47.83	13.16
	Placebo	10	51.95	17.46
ROCFT Delayed Recall	OM	9	48.06	13.00
	Placebo	10	49.50	18.05
RME	OM	9	46.00	10.83
	Placebo	9	47.44	10.97
SRT Explicit	OM	7	13.60	7.60
	Placebo	9	16.61	8.78
SRT Implicit	OM	7	83.06	70.63
	Placebo	9	210.46	288.23

Independent Samples Test

		Levene's Test		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	p.	t	df	p. (2-tailed)	Mean Diff.	SE Diff	Lower	Upper
NEADL	Equal variances assumed	1.38	.256	0.14	17	.894	1.92	14.25	-28.13	31.98
	Equal variances not assumed			0.14	15.17	.892	1.92	13.89	-27.66	31.51
PANAS PA	Equal variances assumed	0.67	.424	-0.12	17	.906	-0.73	6.14	-13.70	12.23
	Equal variances not assumed			-0.12	16.73	.905	-0.73	6.06	-13.54	12.08
PANAS NA	Equal variances assumed	0.45	.512	1.19	17	.251	8.17	6.86	-6.32	22.65
	Equal variances not assumed			1.18	13.86	.264	8.17	7.01	-6.88	23.21

Digit Span	Equal variances assumed	1.23	.283	-2.00	17	.062	-5.32	2.67	-10.95	0.30
	Equal variances not assumed			-1.98	15.73	.066	-5.32	2.69	-11.04	0.39
Symbol Search	Equal variances assumed	0.43	.519	0.10	17	.919	0.44	4.30	-8.62	9.51
	Equal variances not assumed			0.11	16.86	.918	0.44	4.25	-8.52	9.41
VPA Immediate Recall	Equal variances assumed	1.78	.199	-0.48	17	.639	-1.66	3.47	-8.97	5.66
	Equal variances not assumed			-0.49	15.62	.632	-1.66	3.39	-8.85	5.54
VPA Delayed Recall	Equal variances assumed	0.15	.705	-0.56	17	.585	-1.94	3.49	-9.31	5.43
	Equal variances not assumed			-0.56	17.00	.583	-1.94	3.47	-9.27	5.39
Doors	Equal variances assumed	7.23	.016	-0.12	16	.909	-0.44	3.82	-8.53	7.64
	Equal variances not assumed			-0.12	10.34	.910	-0.44	3.82	-8.91	8.02
TMT Visual Scaning	Equal variances assumed	0.05	.823	0.21	17	.838	0.92	4.43	-8.43	10.28
	Equal variances not assumed			0.21	16.58	.838	0.92	4.45	-8.48	10.32
TMT Number Sequencing	Equal variances assumed	1.61	.221	-0.54	17	.600	-2.22	4.16	-10.99	6.55
	Equal variances not assumed			-0.53	15.56	.604	-2.22	4.20	-11.15	6.71
TMT Letter Sequencing	Equal variances assumed	0.39	.543	0.24	17	.814	0.88	3.68	-6.88	8.63
	Equal variances not assumed			0.24	16.27	.815	0.88	3.70	-6.95	8.71

TMT Switching	Equal variances assumed	0.01	.913	0.01	17	.992	0.03	3.29	-6.92	6.98
	Equal variances not assumed			0.01	16.82	.992	0.03	3.26	-6.84	6.91
TMT Motor Speed	Equal variances assumed	0.77	.393	-0.19	17	.851	-0.68	3.55	-8.16	6.80
	Equal variances not assumed			-0.19	15.40	.853	-0.68	3.59	-8.31	6.95
Verbal Fluency Letters	Equal variances assumed	0.06	.814	-1.21	17	.241	-3.57	2.94	-9.76	2.63
	Equal variances not assumed			-1.21	16.78	.242	-3.57	2.94	-9.77	2.64
Verbal Fluency Categories	Equal variances assumed	0.21	.650	-0.33	17	.743	-1.61	4.84	-11.82	8.60
	Equal variances not assumed			-0.33	16.13	.745	-1.61	4.87	-11.93	8.71
Verbal Fluency Switching	Equal variances assumed	0.20	.658	-1.16	17	.263	-3.43	2.96	-9.68	2.82
	Equal variances not assumed			-1.17	16.98	.259	-3.43	2.94	-9.63	2.77
CWIT Naming	Equal variances assumed	1.01	.329	0.14	16	.894	0.55	4.04	-8.02	9.12
	Equal variances not assumed			0.14	16.00	.891	0.55	3.94	-7.81	8.91
CWIT Reading	Equal variances assumed	0.17	.689	-0.44	15	.668	-1.69	3.87	-9.94	6.56
	Equal variances not assumed			-0.44	14.96	.666	-1.69	3.85	-9.91	6.52
CWIT Inhibition	Equal variances assumed	0.03	.876	0.04	15	.973	0.14	4.00	-8.39	8.67
	Equal variances not assumed			0.04	14.56	.973	0.14	4.02	-8.44	8.72

CWIT Inhibition Switching	Equal variances assumed	0.14	.718	-.003	15	.997	-0.01	4.09	-8.73	8.70
	Equal variances not assumed			-.003	14.82	.997	-0.01	4.08	-8.73	8.70
ROCFT Copy	Equal variances assumed	2.86	.109	1.08	17	.294	4.76	4.39	-4.52	14.03
	Equal variances not assumed			1.14	9.39	.282	4.76	4.17	-4.61	14.12
ROCFT Immediate Recall	Equal variances assumed	0.05	.834	-0.58	17	.573	-4.12	7.16	-19.21	10.99
	Equal variances not assumed			-0.58	16.53	.567	-4.12	7.05	-19.03	10.79
ROCFT Delayed Recall	Equal variances assumed	0.31	.587	-0.20	17	.845	-1.44	7.29	-16.83	13.94
	Equal variances not assumed			-0.20	16.28	.843	-1.44	7.17	-16.61	13.72572
RME	Equal variances assumed	0.19	.667	-0.28	16	.782	-1.44	5.14	-12.34	9.45
	Equal variances not assumed			-0.28	16.00	.782	-1.44	5.14	-12.34	9.45
SRT Explicit	Equal variances assumed	0.04	.848	-0.72	14	.483	-3.01	4.18	-11.98	5.96
	Equal variances not assumed			-0.73	13.78	.475	-3.01	4.10	-11.82	5.80
SRT Implicit	Equal variances assumed	2.01	.178	-1.14	14	.275	-127.40	112.25	-368.15	113.34
	Equal variances not assumed			-1.28	9.21	.233	-127.40	99.72	-352.20	97.39

MO vs Placebo

Group Statistics

	Group	N	Mean	SD	SE Mean
NEADL	MO	9	104.11	19.86	6.62

	Placebo	10	101.30	36.84	11.65
PANAS PA	MO	9	61.44	21.08	7.03
	Placebo	10	62.40	14.77	4.67
PANAS NA	MO	9	45.78	18.46	6.15
	Placebo	10	37.50	11.97	3.79
Digit Span	MO	9	22.56	5.59	1.86
	Placebo	10	22.10	5.30	1.68
Symbol Search	MO	9	22.44	6.29	2.10
	Placebo	10	20.00	10.19	3.22
VPA Immediate Recall	MO	9	22.44	7.63	2.54
	Placebo	10	22.10	8.82	2.79
VPA Delayed Recall	MO	9	22.11	7.06	2.35
	Placebo	10	21.50	7.95	2.51
Doors	MO	8	22.13	9.01	3.19
	Placebo	9	20.44	4.13	1.38
TMT Visual Scanning	MO	9	22.11	4.51	1.50
	Placebo	10	17.30	9.43	2.98
TMT Number Sequencing	MO	9	24.11	4.31	1.44
	Placebo	10	21.00	8.16	2.58
TMT Letter Sequencing	MO	9	23.78	4.32	1.44
	Placebo	10	20.90	7.61	2.41
TMT Switching	MO	9	23.56	4.67	1.56
	Placebo	10	21.30	7.85	2.48
TMT Motor Speed	MO	9	24.22	1.56	0.52
	Placebo	10	19.90	6.89	2.18
Verbal Fluency Letters	MO	9	24.56	10.17	3.39
	Placebo	10	22.90	6.38	2.02
Verbal Fluency Categories	MO	9	24.67	10.00	3.33
	Placebo	10	22.50	9.90	3.13
Verbal Fluency Switching	MO	9	22.11	6.97	2.32
	Placebo	10	24.10	6.87	2.17
CWIT Naming	MO	9	19.89	6.47	2.16
	Placebo	10	17.20	9.28	2.94
CWIT Reading	MO	9	20.89	5.18	1.73
	Placebo	9	20.44	8.23	2.74
CWIT Inhibition	MO	9	23.00	4.72	1.57
	Placebo	9	21.11	8.05	2.68
CWIT Inhibition Switching	MO	9	22.89	5.46	1.82
	Placebo	9	20.89	8.48	2.83
ROCFT Copy	MO	9	69.06	3.34	1.11
	Placebo	10	64.80	13.03	4.12
ROCFT Immediate Recall	MO	9	53.50	14.88	4.96
	Placebo	10	51.95	17.46	5.52
ROCFT Delayed Recall	MO	9	54.67	15.07	5.02
	Placebo	10	49.50	18.05	5.70
RME	MO	8	48.38	9.64	3.41
	Placebo	9	47.44	10.97	3.66
SRT Explicit	MO	8	17.85	7.03	2.49
	Placebo	9	16.61	8.78	2.93
SRT Implicit	MO	8	69.81	61.23	21.65
	Placebo	9	210.46	288.23	96.08

Independent Samples Test

		Levene's Test		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	*p.*	*t*	df	*p* (2-tailed)	Mean Diff	SE Diff	Lower	Upper
NEADL	Equal variances assumed	2.11	.164	0.20	17	.841	2.81	13.82	-26.34	31.96
	Equal variances not assumed			0.21	14.10	.837	2.81	13.40	-25.91	31.53
PANAS PA	Equal variances assumed	1.22	.284	-0.12	17	.909	-0.96	8.28	-18.42	16.51
	Equal variances not assumed			-0.11	14.17	.911	-0.96	8.44	-19.03	17.12
PANAS NA	Equal variances assumed	1.35	.261	1.17	17	.257	8.28	7.06	-6.62	23.18
	Equal variances not assumed			1.15	13.49	.272	8.28	7.22	-7.27	23.83
Digit Span	Equal variances assumed	0.06	.803	0.18	17	.858	0.46	2.50	-4.81	5.73
	Equal variances not assumed			0.18	16.55	.858	0.46	2.51	-4.84	5.76
Symbol Search	Equal variances assumed	1.93	.182	0.62	17	.543	2.44	3.94	-5.87	10.76
	Equal variances not assumed			0.64	15.17	.534	2.44	3.84	-5.74	10.63
VPA Immediate Recall	Equal variances assumed	0.51	.486	0.09	17	.929	0.34	3.81	-7.69	8.38
	Equal variances not assumed			0.09	16.98	.928	0.34	3.78	-7.62	8.31
VPA Delayed Recall	Equal variances assumed	0.68	.421	0.18	17	.862	0.61	3.47	-6.70	7.92
	Equal variances not assumed			0.18	17.00	.861	0.61	3.44	-6.65	7.88
Doors	Equal variances assumed	2.45	.139	0.50	15	.621	1.68	3.33	-5.42	8.78

	Equal variances not assumed			0.48	9.56	.639	1.68	3.47	-6.10	9.46
TMT Visual Scanning	Equal variances assumed	4.94	.040	1.39	17	.182	4.81	3.46	-2.48	12.11
	Equal variances not assumed			1.44	13.20	.173	4.81	3.34	-2.39	12.01
TMT Number Sequencing	Equal variances assumed	0.78	.390	1.02	17	.322	3.11	3.05	-3.32	9.55
	Equal variances not assumed			1.05	13.94	.310	3.11	2.96	-3.23	9.45
TMT Letter Sequencing	Equal variances assumed	0.69	.419	1.00	17	.333	2.88	2.89	-3.21	8.97
	Equal variances not assumed			1.03	14.52	.322	2.88	2.80	-3.12	8.87
TMT Switching	Equal variances assumed	0.28	.605	0.75	17	.464	2.26	3.01	-4.09	8.60
	Equal variances not assumed			0.77	14.88	.453	2.26	2.93	-3.99	8.50
TMT Motor Speed	Equal variances assumed	3.98	.062	1.84	17	.084	4.32	2.35	-0.65	9.29
	Equal variances not assumed			1.93	10.02	.082	4.32	2.24	-0.67	9.31
Verbal Fluency Letters	Equal variances assumed	3.75	.070	0.43	17	.673	1.66	3.85	-6.47	9.78
	Equal variances not assumed			0.42	13.20	.682	1.66	3.95	-6.86	10.17
Verbal Fluency Categories	Equal variances assumed	<.01	.967	0.47	17	.642	2.17	4.57	-7.48	11.81
	Equal variances not assumed			0.47	16.75	.642	2.17	4.57	-7.49	11.83
Verbal Fluency Switching	Equal variances assumed	0.13	.720	-0.63	17	.540	-1.99	3.18	-8.70	4.72
	Equal variances not assumed			-0.63	16.73	.540	-1.99	3.18	-8.71	4.73
CWIT Naming	Equal variances assumed	1.78	.200	0.72	17	.479	2.69	3.71	-5.15	10.52

	Equal variances not assumed			0.74	16.07	.471	2.69	3.64	-5.03	10.41
CWIT Reading	Equal variances assumed	1.57	.228	0.14	16	.893	0.44	3.24	-6.43	7.32
	Equal variances not assumed			0.14	13.48	.893	0.44	3.24	-6.54	7.42
CWIT Inhibition	Equal variances assumed	2.34	.146	0.61	16	.552	1.89	3.11	-4.71	8.48
	Equal variances not assumed			0.61	12.91	.554	1.89	3.11	-4.84	8.61
CWIT Inhibition Switching	Equal variances assumed	1.56	.230	0.60	16	.560	2.00	3.36	-5.13	9.13
	Equal variances not assumed			0.60	13.67	.562	2.00	3.36	-5.23	9.23
ROCFT Copy	Equal variances assumed	1.71	.209	0.95	17	.356	4.26	4.48	-5.20	13.71
	Equal variances not assumed			1.00	10.30	.342	4.26	4.27	-5.22	13.73
ROCFT Immediate Recall	Equal variances assumed	0.07	.798	0.21	17	.838	1.55	7.49	-14.25	17.35
	Equal variances not assumed			0.21	16.96	.837	1.55	7.42	-14.11	17.21
ROCFT Delayed Recall	Equal variances assumed	0.01	.918	0.67	17	.510	5.17	7.68	-11.03	21.37
	Equal variances not assumed			0.68	16.92	.506	5.17	7.60	-10.88	21.21
RME	Equal variances assumed	0.27	.612	0.19	15	.856	0.93	5.04	-9.81	11.67
	Equal variances not assumed			0.19	15.00	.855	0.930	5.00	-9.72	11.58
SRT Explicit	Equal variances assumed	0.16	.696	0.31	15	.762	1.20	3.89	-7.10	9.50
	Equal variances not assumed			0.31	14.86	.759	1.20	3.84	-6.99	9.39
SRT Implicit	Equal variances assumed	2.40	.142	-1.35	15	.197	-140.63	104.28	-362.90	81.64

	Equal variances not assumed	-1.43	8.81	.188	-140.63	98.49	-364.17	82.91

E.10 Non-parametric analyses of cross-over effect

OM vs MO

Ranks

	Group	N	Mean Rank	Sum of Ranks
NEADL	OM	9	9.33	84.00
	MO	9	9.67	87.00
	Total	18		
PANAS PA	OM	9	8.83	79.50
	MO	9	10.17	91.50
	Total	18		
PANAS NA	OM	9	9.22	83.00
	MO	9	9.78	88.00
	Total	18		
Digit Span	OM	9	7.83	70.50
	MO	9	11.17	100.50
	Total	18		
Symbol Search	OM	9	9.11	82.00
	MO	9	9.89	89.00
	Total	18		
VPA Immediate Recall	OM	9	8.56	77.00
	MO	9	10.44	94.00
	Total	18		
VPA Delayed Recall	OM	9	8.72	78.50
	MO	9	10.28	92.50
	Total	18		
Doors	OM	9	8.56	77.00
	MO	8	9.50	76.00
	Total	17		

	NEADL	PANAS PA	PANAS NA	Digit Span	Symbol Search	VPA Imm.	VPA Delay	Doors
Mann-Whitney U	39.00	34.50	38.00	25.50	37.00	32.00	33.50	32.000
Wilcoxon W	84.00	79.50	83.00	70.50	82.00	77.00	78.50	77.000
Z	-0.13	-0.53	-0.22	-1.33	-0.31	-0.75	-0.62	-.387
Asymp. Sig. (2-tailed)	.895	.595	.825	.183	.756	.452	.535	.699
Exact Sig. [2*(1-tailed Sig.)]	.931	.605	.863	.190	.796	.489	.546	.743[b]

Ranks

	Group	N	Mean Rank	Sum of Ranks
TMT Visual Scanning	OM	9	8.78	79.00
	MO	9	10.22	92.00
	Total	18		
TMT Number Sequencing	OM	9	8.22	74.00
	MO	9	10.78	97.00
	Total	18		
TMT Letter Sequencing	OM	9	9.39	84.50
	MO	9	9.61	86.50
	Total	18		
TMT Switching	OM	9	8.28	74.50
	MO	9	10.72	96.50
	Total	18		
TMT Motor Speed	OM	9	7.83	70.50
	MO	9	11.17	100.50
	Total	18		
Verbal Fluency Letters	OM	9	8.17	73.50
	MO	9	10.83	97.50
	Total	18		
Verbal Fluency Categories	OM	9	8.61	77.50
	MO	9	10.39	93.50
	Total	18		
Verbal Fluency Switching	OM	9	8.33	75.00
	MO	9	10.67	96.00
	Total	18		

Test Statistics

	TMT VisScan	TMT NumSeq	TMT LettSeq	TMT Switch	TMT Motor Speed	Verbal Flu Lett	Verbal Flu Cat	Verbal Flu Switch
Mann-Whitney U	34.00	29.00	39.50	29.50	25.50	28.50	32.50	30.00
Wilcoxon W	79.00	74.00	84.50	74.50	70.50	73.50	77.50	75.00
Z	-0.58	-1.02	-0.09	-0.98	-1.34	-1.06	-0.71	-0.93
Asymp. Sig. (2-tailed)	.563	.309	.929	.329	.179	.288	.479	.351
Exact Sig. [2*(1-tailed Sig.)]	.605	.340	.931	.340	.190	.297	.489	.387

Ranks

	Group	N	Mean Rank	Sum of Ranks
CWIT Naming	OM	8	8.13	65.00
	MO	9	9.78	88.00
	Total	17		
CWIT Reading	OM	8	8.44	67.50
	MO	9	9.50	85.50
	Total	17		
CWIT Inhibition	OM	8	8.69	69.50
	MO	9	9.28	83.50
	Total	17		
	OM	8	8.13	65.00

CWIT Inhibition Switching	MO	9	9.78	88.00
	Total	17		

Test Statistic

	CWIT Naming	CWIT Reading	CWIT Inhibition	CWIT Switching
Mann-Whitney U	29.00	31.50	33.50	29.00
Wilcoxon W	65.00	67.50	69.50	65.00
Z	-0.68	-0.43	-0.24	-0.68
Asymp. Sig. (2-tailed)	.498	.664	.808	.499
Exact Sig. [2*(1-tailed Sig.)]	.541	.673	.815	.541

Ranks

	Group	N	Mean Rank	Sum of Ranks
ROCFT Copy	OM	9	9.61	86.50
	MO	9	9.39	84.50
	Total	18		
ROCFT Immediate Recall	OM	9	8.22	74.00
	MO	9	10.78	97.00
	Total	18		
ROCFT Delayed Recall	OM	9	8.11	73.00
	MO	9	10.89	98.00
	Total	18		
RME	OM	9	8.56	77.00
	MO	8	9.50	76.00
	Total	17		
SRT Explicit	OM	7	6.71	47.00
	MO	8	9.13	73.00
	Total	15		
SRT Implicit	OM	7	8.64	60.50
	MO	8	7.44	59.50
	Total	15		

Test Statistics

	ROCFT Copy	ROCFT Immediate	ROCFT Delay	RME	SRT Explicit	SRT Implicit
Mann-Whitney U	39.50	29.00	28.00	32.00	19.00	23.50
Wilcoxon W	84.50	74.00	73.00	77.00	47.00	59.50
Z	-0.09	-1.02	-1.10	-.385	-1.04	-0.52
Asymp. Sig. (2-tailed)	.928	.309	.270	.700	.297	.602
Exact Sig. [2*(1-tailed Sig.)]	.931	.340	.297	.743	.336	.613

OM vs Placebo

Ranks

	Group	N	Mean Rank	Sum of Ranks
NEADL	OM	9	9.39	84.50

	Placebo	10	10.55	105.50
	Total	19		
PANAS PA	OM	9	9.28	83.50
	Placebo	10	10.65	106.50
	Total	19		
PANAS NA	OM	9	12.00	108.00
	Placebo	10	8.20	82.00
	Total	19		
Digit Span	OM	9	7.56	68.00
	Placebo	10	12.20	122.00
	Total	19		
Symbol Search	OM	9	10.33	93.00
	Placebo	10	9.70	97.00
	Total	19		
VPA Immediate Recall	OM	9	9.22	83.00
	Placebo	10	10.70	107.00
	Total	19		
VPA Delayed Recall	OM	9	8.94	80.50
	Placebo	10	10.95	109.50
	Total	19		
Doors	OM	9	10.22	92.00
	Placebo	9	8.78	79.00
	Total	18		

Test Statistics[a]

	NEADL	PANAS PA	PANAS NA	Digit Span	Symbol Search	VPA Imm	VPA Delay	Doors
Mann-Whitney U	39.50	38.50	27.00	23.00	42.00	38.00	35.50	34.00
Wilcoxon W	84.50	83.50	82.00	68.00	97.00	83.00	80.50	79.00
Z	-0.45	-0.53	-1.47	-1.80	-0.25	-0.58	-0.78	-0.58
Asymp. Sig. (2-tailed)	.653	.595	.140	.071	.806	.566	.436	.565
Exact Sig. [2*(1-tailed Sig.)]	.661	.604	.156	.079	.842	.604	.447	.605

Ranks

	Group	N	Mean Rank	Sum of Ranks
TMT Visual Scanning	OM	9	10.39	93.50
	Placebo	10	9.65	96.50
	Total	19		
TMT Number Sequencing	OM	9	9.50	85.50
	Placebo	10	10.45	104.50
	Total	19		
TMT Letter Sequencing	OM	9	11.17	100.50
	Placebo	10	8.95	89.50
	Total	19		
TMT Switching	OM	9	9.89	89.00

	Placebo	10	10.10	101.00
	Total	19		
TMT Motor Speed	OM	9	10.56	95.00
	Placebo	10	9.50	95.00
	Total	19		
Verbal Fluency Letters	OM	9	8.61	77.50
	Placebo	10	11.25	112.50
	Total	19		
Verbal Fluency Categories	OM	9	9.67	87.00
	Placebo	10	10.30	103.00
	Total	19		
Verbal Fluency Switching	OM	9	8.17	73.50
	Placebo	10	11.65	116.50
	Total	19		

Test Statistic

	TMT Vis Scan	TMT Num Seq	TMT Lett Seq	TMT Switch	TMT Motor Speed	Verb Flu Lett	Verbal Fluency Cat	Verbal Fluency Switch
Mann-Whitney U	41.50	40.50	34.50	44.00	40.00	32.50	42.00	28.50
Wilcoxon W	96.50	85.50	89.50	89.00	95.00	77.50	87.00	73.50
Z	-0.29	-0.37	-0.86	-0.08	-0.41	-1.03	-0.25	-1.35
Asymp. Sig. (2-tailed)	.774	.712	.388	.934	.680	.305	.806	.177
Exact Sig. [2*(1-tailed Sig.)]	.780	.720	.400	.968	.720	.315	.842	.182

Ranks

	Group	N	Mean Rank	Sum of Ranks
CWIT Naming	OM	8	9.00	72.00
	Placebo	10	9.90	99.00
	Total	18		
CWIT Reading	OM	8	7.94	63.50
	Placebo	9	9.94	89.50
	Total	17		
CWIT Inhibition	OM	8	8.94	71.50
	Placebo	9	9.06	81.50
	Total	17		
CWIT Inhibition Switching	OM	8	9.00	72.00
	Placebo	9	9.00	81.00
	Total	17		

Test Statistics

	CWIT Naming	CWIT Reading	CWIT Inhibition	CWIT Switching Inhibition
Mann-Whitney U	36.00	27.50	35.50	36.00
Wilcoxon W	72.00	63.50	71.50	81.00
Z	-0.36	-0.83	-0.05	<0.01
Asymp. Sig. (2-tailed)	.720	.409	.961	1.000

Exact Sig. [2*(1-tailed Sig.)]	.762	.423	.963	1.000

Ranks

	Group	N	Mean Rank	Sum of Ranks
ROCFT Copy	OM	9	10.89	98.00
	Placebo	10	9.20	92.00
	Total	19		
ROCFT Immediate Recall	OM	9	8.56	77.00
	Placebo	10	11.30	113.00
	Total	19		
ROCFT Delayed Recall	OM	9	9.33	84.00
	Placebo	10	10.60	106.00
	Total	19		
RME	OM	9	9.22	83.00
	Placebo	9	9.78	88.00
	Total	18		
SRT Explicit	OM	7	7.00	49.00
	Placebo	9	9.67	87.00
	Total	16		
SRT Implicit	OM	7	7.14	50.00
	Placebo	9	9.56	86.00
	Total	16		

Test Statistics

	ROCFT Copy	ROCFT Imm	ROCFT Delay	RME	SRT Explicit	SRT Implicit
Mann-Whitney U	37.00	32.00	39.00	38.00	21.00	22.00
Wilcoxon W	92.00	77.00	84.00	83.00	49.00	50.00
Z	-0.66	-1.06	-0.49	-0.22	-1.12	-1.01
Asymp. Sig. (2-tailed)	.510	.288	.624	.825	.265	.315
Exact Sig. [2*(1-tailed Sig.)]	.549	.315	.661	.863	.299	.351

MO vs Placebo

Ranks

	Group	N	Mean Rank	Sum of Ranks
NEADL	MO	9	9.11	82.00
	Placebo	10	10.80	108.00
	Total	19		
PANAS PA	MO	9	9.89	89.00
	Placebo	10	10.10	101.00
	Total	19		
PANAS NA	MO	9	11.44	103.00
	Placebo	10	8.70	87.00
	Total	19		
Digit Span	MO	9	10.22	92.00

	Placebo	10	9.80	98.00
	Total	19		
Symbol Search	MO	9	11.11	100.00
	Placebo	10	9.00	90.00
	Total	19		
VPA Immediate Recall	MO	9	10.17	91.50
	Placebo	10	9.85	98.50
	Total	19		
VPA Delayed Recall	MO	9	9.94	89.50
	Placebo	10	10.05	100.50
	Total	19		
Doors	MO	8	10.13	81.00
	Placebo	9	8.00	72.00
	Total	17		

Test Statistics

	NEADL	PANAS PA	PANAS NA	Digit Span	Symbol Search	VPA Imm	VPA Delay	Doors
Mann-Whitney U	37.00	44.00	32.00	43.00	35.00	43.50	44.50	27.00
Wilcoxon W	82.00	89.00	87.00	98.00	90.00	98.50	89.50	72.00
Z	-0.65	-0.08	-1.06	-0.16	-0.82	-0.12	-0.04	-0.87
Asymp. Sig. (2-tailed)	.513	.935	.287	.870	.412	.902	.967	.384
Exact Sig. [2*(1-tailed Sig.)]	.549[b]	.968[b]	.315[b]	.905[b]	.447[b]	.905[b]	.968[b]	.423[b]

Ranks

	Group	N	Mean Rank	Sum of Ranks
TMT Visual Scanning	MO	9	11.44	103.00
	Placebo	10	8.70	87.00
	Total	19		
TMT Number Sequencing	MO	9	11.00	99.00
	Placebo	10	9.10	91.00
	Total	19		
TMT Letter Sequencing	MO	9	11.00	99.00
	Placebo	10	9.10	91.00
	Total	19		
TMT Switching	MO	9	10.56	95.00
	Placebo	10	9.50	95.00
	Total	19		
TMT Motor Speed	MO	9	12.50	112.50
	Placebo	10	7.75	77.50
	Total	19		
Verbal Fluency Letters	MO	9	10.56	95.00

	Placebo	10	9.50	95.00
	Total	19		
Verbal Fluency Categories	MO	9	10.72	96.50
	Placebo	10	9.35	93.50
	Total	19		
Verbal Fluency Switching	MO	9	9.33	84.00
	Placebo	10	10.60	106.00
	Total	19		

Test Statistics

	TMT Vis Scan	TMT Num Seq	TMT Lett Seq	TMT Switch	TMT Motor Sp	Verb Flu Lett	Verb Flu Cat	Verb Flu Switch
Mann-Whitney U	32.00	36.00	36.00	40.00	22.50	40.00	38.50	39.00
Wilcoxon W	87.00	91.00	91.00	95.00	77.50	95.00	93.50	84.00
Z	-1.06	-0.74	-0.74	-0.41	-1.87	-0.41	-0.53	-0.49
Asymp. Sig. (2-tailed)	.288	.460	.461	.680	.061	.683	.595	.622
Exact Sig. [2*(1-tailed Sig.)]	.315	.497	.497	.720	.065	.720	.604	.661

Ranks

	Group	N	Mean Rank	Sum of Ranks
CWIT Naming	MO	9	10.44	94.00
	Placebo	10	9.60	96.00
	Total	19		
CWIT Reading	MO	9	9.17	82.50
	Placebo	9	9.83	88.50
	Total	18		
CWIT Inhibition	MO	9	10.00	90.00
	Placebo	9	9.00	81.00
	Total	18		
CWIT Inhibition Switching	MO	9	9.89	89.00
	Placebo	9	9.11	82.00
	Total	18		

Test Statistics

	CWIT Naming	CWIT Read	CWIT Inhib	CWIT Switch
Mann-Whitney U	41.00	37.50	36.00	37.00
Wilcoxon W	96.00	82.50	81.00	82.00
Z	-0.33	-0.27	-0.40	-0.31
Asymp. Sig. (2-tailed)	.741	.791	.690	.756
Exact Sig. [2*(1-tailed Sig.)]	.780	.796	.730	.796

Ranks

	Group	N	Mean Rank	Sum of Ranks
ROCFT Copy	MO	9	10.89	98.00
	Placebo	10	9.20	92.00
	Total	19		
ROCFT Immediate Recall	MO	9	10.33	93.00
	Placebo	10	9.70	97.00
	Total	19		
ROCFT Delayed Recall	MO	9	11.06	99.50
	Placebo	10	9.05	90.50
	Total	19		
RME	MO	8	9.38	75.00
	Placebo	9	8.67	78.00
	Total	17		
SRT Explicit	MO	8	9.75	78.00
	Placebo	9	8.33	75.00
	Total	17		
SRT Immediate Recall	MO	8	7.63	61.00
	Placebo	9	10.22	92.00
	Total	17		

Test Statistics

	ROCFT Copy	ROCFT Imm	ROCFT Delay	RME	SRT Explicit	SRT Implict
Mann-Whitney U	37.00	42.00	35.50	33.00	30.00	25.00
Wilcoxon W	92.00	97.00	90.50	78.00	75.00	61.00
Z	-0.66	-0.25	-0.78	-0.29	-0.58	-1.06
Asymp. Sig. (2-tailed)	.507	.806	.438	.773	.561	.290
Exact Sig. [2*(1-tailed Sig.)]	.549[b]	.842[b]	.447[b]	.815[b]	.606[b]	.321[b]

E.11 Analyses of Treatment Effects (standard and bootstrapped t-tests) Period 1

Paired Samples Statistics

				Bootstrap			
						BCa 95% Confidence Interval	
Group			Stat.	Bias	SE	Lower	Upper
OM	WAIS Digit Span Baseline	Mean	7.56	.01	.78	6.33	8.89
		N	9				
		SD	2.46	-.19	.44	1.87	2.67
		SE Mean	.82				
	WAIS Digit Span Follow-up 1	Mean	8.33	.01	.96	6.33	10.22
		N	9				
		SD	3.08	-.21	.43	2.65	3.16
		SE Mean	1.03				
	VPA Immediate Baseline	Mean	8.22	-<.01	.49	7.33	9.00
		N	9				
		SD	1.56	-.15	.39	0.87	1.94
		SE Mean	.52				
	VPA Immediate Follow-up 1	Mean	10.33	.01	.95	8.67	12.11
		N	9				
		SD	3.00	-.21	.45	2.40	3.19
		SE Mean	1.00				
	VPA Delayed Baseline	Mean	8.00	<.01	.81	6.67	9.22
		N	9				
		SD	2.55	-.24	.63	1.41	3.10
		SE Mean	.85				
	VPA Delayed Follow-up 1	Mean	10.11	.01	1.26	7.84	12.33
		N	9				
		SD	4.01	-.30	.76	2.78	4.54
		SE Mean	1.34				
	Doors Baseline	Mean	8.22	.01	1.18	6.22	10.22
		N	9				
		SD	3.80	-.29	.74	2.76	4.31
		SE Mean	1.27				
	Doors Follow-up 1	Mean	9.89	.01	1.56	6.56	12.78
		N	9				
		SD	5.04	-.43	1.19	3.12	5.89
		SE Mean	1.68				
	ROCFT Copy Baseline	Mean	35.22	-<.01	.26	34.78	35.67
		N	9				
		SD	.83	-.06	.13	0.71	0.88
		Std. Error Mean	.27778				
	ROCFT Copy Follow-Up 1	Mean	34.78	-<.01	.41	34.11	35.33
		N	9				
		SD	1.30	-0.12	.34	0.67	1.66
		SE Mean	.43				
	ROCFT Immediate Baseline	Mean	23.72	.02	1.69	20.78	26.56
		N	9				

		SD	5.47	-.45	1.24	3.38	6.54
		SE Mean	1.82				
	ROCFT Immediate Follow-up 1	Mean	24.50	.03	2.03	20.88	28.11
		N	9				
		SD	6.54	-.53	1.47	4.08	7.76
		SE Mean	2.18				
	ROCFT Delay Baseline	Mean	22.94	.02	2.08	18.67	26.72
		N	9				
		SD	6.78	-.55	1.50	4.41	7.88
		SE Mean	2.26				
	ROCFT Delay Follow-up 1	Mean	23.50	.025	2.15	19.78	27.28
		N	9				
		SD	6.97	-.62	1.76	4.41	8.26
		SE Mean	2.32				
MO	WAIS Digit Span Baseline	Mean	10.22	.01	.87	8.33	12.22
		N	9				
		Std. Deviation	2.73	-.21	.48	1.99	3.05
		Std. Error Mean	.91				
	WAIS Digit Span Follow-up 1	Mean	11.00	-.01	.87	9.32	12.89
		N	9				
		SD	2.69	-.24	.62	1.45	3.30
		SE Mean	.90				
	VPA Immediate Baseline	Mean	8.78	-.01	1.04	6.67	10.80
		N	9				
		SD	3.35	-.22	.55	2.50	3.72
		SE Mean	1.12				
	VPA Immediate Follow-up 1	Mean	10.44	-.03	1.24	7.89	12.67
		N	9				
		SD	4.03	-.36	1.06	1.99	5.11
		SE Mean	1.34				
	VPA Delayed Baseline	Mean	8.89	-.02	1.27	6.40	11.67
		N	9				
		SD	4.04	-.30	.68	3.17	4.33
		SE Mean	1.35				
	VPA Delayed Follow-up 1	Mean	10.67	-.03	1.23	8.22	12.89
		N	9				
		SD	4.03	-.31	.88	2.45	4.76
		SE Mean	1.34				
	Doors Baseline	Mean	9.78	-.01	.95	7.67	11.67
		N	9				
		SD	2.99	-.24	.64	1.94	3.54
		SE Mean	1.00				
	Doors Follow-up 1	Mean	10.67	-.03	1.39	8.11	13.11
		N	9				
		SD	4.36	-.39	1.05	2.57	5.20
		SE Mean	1.45				
	ROCFT Copy Baseline	Mean	34.56	-.02	.49	33.67	35.22
		N	9				
		SD	1.59	-.14	.45	.78	2.07
		SE Mean	.53				
		Mean	34.39	<.01	.71	32.72	35.78

	ROCFT Copy Follow-up 1	N	9				
		SD	2.23	-.20	.50	.88	2.66
		SE Mean	.74				
	ROCFT Immediate Baseline	Mean	24.56	-.01	1.83	20.06	28.56
		N	9				
		SD	5.80	-.48	1.24	2.87	6.77
		SE Mean	1.93				
	ROCFT Immediate Follow-up 1	Mean	25.67	-.06	3.01	20.11	30.67
		N	9				
		SD	9.51	-.69	1.54	7.24	10.26
		SE Mean	3.17				
	ROCFT Delay Baseline	Mean	22.72	<.01	2.44	17.26	28.17
		N	9				
		SD	7.74	-.57	1.34	5.70	8.58
		SE Mean	2.58				
	ROCFT Delay Follow-up 1	Mean	25.72	-.05	2.92	20.39	30.61
		N	9				
		SD	9.15	-.70	1.57	7.02	10.01
		SE Mean	3.05				
Placebo	Digit Span Baseline	Mean	10.50	.01	.90	8.90	12.30
		N	10				
		SD	2.95	-.20	.53	2.16	3.31
		SE Mean	.93				
	Digit Span Follow-up 1	Mean	10.30	<.01	.80	9.00	11.70
		N	10				
		SD	2.67	-.20	.51	1.81	3.10
		SE Mean	.84				
	VPA Immediate Baseline	Mean	8.40	-.04	.98	6.80	9.90
		N	10				
		SD	3.27	-.21	.47	2.64	3.49
		SE Mean	1.03				
	VPA Immediate Follow-up 1	Mean	10.20	-.06	1.36	7.90	12.40
		N	10				
		SD	4.57	-.30	.81	3.33	5.16
		SE Mean	1.44				
	VPA Delayed Baseline	Mean	9.50	-.04	1.06	7.80	11.20
		N	10				
		SD	3.57	-.21	.54	2.81	3.91
		SE Mean	1.13				
	VPA Delayed Follow-up 1	Mean	10.40	-.05	1.33	7.90	12.50
		N	10				
		SD	4.38	-.32	1.03	2.731	5.36
		SE Mean	1.38				
	Doors Baseline	Mean	9.60	-.03	.82	8.30	10.80
		N	10				
		SD	2.76	-.20	.51	2.01	3.10
		SE Mean	.87				
	Doors Follow-up 1	Mean	9.90	-.04	.96	8.20	11.50
		N	10				
		SD	3.18	-.21	.54	2.32	3.59
		SE Mean	1.00				
	ROCFT Copy Baseline	Mean	32.50	-.05	1.91	28.20	35.30

	N	10				
	SD	6.19	-.84	2.61	1.20	8.74
	SE Mean	1.96				
ROCFT Copy Follow-up 1	Mean	32.20	-.10	2.46	27.00	35.35
	N	10				
	SD	7.97	-1.34	3.85	1.35	11.97
	SE Mean	2.52				
ROCFT Immediate Baseline	Mean	22.65	-.06	2.89	16.44	27.65
	N	10				
	SD	9.43	-.76	2.48	4.81	12.41
	SE Mean	2.98				
ROCFT Immediate Follow-up 1	Mean	25.55	-.12	2.59	20.09	29.65
	N	10				
	SD	8.44	-.83	2.74	3.22	11.73
	SE Mean	2.67				
ROCFT Delay Baseline	Mean	21.00	-.06	2.69	15.65	25.60
	N	10				
	Std. Deviation	8.80	-.62	1.90	5.20	11.13
	Std. Error Mean	2.78				
ROCFT Delay Follow-up 1	Mean	24.35	-.10	2.6727	18.82	28.80
	N	10				
	SD	8.71	-.70	2.32276	4.29	11.47
	SE Mean	2.75				

Paired Samples Correlations

						Bootstrap for Correlation			
								BCa 95% Confidence Interval	
Group			N	Correlation	p.	Bias	Std. Error	Lower	Upper
OM	Pair 1	WAIS Digit Span B & WAIS Digit Span F1	9	.75	.020	-.02	.19	.308	.970
	Pair 2	WMS VPA Imm B & WMS VPA Imm F1	9	.30	.430	-.09	.42	-.632	.792
	Pair 3	WMS_VPAII_B & WMS_VPAII_F1	9	.45	.222	-.01	.23	-.095	.903
	Pair 4	Doors B & Doors F1	9	.79	.011	-.02	.13	.510	.955
	Pair 5	ROCFT Copy B & ROCFT Copy F1	9	.63	.071	-.05	.29	-.139	.895
	Pair 6	ROCFT Imm B & ROCFT Imm F1	9	.98	<.001	<-.01	.02	.936	.998
	Pair 7	ROCFT Delay B & ROCFT Delay F1	9	.93	<.001	-.01	.07	.746	.988
MO	Pair 1	WAIS Digit Span B & WAIS Digit Span F1	9	.89	.002	-.01	.10	.603	.981
	Pair 2	VPA Imm B & VPA Imm F1	9	.89	.001	-.02	.10	.683	.976

	Pair 3	VPA Delay B & VPA Delay F1	9	.83	.005	-.02	.13	.440	.974
	Pair 4	Doors B & Doors F1	9	.83	.006	-.04	.18	.354	.971
	Pair 5	ROCFT Copy B & ROCFT Copy F1	9	.09	.818	.10	.36	-.487	.884
	Pair 6	ROCFT Imm B & ROCFT Imm F1	9	.90	.001	-.02	.12	.763	.991
	Pair 7	ROCFT Delay B & ROCFT Delay F1	9	.85	.004	-.02	.14	.283	.985
Placebo	Pair 1	WAIS Digit Span B & WAIS Digit Span F1	10	.80	.006	.02	.10	.263	.992
	Pair 2	VPA Imm B & VPA Imm F1	10	.94	<.001	<-.01	.05	.799	.995
	Pair 3	WMS_VPAII_B & WMS_VPAII_F1	10	.85	.002	<-.01	.12	-.033	.998
	Pair 4	Doors B & Doors F1	10	.55	.097	<-.01	.20	.060	.892
	Pair 5	ROCFT Copy B & ROCFT Copy F1	10	.98	<.001	-.05	.10	.723	.999
	Pair 6	ROCFTImmediate B & ROCFTImmediate F1	10	.87	.001	-.08	.23	.234	.979
	Pair 7	ROCFT Delay B & ROCFT Delay F1	10	.92	<.001	-.03	.09	.700	.977

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	SD	SE Mean	Lower	Upper	t	df	p (2-tailed)
OM	Digit Span B Digit Span F1	-.78	2.05	.68	-2.35	.80	-1.14	8	.288
	VPA Imm. B VPA Imm F1	-2.11	2.93	.98	-4.37	.14	-2.15	8	.063
	VPA Delay B VPA Delay F1	-2.11	3.66	1.21	-4.92	.70	-1.73	8	.121
	Doors B – Doors F1	-1.67	3.08	1.03	-4.04	.70	-1.62	8	.143
	ROCFT Copy B – ROCFT Copy F1	.44	1.01	.34	-.33	1.22	1.32	8	.225
	ROCFT Imm B – ROCFT Imm F1	-.78	1.56	.52	-1.98	.42	-1.49	8	.174
	ROCFT Delay B – ROCFT Delay F1	-.56	2.67	.89	-2.61	1.50	-0.62	8	.551
MO	DigitSpan B –DigitSpan F1	-.78	1.30	.43	-1.78	.22	-1.79	8	.111
	VPA Imm B – VPA Imm F1	-1.67	1.87	.62361	-3.10	-.23	-2.67	8	.028
	VPA Delay B – VPA Delay F1	-1.78	2.33	.78	-3.57	.02	-2.29	8	.052
	Doors B – Doors_F1	-.89	2.52	.84	-2.83	1.05	-1.06	8	.321

	ROCFT Copy B – ROCFT Copy F1	.17	2.622	.87	-1.85	2.18	0.19	8	.854
	ROCFT Imm B – ROCFT Imm F1	-1.11	4.95	1.65	-4.915	2.69	-0.67	8	.520
	ROCFT Delay B – ROCFT Delay F1	-3.00	4.89	1.63	-6.76	.76	-1.84	8	.103
Placebo	DigitSpan B –DigitSpan F1	.20	1.81	.57	-1.10	1.50	0.35	9	.735
	VPA Imm B – VPA Imm F1	-1.80	1.87	.59	-3.14	-.46	-3.04	9	.014
	VPA Delay B – VPA Delay F1	-.90	2.28	.72	-2.53	.73	-1.25	9	.244
	Doors B – Doors F1	-.30	2.83	.90	-2.32	1.72	-0.34	9	.745
	ROCFT Copy B – ROCFT Copy F1	.30	2.36	.75	-1.39	1.99	0.40	9	.697
	ROCFT Imm B – ROCFT Imm F1	-2.90	4.69	1.48	-6.25	0.45	-1.96	9	.082
	ROCFT Delay B ROCFT Delay F1	-3.35	3.55	1.12	-5.89	-0.81	-2.98	9	.015

Bootstrap for Paired Samples Test

			Bootstrap				
						BCa 95% Confidence Interval	
Group		Mean	Bias	Std. Error	p. (2-tail)	Lower	Upper
OM	Digit Span B – Digit Span F1	-0.78	<-.01	0.64	.283	-2.11	0.44
	VPA Imm. B – VPA Imm. F1	-2.11	-.01	0.93	.078	-4.00	-0.44
	VPA Delay B – VPA Delay F1	-2.11	-.01	1.14	.133	-4.00	-0.11
	Doors B – Doors F1	-1.67	<-.01	0.98	.144	-3.56	0.11
	ROCFT Copy B – ROCFT Copy F1	0.44	<.01	0.31	.197	-0.11	1.11
	ROCFT Imm. – ROCFT Imm. F1	-0.78	<-.01	0.50	.197	-1.87	0.17
	ROCFT Delay B – ROCFT Delay F1	-0.56	0.01	0.86	.547	-2.61	1.28
MO	Digit Span B – Digit Span F1	-0.78	0.02	0.39	.098	-1.67	0.11
	VPA Imm. B – VPA Imm. F1	-1.67	0.02	0.57	.026	-2.78	-0.56
	VPA Delay B – VPA Delay F1	-1.78	0.01	0.73	.053	-3.44	-0.22
	Doors B – Doors F1	-0.89	0.02	0.79	.335	-2.56	0.67
	ROCFT Copy B – ROCFT Copy F1	0.17	-0.02	0.82	.837	-1.33	1.56
	ROCFT Immediate B – ROCFT Immediate F1	-1.11	0.05	1.54	.507	-4.33	2.42

	ROCFT Delay B – ROCFT Delay F1	-3.00	0.05	1.50	.112	-6.71	0.28
Placebo	Digit Span B – Digit SpanF1	.20	0.01	0.53	.726	-1.00	1.30
	WMS VPA Imm B – WMS VPA Imm F1	-1.80	0.01	0.56	.010	-2.90	-0.60
	WMS VPA Delayed B WMS VPA Delayed F1	-0.90	0.02	0.69	.277	-2.59	0.70
	Doors B – Doors F1	-0.30	<0.01	0.85	.728	-2.20	1.50
	ROCFT Copy B – ROCFT Copy F1	0.30	0.05	0.71	.742	-1.00	2.00
	ROCFT Imm. B ROCFT Imm. F1	-2.90	0.06	1.40	.103	-5.50	-0.45
	ROCFT_Delay_B ROCFT_Delay_F1	-3.35	0.04	1.05	.021	-5.40	-1.15

Paired Samples Statistics

Group			Statistic	Bootstrap Bias	Bootstrap Std. Error	Bootstrap BCa 95% Confidence Interval Lower	Bootstrap BCa 95% Confidence Interval Upper
OM	TMT Visual Scanning B	Mean	7.44	-.04	1.45	4.89	9.78
		N	9				
		SD	4.61	-.31	0.73	3.54	5.04
		SE Mean	1.54				
	TMT Visual Scanning F1	Mean	9.00	-.05	1.60	6.11	11.56
		N	9				
		SD	5.07	-.39	1.06	3.21	5.80
		SE Mean	1.69				
	TMT Number Sequencing B	Mean	9.67	-.04	1.33	6.78	12.00
		N	9				
		SD	4.24	-.37	1.12	2.40	5.13
		SE Mean	1.41				
	TMT Number Sequencing F1	Mean	9.00	-.04	1.71	5.67	12.00
		N	9				
		SD	5.52	-.38	0.94	4.12	6.06
		Std. Error Mean	1.84				
	TMT Letter Sequencing B	Mean	8.89	-.03	1.44	6.00	11.33
		N	9				
		SD	4.62	-.37	1.06	2.60	5.32
		SE Mean	1.54				
	TMT Letter Sequencing F1	Mean	10.67	-.04	1.52	7.56	13.00
		N	9				
		SD	4.74	-.49	1.46	0.87	5.83
		SE Mean	1.58				
	TMT Switching B	Mean	10.44	-.03	0.98	8.56	12.11
		N	9				
		SD	3.13	-.27	0.79	1.81	3.84
		SE Mean	1.04				
	TMT Switching F1	Mean	10.67	-.03	1.00	8.78	12.33
		N	9				
		SD	3.20	-.23	0.64	2.24	3.64
		SE Mean	1.07				
	TMT Motor Speed B	Mean	9.00	-.04	1.29	6.44	11.11
		N	9				
		SD	4.06	-.34	1.00	2.32	4.83
		SE Mean	1.35				
	Motor Speed F1	Mean	9.33	-.038	1.34	6.78	11.56
		N	9				
		SD	4.27	-.39	1.16	1.12	5.10
		SE Mean	1.42				
MO	TMT Visual Scanning B	Mean	9.56	<-.01	.89	7.78	11.33
		N	9				
		SD	2.83	-.20	.40	2.32	2.98
		SE Mean	.94				
	TMT Visual Scanning F1	Mean	10.56	.01	.94	8.82	12.00
		N	9				

		SD	2.96	-.30	.85	1.50	3.77
		SE Mean	.99				
	TMT Number Sequencing B	Mean	9.44	<-.01	.84	7.67	11.33
		N	9				
		SD	2.74	-.21	.50	2.05	3.04
		SE Mean	.91				
	TMT Number Sequencing F1	Mean	12.33	.02	.64	11.11	13.56
		N	9				
		SD	2.06	-.17	.34	1.62	2.19
		SE Mean	.69				
	TMT Letter Sequencing B	Mean	10.67	.02	.85	9.00	12.22
		N	9				
		SD	2.74	-.24	.54	1.96	3.05
		SE Mean	.91				
	TMT Letter Sequencing F1	Mean	11.00	-.02	.99	9.22	12.56
		N	9				
		SD	3.12	-.23	.68	1.96	3.76
		SE Mean	1.04				
	TMT Switching B	Mean	10.33	<.01	.94	8.56	12.03
		N	9				
		SD	2.96	-.21	.46	2.19	3.24
		SE Mean	.99				
	TMT Switching F1	Mean	11.22	<.01	.87	9.78	12.67
		N	9				
		SD	2.77	-.19	.41	2.19	2.96
		SE Mean	.92				
	Motor Speed B	Mean	11. 33	-.01	.48	10.44	12.00
		N	9				
		SD	1.50	-.15	.46	.67	1.90
		SE Mean	.50				
	TMT Motor Speed F1	Mean	12.11	.01	.29	11.78	12.56
		N	9				
		SD	.93	-.08	.24	.53	1.12
		SE Mean	.31				
Placebo	TMT Visual Scanning B	Mean	8.70	.06	1.42	4.90	12.10
		N	10				
		SD	4.69	-.36	.93	2.75	5.41
		SE Mean	1.48				
	DKEFS_TMT_VisScan_F1	Mean	8.40	.06	1.56	4.70	11.80
		N	10				
		Std. Deviation	5.21	-.34	.83	3.86	5.71
		Std. Error Mean	1.65				
	TMT Number Sequencing B	Mean	10.00	.05	1.34	6.01	13.00
		N	10				
		SD	4.37	-.37	1.00	2.79	5.09
		SE Mean	1.38				
	TMT Number Sequencing F1	Mean	10.30	.04	1.29	7.30	12.80
		N	10				
		Std. Deviation	4.30	-.38	1.12	1.87	5.38

	Std. Error Mean	1.36				
TMT Letter Sequencing B	Mean	9.70	.05	1.44	5.85	13.00
	N	10				
	SD	4.69	-.36	.88	3.36	5.24
	SE Mean	1.48				
TMT Letter Sequencing F1	Mean	9.90	.03	1.09	6.80	12.03
	N	10				
	SD	3.54	-.44	1.22	1.42	4.69
	SE Mean	1.12				
TMT Switching B	Mean	10.10	.05	1.24	6.60	12.70
	N	10				
	SD	4.07	-.37	1.05	2.45	4.92
	Std. Error Mean	1.29				
TMT Switching F1	Mean	10.40	.04	1.20	7.20	12.90
	N	10				
	SD	3.95	-.41	1.18	1.95	5.12
	SE Mean	1.25				
TMT Motor Speed B	Mean	10.10	.03	1.04	7.10	11.90
	N	10				
	SD	3.41	-.51	1.39	.99	4.62
	Std. Error Mean	1.08				
DKEFS_TMT_MotorSp_F1	Mean	9.70	.03	1.07	7.00	11.63
	N	10				
	SD	3.56	-.41	1.16	1.62	4.52
	SE Mean	1.13				

Paired Samples Statistics

Group			Statistic	Bootstrap Bias	Bootstrap Std. Error	Bootstrap BCa 95% Confidence Interval Lower	Bootstrap BCa 95% Confidence Interval Upper
OM	Colour Word Interference Naming B	Mean	8.38	-.01	1.22	5.88	10.50
		N	8				
		SD	3.58	-.40	1.07	1.51	4.50
		SE Mean	1.27				
	Colour Word Interference Naming F1	Mean	9.00	-.01	1.28	6.50	11.13
		N	8				
		SD	3.78	-.45	1.22	1.51	4.75
		SE Mean	1.34				
	Colour Word Interference Reading B	Mean	8.75	-.03	1.23	6.05	11.00
		N	8				
		SD	3.65	-.43	1.15	1.64	4.69
		SE Mean	1.29				
	Colour Word Interference Reading F1	Mean	9.75	-.02	1.30	6.75	11.88
		N	8				
		SD	3.85	-.54	1.46	1.13	5.14
		SE Mean	1.36				
	Colour Word Interference Inhibition B	Mean	8.75	-.03	1.35	5.63	11.25
		N	8				
		SD	4.03	-.38	1.04	1.81	5.01
		SE Mean	1.42				
	Colour Word Interference Inhibition F1	Mean	10.63	-.02	1.46	7.00	13.25
		N	8				
		SD	4.31	-.56	1.51	1.60	5.63
		SE Mean	1.52				
	Colour Word Interference Switching B	Mean	8.38	-.05	1.58	5.17	11.00
		N	8				
		SD	4.69	-.42	1.18	1.28	5.54
		SE Mean	1.66				
	Colour Word Interference Switching F1	Mean	10.50	-.02	1.36	6.88	12.50
		N	8				
		SD	4.04	-.67	1.73	1.16	5.22
		SE Mean	1.43				
MO	Colour Word Interference Naming B	Mean	8.44	-.01	0.73	7.33	9.44
		N	9				
		SD	2.30	-.21	0.52	1.42	2.65
		SE Mean	0.77				
	Colour Word Interference Naming F1	Mean	10.11	-.01	0.90	8.33	11.78
		N	9				
		SD	2.93	-.30	0.87	1.30	3.64
		SE Mean	.98				
	Colour Word Interference Reading B	Mean	10.00	<.01	0.69	8.56	11.33
		N	9				
		SD	2.18	-.16	0.36	1.59	2.40
		SE Mean	0.73				
	Colour Word Interference Reading F1	Mean	10.44	.01	0.66	9.33	11.78
		N	9				
		SD	2.13	-.16	0.38	1.58	2.35
		SE Mean	0.71				
		Mean	9.44	-.02	1.02	7.56	11.11

	Colour Word Interference Inhibition B	N	9				
		SD	3.24	-.28	0.76	1.90	3.94
		SE Mean	1.08				
	Colour Word Interference Inhibition F1	Mean	11.78	<-.01	0.49	10.78	12.56
		N	9				
		SD	1.56	-.21	.57	0.53	2.07
		SE Mean	0.52				
	Colour Word Interference Switching B	Mean	9.56	.01	1.31	6.44	12.11
		N	9				
		SD	4.10	-.37	1.03	2.24	5.14
		SE Mean	1.37				
	Colour Word Interference Switching F1	Mean	11.4444	.0101	.7645	10.2222	12.6667
		N	9				
		SD	2.45515	-.16050	.32686	2.10065	2.54951
		SE Mean	.81838				
Placebo	Colour Word Interference Naming B	Mean	8.67	-.02	1.28	5.56	11.44
		N	9				
		SD	4.03	-.38	1.03	2.55	4.68
		SE Mean	1.34				
	Colour Word Interference Naming F1	Mean	9.22	-.03	1.37	5.85	12.04
		N	9				
		SD	4.32	-.39	1.02	2.71	5.04
		SE Mean	1.44				
	Colour Word Interference Reading B	Mean	9.67	-.03	1.07	7.44	11.67
		N	9				
		SD	3.39	-.26	0.60	2.59	3.70
		SE Mean	1.13				
	Colour Word Interference Reading F1	Mean	10.22	-.03	1.42	6.67	12.89
		N	9				
		SD	4.49	-.43	1.19	2.54	5.39
		SE Mean	1.50				
	Colour Word Interference Inhibition B	Mean	10.33	-.02	1.25	7.22	12.67
		N	9				
		SD	4.00	-.46	1.32	1.69	5.22
		SE Mean	1.33				
	Colour Word Interference Inhibition F1	Mean	10.56	-.03	1.57	6.89	13.56
		N	9				
		SD	4.95	-.45	1.23	3.07	5.81
		SE Mean	1.65				
	Colour Word Interference Switching B	Mean	9.67	-.03	1.40	6.22	12.62
		N	9				
		SD	4.47	-.33	0.87	3.20	5.00
		SE Mean	1.49				
	Colour Word Interference Switching F1	Mean	9.44	-.03	1.72	5.35	13.00
		N	9				
		SD	5.46	-.41	1.07	4.03	6.14
		SE Mean	1.82				

Paired Samples Correlations

Group	N	Correlation	Sig.	Bootstrap for Correlation

							BCa 95% Confidence Interval	
					Bias	Std. Error	Lower	Upper
OM	Colour Word Naming B & Colour Word Naming F1	8	.99	<.001	-.01	.06	0.95	1.00
	Colour Word Reading B & Colour Word Reading F1	8	.98	<.001	-.01	.04	0.90	1.00
	Colour Word Inhibition B & Colour Word Inhibition F1	8	.67	.070	-.20	.49	-0.42	0.99
	Colour Word Switching B & Colour Word Switching F1	8	.65	.084	-.05	.32	0.03	1.00
MO	Colour Word Naming B & Colour Word Naming F1	9	.44	.240	-.06	.54	-0.71	0.99
	Colour Word Reading B & Colour Word Reading F1	9	.19	.627	.05	.44	-0.56	0.90
	Colour Word Inhibition B Colour Word Inhibition F1	9	.02	.955	.07	.39	-0.59	0.91
	Colour Word Switching B Colour Word Switching F1	9	.17	.660	.10	.45	-0.84	0.97
Placebo	Colour Word Naming B & Colour Word Naming F1	9	.97	<.001	-.02	.08	0.87	1.00
	Colour Word Reading B & Colour Word Reading F1	9	.93	<.001	<-.01	.04	0.84	0.99
	Colour Word Inhibition B & Colour Word Inhibition F1	9	.92	<.001	<.01	.06	0.80	1.00
	Colour Word Switching B & Colour Word Switching F1	9	.99	<.001	<-.01	.02	0.95	1.00

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	SD	SE Mean	Lower	Upper	t	df	p. (2-tailed)
OM	Colour Word Naming B – Colour Word Naming F1	-0.63	.52	.18	-1.06	-0.19	-3.41	7	.011
	Colour Word Reading B – Colour Word Reading F1	-1.00	.76	.27	-1.63	-0.37	-3.74	7	.007
	Colour Word Inhibition B – Colour Word Inhibition F1	-1.88	3.40	1.20	-4.72	0.97	-1.56	7	.163
	Colour Word Switching B – Colour Word Switching F1	-2.13	3.72	1.32	-5.24	0.99	-1.62	7	.150
MO	Colour Word Naming B – Colour Word Naming F1	-1.67	2.83	0.94	-3.84	0.51	-1.77	8	.115
	Colour Word Reading B – Colour Word Reading F1	-0.44	2.74	0.91	-2.55	1.66	-0.49	8	.640
	Colour Word Inhibition B – Colour Word Inhibition F1	-2.33	3.57	1.19	-5.08	0.41	-1.96	8	.086
	Colour Word Switching B – Colour Word Switching F1	-1.89	4.40	1.47	-5.27	1.49	-1.29	8	.234
Placebo	Colour Word Naming B – Colour Word Naming F1	-0.56	1.01	0.34	-1.33	0.22	-1.64	8	.139

Colour Word Reading B – Colour Word Reading F1	-0.56	1.81	0.60	-1.95	0.84	-0.92	8	.384
Colour Word Inhibition B – Colour Word Inhibition F1	-0.22	2.05	0.68	-1.80	1.35	-0.32	8	.753
Colour Word Switching B – Colour Word Switching F1	0.22	1.30	0.43	-0.78	1.22	.512	8	.622

Bootstrap for Paired Samples Test

			Bootstrap				
						BCa 95% Confidence Interval	
Group		Mean	Bias	Std. Error	p. (2-tailed)	Lower	Upper
OM	Colour Word Naming B – Colour Word Naming F1	-0.63	.01	0.16	.008	-0.88	-0.38
	Colour Word Reading B – Colour Word Reading F1	-1.00	-.01	0.25	.002	-1.25	-0.75
	Colour Word Inhibition B – Colour Word Inhibition F1	-1.88	-.01	1.17	.245	-4.38	0.00
	Colour Word Switching B - Colour Word Switching F1	-2.13	-.03	1.29	.345	-4.75	-0.38
MO	Colour Word Naming B – Colour Word Naming F1	-1.67	<-.01	0.89	.342	-3.56	-0.44
	Colour Word Reading B – Colour Word Reading F1	-0.44	-.01	0.86	.627	-2.33	1.00
	Colour Word Inhibition B – Colour Word Inhibition F1	-2.33	-.01	1.10	.103	-4.56	-0.44
	Colour Word Switching B – Colour Word Switching F1	-1.89	-.01	1.373	.380	-5.00	0.11
Placebo	Colour Word Naming B – Colour Word Naming F1	-0.56	<.01	0.33	.158	-1.00	-0.11
	Colour Word Reading B – Colour Word Reading F1	-0.56	<.01	0.58	.386	-1.33	0.33
	Colour Word Inhibition B – Colour Word Inhibition F1	-0.22	.01	0.63	.703	-1.00	0.67
	Colour Word Switching B - Colour Word Switching F1	0.22	<.01	0.41	.615	-0.44	0.89

Paired Samples Statistics

				Bootstrap			
						BCa 95% Confidence Interval	
Group			Statistic	Bias	Std. Error	Lower	Upper
OM	NEADL B	Mean	50.17	-.10	3.96	42.22	56.83
		N	9				
		SD	12.82	-.89	2.57	8.54	14.84

		SE Mean	4.27				
	NEADL F1	Mean	50.11	-.13	4.57	41.89	58.00
		N	9				
		SD	14.50	-1.06	3.16	8.71	17.94
		SE Mean	4.83				
	PANAS PA B	Mean	28.22	-.07	2.72	23.11	33.22
		N	9				
		SD	8.87	-.78	1.92	5.72	10.23
		SE Mean	2.96				
	PANAS PA F1	Mean	33.44	-.01	2.21	29.45	37.56
		N	9				
		SD	7.09	-.61	1.52	4.58	8.14
		SE Mean	2.36				
	PANAS NA B	Mean	24.00	.07	3.38	17.67	32.24
		N	9				
		SD	10.56	-1.01	3.04	5.09	13.18
		SE Mean	3.52				
	PANAS NA F1	Mean	20.5556	-.06	3.22	15.85	27.67
		N	9				
		SD	10.33	-1.76	4.49	2.42	14.16
		SE Mean	3.44				
	RME B	Mean	24.67	-.01	1.22	22.00	27.33
		N	9				
		SD	3.94	-.25	.65	2.93	4.36
		SE Mean	1.31				
	RME F1	Mean	22.78	-.06	1.69	19.33	25.78
		N	9				
		SD	5.43	-.40	1.13	3.54	6.41
		SE Mean	1.81				
MO	NEADL B	Mean	53.67	-.04	2.28	49.67	58.11
		N	9				
		SD	7.21	-.55	1.43	5.17	8.11
		SE Mean	2.40				
	NEADL F1	Mean	52.67	-.07	3.21	46.22	58.33
		N	9				
		SD	9.91	-.72	1.39	8.10	10.36
		SE Mean	3.30				
	PANAS PA B	Mean	28.67	-.12	3.70	23.22	34.56
		N	9				
		SD	11.91	-.88	2.05	8.94	13.07
		SE Mean	3.97				
	PANAS PA F1	Mean	32.11	-.08	3.44	26.11	37.56
		N	9				
		SD	10.84	-.83	2.21	7.26	12.38
		SE Mean	3.61				
	PANAS NA B	Mean	20.89	.01	2.29	16.56	25.67
		N	9				
		SD	7.24	-.55	1.41	4.95	8.25
		SE Mean	2.41				
	PANAS NA F1	Mean	23.72	.02	2.88	17.22	29.95
		N	9				
		SD	9.33	-.64	1.69	6.88	10.48

		SE Mean	3.11				
	RME B	Mean	23.22	.01	1.36	20.00	26.00
		N	9				
		SD	4.27	-.31	.71	3.24	4.69
		SE Mean	1.42				
	RME F1	Mean	24.22	-.02	1.79	19.00	28.44
		N	9				
		SD	5.70	-.43	1.06	4.07	6.42
		SE Mean	1.90				
Placebo	NEADL B	Mean	48.90	.08	5.16	37.93	58.56
		N	10				
		SD	17.48	-1.54	4.09	10.91	20.47
		SE Mean	5.53				
	NEADL F1	Mean	51.10	.04	5.75	37.85	61.70
		N	10				
		SD	19.40	-1.90	5.44	5.05	23.66
		SE Mean	6.14				
	PANAS PA B	Mean	30.90	.04	2.58	24.28	37.00
		N	10				
		SD	8.72	-.88	2.23	4.89	10.49
		SE Mean	2.76				
	PANAS PA F1	Mean	31.90	.10	2.11	26.90	36.00
		N	10				
		SD	7.26	-.77	2.06	3.86	9.00
		SE Mean	2.30				
	PANAS NA B	Mean	19.30	.03	1.55	16.40	22.29
		N	10				
		SD	5.19	-.36	1.06	3.63	5.97
		SE Mean	1.64				
	PANAS NA F1	Mean	18.90	-.10	2.28	15.40	22.80
		N	10				
		SD	7.56	-.83	2.16	4.22	9.08
		SE Mean	2.39				
	RME B	Mean	23.30	.01	1.82	20.10	26.30
		N	10				
		SD	5.89	-.38	1.03	4.30	6.72
		SE Mean	1.86				
	RME F1	Mean	24.30	-.02	1.87	20.40	27.80
		N	10				
		SD	6.06	-.41	1.08	4.17	6.92
		SE Mean	1.92				

Paired Samples Correlations

					Bootstrap for Correlation			
							BCa 95% Confidence Interval	
Group		N	Correlation	p.	Bias	Std. Error	Lower	Upper
OM	NEADL B & NEADL F1	9	.81	.008	-.04	.21	0.25	0.99
	PANAS PA B & PANAS PA F1	9	.62	.072	-.08	.31	-0.07	0.90
	PANAS NA B & PANAS NA F1	9	.23	.549	-.07	.52	-0.68	0.92

	RME B & RME F1	9	.76	.017	-.02	.16	0.09	0.97
MO	NEADL B & NEADL F1	9	.46	.215	.01	.30	-0.23	0.93
	PANAS PA B & PANAS PA F1	9	.67	.050	-.03	.24	0.09	0.97
	PANAS_NA_B & PANAS_NA_F1	9	.85	.004	-.02	.13	0.52	0.97
	RME B & RME F1	9	.67	.048	-.04	.25	-0.07	0.93
Placebo	NEADL B & NEADL F1	10	.95	<.001	-.01	.06	0.76	1.00
	PANAS PA B & PANAS PA F1	10	.65	.041	-.13	.42	-0.42	0.96
	PANAS NA B & PANAS NA F1	10	-.01	.977	.02	.39	-0.70	0.65
	RME B & RME F1	10	.91	<.001	-.02	.11	0.64	0.99

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	SD	SE Mean	Lower	Upper	t	df	Sig. (2-tailed)
OM	NEADL B – NEADL F1	0.06	8.58	2.86	-6.54	6.65	0.02	8	.985
	PANAS PA B – PANAS PA F1	-5.22	7.10	2.37	-10.68	0.24	-2.21	8	.058
	PANAS NA B – PANAS NA F1	3.44	12.95	4.32	-6.51	13.40	0.80	8	.448
	RME B – RME F1	1.89	3.52	1.17	-0.81	4.59	1.61	8	.146
MO	NEADL B – NEADL F1	1.00	9.21	3.07	-6.08	8.08	0.33	8	.753
	PANAS PA B – PANAS PA F1	-3.44	9.36	3.12	-10.64	3.74	-1.11	8	.301
	PANAS NA B – PANAS NA F1	-2.83	5.04	1.68	-6.71	1.04	-1.69	8	.130
	RME B – RME F1	-1.00	4.24	1.41	-4.26	2.26	-0.71	8	.500
Placebo	NEADL B – NEADL F1	-2.20	5.92	1.87	-6.44	2.04	-1.18	9	.270
	PANAS PA B – PANAS PA F1	-1.00	6.80	2.15	-5.86	3.86	-0.47	9	.653
	PANAS NA B – PANAS NA F1	0.40	9.22	2.91	-6.19	6.99	0.14	9	.894
	RME B – RME F1	-1.00	2.49	0.79	-2.78	0.78	-1.27	9	.237

Bootstrap for Paired Samples Test

		Bootstrap				
					Sig. (2-tailed)	BCa 95% Confidence Interval
Group	Mean	Bias	Std. Error			

						Lower	Upper
OM	NEADL B – NEADL F1	0.06	.03	2.66	.986	-4.67	5.80
	PANAS PA B – PANAS PA F1	-5.22	-.06	2.22	.059	-9.91	-1.00
	PANAS NA B – PANAS NA F1	3.44	.13	4.15	.488	-3.78	12.93
	RME B – RME F1	1.89	.05	1.09	.137	-0.22	4.00
MO	NEADL B – NEADL F1	1.00	.03	2.96	.752	-4.45	7.33
	PANAS PA B – PANAS PA F1	-3.44	-.03	2.90	.304	-10.67	2.31
	PANAS NA B – PANAS NA F1	-2.83	-.01	1.58	.128	-5.56	0.00
	RME B – RME F1	-1.00	.03	1.34	.474	-3.56	1.67
Placebo	NEADL B – NEADL F1	-2.20	.03	1.79	.283	-5.40	1.05
	PANAS PA B – PANAS PA F1	-1.00	-.07	2.05	.681	-4.40	3.40
	PANAS NA B – PANAS NA F1	0.40	.13	2.78	.894	-4.90	5.30
	RME_B - RME_F1	-1.00	.02	0.74	.245	-2.40	0.30

Paired Samples Statistics

				Bootstrap			
						BCa 95% Confidence Interval	
Group			Statistic	Bias	Std. Error	Lower	Upper
OM	Symbol Search B	Mean	9.57	.03	.52	8.71	10.43
		N	7				
		SD	1.51	-.15	.34	0.98	1.80
		SE Mean	.57				
	Symbol Search F1	Mean	11.86	.02	.67	11.00	12.71
		N	7				
		SD	1.95	-.20	.45	1.51	2.14
		SE Mean	.74				
	SRT Explicit B	Mean	3.36	<-.01	1.07	2.07	4.93
		N	7				
		SD	3.06	-.32	0.71	1.93	3.52
		SE Mean	1.16				

	SRT Explicit F1	Mean	7.03	.06	1.33	4.29	10.20
		N	7				
		SD	3.85	-.40	0.96	2.10	4.68
		SE Mean	1.45				
	SRT Implicit B	Mean	34.51	.19	15.51	1.5389	72.7364
		N	7				
		SD	44.69	-4.23	10.29	29.83	50.72
		SE Mean	16.89				
	SRT Implicit F1	Mean	38.90	.49	17.21	5.05	78.91
		N	7				
		SD	48.50	-5.04	13.53	19.55	63.94
		SE Mean	18.33				
MO	Symbol Search B	Mean	8.89	<.01	.51	7.78	10.11
		N	9				
		SD	1.62	-.13	.35	1.01	1.92
		SE Mean	.54				
	Symbol Search F1	Mean	11.00	.01	1.02	9.00	13.11
		N	9				
		SD	3.24	-.24	.56	2.26	3.71
		SE Mean	1.08				
	SRT Explicit B	Mean	7.33	.05	1.57	4.22	11.11
		N	9				
		SD	4.92	-.39	.98	3.55	5.51
		SE Mean	1.64				
	SRT Explicit F1	Mean	8.83	-.01	1.69	6.51	11.44
		N	9				
		SD	5.32	-.59	1.68	2.49	6.67
		SE Mean	1.77				
	SRT Implicit B	Mean	76.57	.24	29.16	26.66	135.45
		N	9				
		SD	90.43	-8.72	22.20	52.15	104.81
		SE Mean	30.14				
	SRT Implicit F1	Mean	21.76	.01	24.87	-22.04	63.66
		N	9				
		SD	79.37	-5.57	13.05	60.29	86.71
		SE Mean	26.46				
Placebo	Symbol Search B	Mean	8.60	-.02	1.01	6.90	10.10
		N	10				
		SD	3.31	-.29	.89	1.43	4.77
		SE Mean	1.05				
	Symbol Search F1	Mean	9.90	-.02	1.41	7.70	12.10
		N	10				
		SD	4.75	-.36	1.03	2.86	5.85
		SE Mean	1.50				
	SRT Explicit B	Mean	6.50	-.01	1.09	4.70	8.50
		N	10				
		SD	3.72	-.27	.82	2.37	4.52
		SE Mean	1.18				
	SRT Explicit F1	Mean	8.65	<.01	1.38	6.65	10.85
		N	10				
		SD	4.61	-.31	.82	3.25	5.25

		SE Mean	1.46				
	SRT Implicit B	Mean	28.64	.04	20.27	-20.40	66.01
		N	10				
		SD	66.21	-6.62	19.21	20.50	79.91
		SE Mean	20.94				
	SRT Implicit F1	Mean	79.82	1.16	42.84	-0.34	188.50
		N	10				
		SD	137.80	-13.03	38.42	54.50	171.05
		SE Mean	43.58				

Paired Samples Correlations

					Bootstrap for Correlation			
							BCa 95% Confidence Interval	
Group		N	Correlation	p.	Bias	Std. Error	Lower	Upper
OM	Symbol Search B Symbol Search F1	7	.71	.074	-.06	.29	-0.07	0.96
	SRT Explicit B & SRT Explicit F1	7	.50	.252	-.01	.28	-0.85	1.00
	SRT Implicit B SRT Implicit F1	7	-.48	.271	.01	.37	-0.98	0.55
MO	Symbol Search B Symbol Search F1	9	.50	.169	-.02	.30	-0.24	0.95
	SRT Explicit B & SRT Explicit F1	9	.26	.495	-.07	.38	-0.41	0.76
	SRT Implicit B & SRT Implicit F1	9	-.58	.103	.07	.33	-0.92	0.55
Placebo	Symbol Search B Symbol Search F1	10	.86	.001	.02	.08	.	.
	SRT Explicit B & SRT Explicit F1	10	.11	.758	.03	.40	-0.72	0.92
	SRT Implicit B & SRT Implicit F1	10	-.46	.179	.15	.49	-0.95	0.67

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	SD	SE Mean	Lower	Upper	t	df	p. (2-tailed)

OM	Symbol Search B – Symbol Search F1	-2.29	1.38	0.52	-3.56	-1.01	-4.38	6	.005
	SRT Explicit B – SRT Explicit F1	-3.67	3.52	1.33	-6.93	-0.42	-2.76	6	.033
	SRT Implicit B – SRT Implicit F1	-4.39	80.30	30.35	-78.66	69.87	-0.15	6	.890
MO	Symbol Search B – Symbol Search F1	-2.11	2.80	0.93	-4.27	0.04	-2.26	8	.054
	SRT Explicit B – SRT Explicit F1	-1.50	6.22	2.07	-6.28	3.28	-0.72	8	.490
	SRT Implicit B – SRT Implicit F1	54.81	150.90	50.30	-61.19	170.80	1.09	8	.308
Placebo	Symbol Search B - Symbol Search F1	-1.30	2.54	0.80	-3.12	0.52	-1.62	9	.140
	SRT Explicit B – SRT Explicit F1	-2.15	5.59	1.77	-6.15	1.85	-1.22	9	.255
	SRT Implicit B – SRT Implicit F1	-51.18	178.35	56.40	-178.76	76.40	-0.91	9	.388

Bootstrap for Paired Samples Test

			Bootstrap				
						BCa 95% Confidence Interval	
Group		Mean	Bias	Std. Error	p. (2-tailed)	Lower	Upper
OM	Symbol Search B – Symbol Search F1	-2.29	.01	0.49	.004	-3.14	-1.14
	SRT Explicit B – SRT Explicit F1	-3.67	-.07	1.22	.042	-5.63	-1.89
	SRT Implicit B – SRT Implicit F1	-4.39	-.30	28.08	.906	-49.10	41.99
MO	Symbol Search B Symbol Search F1	-2.11	-.01	0.87	.061	-3.67	-0.78
	SRT Explicit B – SRT Explicit F1	-1.50	.05	1.93	.470	-5.50	3.33
	SRT Implicit B – SRT Implicit F1	54.81	.23	48.03	.318	-28.78	153.21
Placebo	Symbol Search B – Symbol Search F1	-1.30	<.01	0.74	.283	-3.30	0.00
	SRT Explicit B – SRT Explicit F1	-2.15	-.01	1.66	.266	-7.12	1.45
	SRT Implicit B – SRT Implicit F1	-51.180	-1.07	55.57	.421	-168.23	32.63

E.12 Non-parametric analyses (Wilcoxon Signed Ranks) Period 1

Ranks

Group			N	Mean Rank	Sum of Ranks
MO	Digit Span F1 – Digit Span B	Negative Ranks	2	3.50	7.00
		Positive Ranks	6	4.83	29.00
		Ties	1		
		Total	9		
	Symbol Search F1 – Symbol Search B	Negative Ranks	2	2.00	4.00
		Positive Ranks	6	5.33	32.00
		Ties	1		
		Total	9		
OM	Digit Span F1 – Digit Span B	Negative Ranks	2	2.75	5.50
		Positive Ranks	4	3.88	15.50
		Ties	3		
		Total	9		
	Symbol Search F1 – Symbol Search B	Negative Ranks	2	5.00	10.00
		Positive Ranks	6	4.33	26.00
		Ties	1		
		Total	9		
Placebo	Digit Span F1 – Digit Span B	Negative Ranks	5	4.10	20.50
		Positive Ranks	3	5.17	15.50
		Ties	2		
		Total	10		
	Symbol Search F1 – Symbol Search B	Negative Ranks	1	2.00	2.00
		Positive Ranks	5	3.80	19.00
		Ties	4		
		Total	10		

Test Statistics

Group		Digit Span F1 – Digit Span B	Symbol Search F1 - Symbol Search B
MO	Z	-1.61	-2.00
	Asymp. Sig. (2-tailed)	.107	.046
OM	Z	-1.06	-1.16
	Asymp. Sig. (2-tailed)	.288	.248
Placebo	Z	-0.36	-1.81
	Asymp. Sig. (2-tailed)	.722	.071

Ranks

Group			N	Mean Rank	Sum of Ranks
MO	Verbal Paired Associates Immediate F1 – Verbal Paired Associates Immediate B	Negative Ranks	2	2.50	5.00
		Positive Ranks	7	5.71	40.00
		Ties	0		
		Total	9		
	Verbal Paired Associates Delayed F1 – Verbal Paired Associates Delayed B	Negative Ranks	2	2.00	4.00
		Positive Ranks	6	5.33	32.00
		Ties	1		
		Total	9		

OM	Verbal Paired Associates Immediate F1 – Verbal Paired Associates Immediate B	Negative Ranks	2	2.50	5.00
		Positive Ranks	6	5.17	31.00
		Ties	1		
		Total	9		
	Verbal Paired Associates Delayed F1 – Verbal Paired Associates Delayed B	Negative Ranks	2	3.50	7.00
		Positive Ranks	6	4.83	29.00
		Ties	1		
		Total	9		
Placebo	Verbal Paired Associates Immediate F1 – Verbal Paired Associates Immediate B	Negative Ranks	1	5.50	5.50
		Positive Ranks	9	5.50	49.50
		Ties	0		
		Total	10		
	Verbal Paired Associates Delayed F1 – Verbal Paired Associates Delayed B	Negative Ranks	1	5.00	5.00
		Positive Ranks	5	3.20	16.00
		Ties	4		
		Total	10		

Group		VPA Immediate F1 – VPA Immediate B	VPA Delayed F1 – VPA Delayed B
MO	Z	-2.10	-1.97
	Asymp. Sig. (2-tailed)	.036	.049
OM	Z	-1.84	-1.55
	Asymp. Sig. (2-tailed)	.065	.121
Placebo	Z	-2.27	-1.16
	Asymp. Sig. (2-tailed)	.024	.246

Ranks

Group			N	Mean Rank	Sum of Ranks
MO	Doors F1 – Doors B	Negative Ranks	2	3.00	6.00
		Positive Ranks	4	3.75	15.00
		Ties	3		
		Total	9		
OM	Doors F1 – Doors B	Negative Ranks	2	3.00	6.00
		Positive Ranks	5	4.40	22.00
		Ties	2		
		Total	9		
Placebo	Doors F1 – Doors B	Negative Ranks	4	3.88	15.50
		Positive Ranks	4	5.13	20.50
		Ties	2		
		Total	10		

Test Statistics

Group		Doors F1 – Doors B
MO	Z	-0.95
	Asymp. Sig. (2-tailed)	.340
OM	Z	-1.364
	Asymp. Sig. (2-tailed)	.172
Placebo	Z	-0.35

Asymp. Sig. (2-tailed)			.725		

Ranks

Group			N	Mean Rank	Sum of Ranks
MO	Trial Making Visual Scanning F1 – Trail Making Visual Scanning B	Negative Ranks	1	2.00	2.00
		Positive Ranks	3	2.67	8.00
		Ties	5		
		Total	9		
	Trail Making Number Sequence F1 – Trail Making Number SequenceB	Negative Ranks	0	.00	.00
		Positive Ranks	7	4.00	28.00
		Ties	2		
		Total	9		
	Trail Making Letter Sequencing F1 – Trail Making Letter Sequencing B	Negative Ranks	2	5.50	11.00
		Positive Ranks	6	4.17	25.00
		Ties	1		
		Total	9		
	Trail Making Switching F1 – Trail Making Switching B	Negative Ranks	1	3.00	3.00
		Positive Ranks	6	4.17	25.00
		Ties	2		
		Total	9		
	Trail Making Motor Speed F1 – Trail Making Motor Speed B	Negative Ranks	1	1.50	1.50
		Positive Ranks	3	2.83	8.50
		Ties	5		
		Total	9		
OM	Trail Making Visual Scanning F1 – Trail Making Visual Scanning B	Negative Ranks	0	.00	.00
		Positive Ranks	4	2.50	10.00
		Ties	5		
		Total	9		
	Trail Making Number Sequence F1 – Trail Making Number Sequence B	Negative Ranks	3	4.17	12.50
		Positive Ranks	3	2.83	8.50
		Ties	3		
		Total	9		
	Trail Making Letter Sequence F1 – Trail Making Letter Sequence B	Negative Ranks	1	5.50	5.50
		Positive Ranks	6	3.75	22.50
		Ties	2		
		Total	9		
	Trail Making Switching F1 – Trail Making Switching B	Negative Ranks	2	2.50	5.00
		Positive Ranks	3	3.33	10.00
		Ties	4		
		Total	9		
	Trail Making Motor Speed F1 – Trail Making Motor Speed B	Negative Ranks	2	5.50	11.00
		Positive Ranks	5	3.40	17.00
		Ties	2		
		Total	9		
Placebo	Trail Making Visual Scanning F1 –	Negative Ranks	3	4.00	12.00
		Positive Ranks	3	3.00	9.00

Trail Making Visual Scanning B	Ties	4		
	Total	10		
Trail Making Number Sequence F1 – Trail Making Number Sequence B	Negative Ranks	3	4.83	14.50
	Positive Ranks	5	4.30	21.50
	Ties	2		
	Total	10		
Trail Making Letter Sequencing F1 – Trail Making Letter Sequencing B	Negative Ranks	4	2.50	10.00
	Positive Ranks	2	5.50	11.00
	Ties	4		
	Total	10		
Trail Making Switching F1 – Trail Making Switching B	Negative Ranks	3	4.83	14.50
	Positive Ranks	5	4.30	21.50
	Ties	2		
	Total	10		
Trail Making Motor Speed F1 – Trail Making Motor Speed B	Negative Ranks	3	2.83	8.50
	Positive Ranks	1	1.50	1.50
	Ties	6		
	Total	10		

Test Statistics

Group		TMT Vis. Scan F1 – TMT Vis. Scan B	TMT Num. Seq F1 – TMT Num. Seq B	TMT_Lett. Seq F1 – TMT Lett. Seq B	TMT Switch F1 – TMT Switch B	TMT Motor Sp. F1 – TMT Motor Sp. B
MO	Z	-1.10	-2.38	-1.01	-1.93	-1.29
	Asymp. Sig. (2-tailed)	.273	.017	.315	.054	.197
OM	Z	-1.84	-0.43	-1.47	-0.71	-0.52
	Asymp. Sig. (2-tailed)	.066	.671	.143	.480	.605
Placebo	Z	-0.32	-0.49	-0.11	-0.50	-1.30
	Asymp. Sig. (2-tailed)	.750	.622	.916	.620	.194

Ranks

Group			N	Mean Rank	Sum of Ranks
MO	Verbal Fluency Letters F1 Verbal Fluency Letters B	Negative Ranks	4	3.50	14.00
		Positive Ranks	4	5.50	22.00
		Ties	1		
		Total	9		
	Verbal Fluency Categories F1 – Verbal Fluency Categories B	Negative Ranks	4	5.00	20.00
		Positive Ranks	5	5.00	25.00
		Ties	0		
		Total	9		
	Verbal Fluency Switching F1 – Verbal Fluency Switching B	Negative Ranks	6	4.42	26.50
		Positive Ranks	1	1.50	1.50
		Ties	2		
		Total	9		

OM	Verbal Fluency Letters F1 – Verbal Fluency Letters B	Negative Ranks	2	7.25	14.50
		Positive Ranks	6	3.58	21.50
		Ties	1		
		Total	9		
	Verbal Fluency Categories F1 – Verbal Fluency Categories B	Negative Ranks	4	5.50	22.00
		Positive Ranks	5	4.60	23.00
		Ties	0		
		Total	9		
	Verbal Fluency Switching F1 – Verbal Fluency Switching B	Negative Ranks	5	3.90	19.50
		Positive Ranks	2	4.25	8.50
		Ties	2		
		Total	9		
Placebo	Verbal Fluency Letters F1 – Verbal Fluency Letters B	Negative Ranks	5	3.90	19.50
		Positive Ranks	3	5.50	16.50
		Ties	2		
		Total	10		
	Verbal Fluency Categories F1 – Verbal Fluency Categories B	Negative Ranks	6	4.25	25.50
		Positive Ranks	2	5.25	10.50
		Ties	2		
		Total	10		
	Verbal Fluency Switching F1 – Verbal Fluency Switching B	Negative Ranks	4	4.88	19.50
		Positive Ranks	4	4.13	16.50
		Ties	2		
		Total	10		

Test Statistics

Group		Verbal Fluency Letters F1 – Verbal Fluency Letters B	Verbal Fluency Categories F1 – Verbal Fluency Categories B	Verbal Fluency Switching F1 – Verbal Fluency Switching B
MO	Z	-0.57	-0.30	-2.13
	Asymp. Sig. (2-tailed)	.572	.766	.033
OM	Z	-0.49	-0.06	-0.95
	Asymp. Sig. (2-tailed)	.621	.953	.344
Placebo	Z	-0.21	-1.06	-0.21
	Asymp. Sig. (2-tailed)	.831	.291	.832

Ranks

Group			N	Mean Rank	Sum of Ranks
MO	Colour Word Naming F1 – Colour Word Naming B	Negative Ranks	0	.00	.00
		Positive Ranks	6	3.50	21.00
		Ties	3		
		Total	9		
	Colour Word Reading F1 - CWIT Reading B	Negative Ranks	4	4.75	19.00
		Positive Ranks	4	4.25	17.00
		Ties	1		
		Total	9		

	Colour Word Inhibition F1 – Colour Word Inhibition B	Negative Ranks	2	2.50	5.00
		Positive Ranks	6	5.17	31.00
		Ties	1		
		Total	9		
	Colour Word Switching F1 - Colour Word Switching B	Negative Ranks	2	3.00	6.00
		Positive Ranks	5	4.40	22.00
		Ties	2		
		Total	9		
OM	Colour Word Naming F1 - Colour Word Naming B	Negative Ranks	0	.00	.00
		Positive Ranks	5	3.00	15.00
		Ties	4		
		Total	9		
	Colour Word Reading F1 – Colour Word Reading B	Negative Ranks	0	.00	.00
		Positive Ranks	6	3.50	21.00
		Ties	3		
		Total	9		
	Colour Word Inhibition F1 – Colour Word Inhibition B	Negative Ranks	1	2.00	2.00
		Positive Ranks	4	3.25	13.00
		Ties	3		
		Total	8		
	Colour Word Switching F1 – Colour Word Switching B	Negative Ranks	0	.00	.00
		Positive Ranks	5	3.00	15.00
		Ties	3		
		Total	8		
Placebo	Colour Word Naming F1 – Colour Word Naming B	Negative Ranks	1	2.00	2.00
		Positive Ranks	4	3.25	13.00
		Ties	5		
		Total	10		
	Colour Word Reading F1 – Colour Word Reading B	Negative Ranks	2	4.25	8.50
		Positive Ranks	5	3.90	19.50
		Ties	2		
		Total	9		
	Colour Word Inhibition F1 – Colour Word Inhibition B	Negative Ranks	1	7.00	7.00
		Positive Ranks	6	3.50	21.00
		Ties	2		
		Total	9		
	Colour Word Switching F1 – Colour Word Switching B	Negative Ranks	3	4.00	12.00
		Positive Ranks	3	3.00	9.00
		Ties	3		
		Total	9		

Test Statistic

Group		Colour Word Naming F1 – Colour Word Naming B	Colour Word Reading F1 – Colour Word Reading B	Colour Word Inhibition F1 – Colour Word Inhibition B	Colour Word Switching F1 – Colour Word Switching B
MO	Z	-2.26	-0.14	-1.83	-1.38
	Asymp. Sig. (2-tailed)	.024	.886	.068	.168
OM	Z	-2.24	-2.27	-1.51	-2.06

	Asymp. Sig. (2-tailed)	.025	.023	.131	.039
Placebo	Z	-1.52	-0.94	-1.23	-0.33
	Asymp. Sig. (2-tailed)	.129	.347	.219	.739

Ranks

Group			N	Mean Rank	Sum of Ranks
MO	ROCFT Copy F1 – ROCFT Copy B	Negative Ranks	2	2.50	5.00
		Positive Ranks	2	2.50	5.00
		Ties	5		
		Total	9		
	ROCFT Immediate F1 – ROCFT Immediate B	Negative Ranks	4	3.88	15.50
		Positive Ranks	5	5.90	29.50
		Ties	0		
		Total	9		
	ROCFT Delay F1 – ROCFT Delay B	Negative Ranks	3	2.67	8.00
		Positive Ranks	6	6.17	37.00
		Ties	0		
		Total	9		
OM	ROCFT Copy F1 – ROCFT Copy B	Negative Ranks	3	2.83	8.50
		Positive Ranks	1	1.50	1.50
		Ties	5		
		Total	9		
	ROCFT Immediate F1 – ROCFT Immediate B	Negative Ranks	2	4.50	9.00
		Positive Ranks	6	4.50	27.00
		Ties	1		
		Total	9		
	ROCFT Delay F1 – ROCFT Delay B	Negative Ranks	4	3.50	14.00
		Positive Ranks	4	5.50	22.00
		Ties	1		
		Total	9		
Placebo	ROCFT Copy F1 – ROCFT Copy B	Negative Ranks	3	2.67	8.00
		Positive Ranks	2	3.50	7.00
		Ties	5		
		Total	10		
	ROCFT Immediate F1 – ROCFT Immediate B	Negative Ranks	3	2.33	7.00
		Positive Ranks	6	6.33	38.00
		Ties	1		
		Total	10		
	ROCFT Delay F1 – ROCFT Delay B	Negative Ranks	2	1.50	3.00
		Positive Ranks	7	6.00	42.00
		Ties	1		
		Total	10		

Test Statistics

Group		ROCFT Copy F1 – ROCFT Copy B	ROCFT ImmediateF1 – ROCFT Immediate B	ROCFT Delay F1 – ROCFT Delay B
MO	Z	0.00	-0.83	-1.72
	Asymp. Sig. (2-tailed)	1.000	.406	.085
OM	Z	-1.30	-1.27	-0.56

	Asymp. Sig. (2-tailed)	.194	.205	.575
Placebo	Z	-0.14	-1.84	-2.31
	Asymp. Sig. (2-tailed)	.892	.066	.021

Ranks

Group			N	Mean Rank	Sum of Ranks
MO	RME F1 – RME B	Negative Ranks	3	6.17	18.50
		Positive Ranks	6	4.42	26.50
		Ties	0		
		Total	9		
	SRT Explicit F1 – SRT Explicit B	Negative Ranks	3	5.33	16.00
		Positive Ranks	6	4.83	29.00
		Ties	0		
		Total	9		
	SRT Implicit F1 – SRT Implicit B	Negative Ranks	5	5.40	27.00
		Positive Ranks	4	4.50	18.00
		Ties	0		
		Total	9		
OM	RME F1 – RME B	Negative Ranks	5	5.70	28.50
		Positive Ranks	3	2.50	7.50
		Ties	1		
		Total	9		
	SRT Explicit F1 – SRT Explicit B	Negative Ranks	1	1.00	1.00
		Positive Ranks	5	4.00	20.00
		Ties	1		
		Total	7		
	SRT Implicit F1 – SRT Implicit B	Negative Ranks	4	3.50	14.00
		Positive Ranks	3	4.67	14.00
		Ties	0		
		Total	7		
Placebo	RME F1 – RME B	Negative Ranks	2	4.00	8.00
		Positive Ranks	5	4.00	20.00
		Ties	3		
		Total	10		
	SRT Explicit F1 – SRT Explicit B	Negative Ranks	4	5.50	22.00
		Positive Ranks	6	5.50	33.00
		Ties	0		
		Total	10		
	SRT Implicit F1 – SRT Implicit B	Negative Ranks	5	5.00	25.00
		Positive Ranks	5	6.00	30.00
		Ties	0		
		Total	10		

Test Statistics

Group		RME F1 – RME B	SRT Explicit F1 – SRT Explicit B	SRT Implicit F1 – SRT Implicit B
MO	Z	-0.48	-0.77	-0.53
	Asymp. Sig. (2-tailed)	.634	.439	.594
OM	Z	-1.47	-1.99	0.00
	Asymp. Sig. (2-tailed)	.141	.046	1.000
Placebo	Z	-1.02	-0.56	-0.26

Asymp. Sig. (2-tailed)	.306	.574	.799

Ranks

Group			N	Mean Rank	Sum of Ranks
MO	NEADL F1 – NEADL B	Negative Ranks	4	5.75	23.00
		Positive Ranks	5	4.40	22.00
		Ties	0		
		Total	9		
	PANAS PA F1 – PANAS PA B	Negative Ranks	3	3.17	9.50
		Positive Ranks	4	4.63	18.50
		Ties	2		
		Total	9		
	PANAS NA F1 – PANAS NA B	Negative Ranks	3	3.50	10.50
		Positive Ranks	6	5.75	34.50
		Ties	0		
		Total	9		
OM	NEADL F1 – NEADL B	Negative Ranks	3	4.83	14.50
		Positive Ranks	5	4.30	21.50
		Ties	1		
		Total	9		
	PANAS PA F1 – PANAS PA B	Negative Ranks	2	3.50	7.00
		Positive Ranks	7	5.43	38.00
		Ties	0		
		Total	9		
	PANAS NA F1 – PANAS NA B	Negative Ranks	4	6.63	26.50
		Positive Ranks	5	3.70	18.50
		Ties	0		
		Total	9		
Placebo	NEADL F1 – NEADL B	Negative Ranks	3	3.00	9.00
		Positive Ranks	5	5.40	27.00
		Ties	2		
		Total	10		
	PANAS PA F1 – PANAS PA B	Negative Ranks	3	5.00	15.00
		Positive Ranks	7	5.71	40.00
		Ties	0		
		Total	10		
	PANAS NA F1 – PANAS NA B	Negative Ranks	7	4.64	32.50
		Positive Ranks	3	7.50	22.50
		Ties	0		
		Total	10		

Test Statistics[a]

Group		NEADL F1 – NEADL B	PANAS PA F1 – PANAS PA B	PANAS NA F1 – PANAS NA B
MO	Z	-0.06	-0.76	-1.42
	Asymp. Sig. (2-tailed)	.953	.446	.154
OM	Z	-0.49	-1.84	-0.48
	Asymp. Sig. (2-tailed)	.623	.065	.635
Placebo	Z	-1.26	-1.28	-0.51
	Asymp. Sig. (2-tailed)	.207	.201	.609

E.13 Analyses of Treatment Effects (standard and bootstrapped t-tests) Period 2

Memory

Paired Samples Statistics

				Bootstrap[b]			
						BCa 95% Confidence Interval	
Group			Statistic	Bias	Std. Error	Lower	Upper
OM	Digit Span Follow-up 1 (F1)	Mean	8.33	.01	.97	6.62	10.00
		N	9				
		SD	3.08	-.21	.41	2.60	3.18
		SE Mean	1.03				
	Digit Span Follow-up 2 (F2)	Mean	8.44	.01	1.05	6.56	10.22
		N	9				
		SD	3.43	-.28	.71	2.29	3.96
		SE Mean	1.14				
	Verbal Paired Associates Immediate F1	Mean	10.33	.02	.95	8.56	12.00
		N	9				
		SD	3.00	-.22	.45	2.50	3.10
		SE Mean	1.00				
	Verbal Paired Associates Immediate F2	Mean	10.11	.03	1.04	8.33	11.89
		N	9				
		SD	3.26	-.26	.58	2.49	3.54
		SE Mean	1.0				
	Verbal Paired Associates Delayed F1	Mean	10.11	.03	1.28	7.78	12.33
		N	9				
		SD	4.01	-.33	.77	2.86	4.44
		SE Mean	1.34				
	Verbal Paired Associates F2	Mean	9.44	.02	1.11	7.56	11.33
		N	9				
		SD	3.47	-.27	.60	2.69	3.71
		SE Mean	1.16				
	Rey Osterreith Figure (ROCFT) Copy F1	Mean	34.78	-.02	.41	34.11	35.33
		N	9				
		SD	1.30	-.11	.34	.60	1.73
		SE Mean	.43				
	Rey Osterreith Figure (ROCFT) Copy F2	Mean	34.78	-.01	.38	34.1111	35.3333
		N	9				
		SD	1.21	-.09	.21	0.87	1.32
		SE Mean	.40				
	ROCFT Immediate Recall F1	Mean	24.50	.05	2.06	20.33	28.39
		N	9				
		SD	6.54	-.56	1.48	4.09	7.73
		SE Mean	2.18				
	ROCFT Immediate Recall F2	Mean	23.33	.02	2.27	18.80	27.28
		N	9				
		SD	7.34	-.65	1.71	3.20	8.56
		SE Mean	2.45				
		Mean	23.50	.04	2.18	19.50	27.25

	ROCFT Delayed Recall F1	N	9				
		SD	6.97	-.66	1.76	4.53	8.13
		SE Mean	2.32				
	ROCFT Delayed Recall F2	Mean	24.56	-.01	2.12	20.72	27.89
		N	9				
		SD	6.86	-.62	1.60	4.23	8.02
		SE Mean	2.29				
MO	Digit Span F1	Mean	11.00	-.02	.84	9.22	12.78
		N	9				
		SD	2.69	-.24	.62	1.64	3.18
		SE Mean	.90				
	Digit Span F2	Mean	11.56	-.01	.96	9.44	13.67
		N	9				
		SD	3.09	-.22	.53	2.40	3.38
		SE Mean	1.03				
	Verbal Paired Associates Immediate F1	Mean	10.44	-.01	1.24	7.56	12.89
		N	9				
		D	4.03	-.40	1.09	2.11	4.92
		SE Mean	1.35				
	Verbal Paired Associates Immediate F2	Mean	12.00	<-.01	1.12	9.28	14.44
		N	9				
		SD	3.64	-.33	.85	2.35	4.24
		SE Mean	1.21				
	Verbal Paired Associates Delayed F1	Mean	10.67	-.01	1.25	7.78	13.28
		N	9				
		SD	4.03	-.34	.89	2.65	4.64
		SE Mean	1.34				
	Verbal Paired Associates Delayed F2	Mean	11.44	-.01	.98	9.22	13.56
		N	9				
		SD	3.17	-.26	.65	2.22	3.57
		SE Mean	1.06				
	ROCFT Copy F1	Mean	34.39	-.01	.70	32.83	35.78
		N	9				
		SD	2.23	-.19	.50	1.00	2.64
		SE Mean	.74				
	ROCFT Copy F2	Mean	34.67	-.01	.55	33.78	35.56
		N	9				
		SD	1.73	-.13	.33	1.33	1.94
		SE Mean	.58				
	ROCFT Immediate Recall F1	Mean	25.67	-.09	2.98	19.02	31.78
		N	9				
		SD	9.51	-.68	1.57	7.30	10.24
		SE Mean	3.17				
	ROCFT Immediate Recall F2	Mean	27.83	-.02	1.84	23.00	31.72
		N	9				
		SD	5.90	-.55	1.55	2.18	7.14
		SE Mean	1.97				
	ROCFT Delayed Recall F1	Mean	25.72	-.08	2.88	19.33	31.61
		N	9				
		SD	9.15	-.71	1.62	6.78	10.16
		SE Mean	3.05				
		Mean	28.94	-.03	1.93	24.22	32.82

	ROCFT Delayed Recall F2	N	9				
		SD	6.15	-.60	1.56	3.81	7.211
		SE Mean	2.05				
Placebo	Digit Span F1	Mean	10.30	.02	.82	8.50	12.20
		N	10				
		SD	2.67	-.18	.52	1.73	3.18
		SE Mean	.84				
	Digit Span F2	Mean	11.80	<.01	.86	10.00	13.70
		N	10				
		SD	2.86	-.20	.54	1.96	3.37
		SE Mean	.90				
	Verbal Paired Associates Immediate F1	Mean	10.20	.02	1.36	7.20	13.00
		N	10				
		SD	4.57	-.27	.79	3.29	5.21
		SE Mean	1.44				
	Verbal Paired Associates Immediate F2	Mean	11.90	.02	1.37	8.90	15.20
		N	10				
		SD	4.56	-.30	.78	3.12	5.37
		SE Mean	1.44				
	Verbal Paired Associates Delayed F1	Mean	10.40	<-.01	1.31	7.50	12.80
		N	10				
		SD	4.38	-.33	.99	2.76	5.27
		SE Mean	1.38				
	Verbal Paired Associates Delayed F2	Mean	11.10	<.01	1.07	8.70	13.20
		N	10				
		SD	3.60	-.24	.68	2.62	4.11
		SE Mean	1.14				
	ROCFT Copy F1	Mean	32.20	-.0467	2.3697	27.0000	35.2091
		N	10				
		SD	7.96939	-1.32970	3.73102	1.39841	11.70755
		SE Mean	2.52014				
	ROCFT Copy F2	Mean	32.60	-.03	1.52	29.05	34.85
		N	10				
		SD	5.12	-.79	2.28	1.11	7.11
		SE Mean	1.62				
	ROCFT Immediate Recall F1	Mean	25.55	.01	2.53	19.73	29.80
		N	10				
		SD	8.44	-.83	2.65	3.61	11.00
		SE Mean	2.67				
	ROCFT Immediate Recall F2	Mean	26.40	<-.01	2.87	19.34	31.21
		N	10				
		SD	9.50	-1.01	3.19	3.70	12.59
		SE Mean	3.01				
	ROCFT Delay F1	Mean	24.35	.03	2.63	18.12	29.34
		N	10				
		SD	8.71	-.73	2.26	4.74	10.81
		SE Mean	2.75				
	ROCFT Delay F2	Mean	25.15	-.01	2. 90	17.95	30.14
		N	10				
		SD	9.62	-1.02	3.22	3.74	12.78
		SE Mean	3.04				

Paired Samples Correlations

					Bootstrap for Correlation			
							BCa 95% Confidence Interval	
Group		N	Correlation	Sig.	Bias	Std. Error	Lower	Upper
OM	Digit Span F1 & Digit Span F2	9	.88	.002	<.01	.12	.	.
	VPA Immediate F1 & VPA Immediate F2	9	.70	.036	-.03	.25	<0.01	0.97
	VPA Delayed F1 & VPA Delayed F2	9	.85	.004	-.01	.11	0.27	1.00
	ROCFT Copy F1 & ROCFT Copy F2	9	.04	.910	.01	.29	-0.47	0.52
	ROCFT Immediate F1 ROCFT Immediate F2	9	.80	.010	-.01	.17	0.41	0.98
	ROCFT Delay F1 & ROCFT Delay F2	9	.77	.016	-.04	.22	0.19	0.96
MO	Digit Span F1 & Digit Span F2	9	.87	.002	<.01	.09	0.69	0.99
	VPA Immediate F1 & VPA Immediate F2	9	.98	<.001	-.01	.04	0.88[d]	1.00
	VPA Delayed F1 & VPA Delayed F2	9	.92	<.001	-.03	.12	0.68	0.99
	ROCFT Copy F1 & ROCFT Copy F2	9	.41	.274	.03	.35	-0.29	1.00
	ROCFT Immediate F1 ROCFT Immediate F2	9	.86	.003	-.03	.15	0.35	0.99
	ROCFT Delay F1 & ROCFT Delay F2	9	.94	<.001	<.01	.05	0.67	1.00
Placebo	Digit Span F1 & Digit Span F2	10	.84	.002	.02	.09	0.40	0.99
	VPA Immediate F1 & VPA Immediate F2	10	.87	.001	<.01	.10	0.52	0.99
	VPA Delayed F1 & VPA Delayed F2	10	.98	<.001	<-.01	.01	0.92	1.00
	ROCFT Copy F1 & ROCFT Copy F2	10	.98	<.001	-.11	.21	0.44	1.00
	ROCFT Immediate F1 ROCFT Immediate F2	10	.90	<.001	-.09	.24	0.19	0.99
	ROCFT Delay F1 & ROCFT Delay F2	10	.94	<.001	-.01	.06	0.77	1.00

Paired Samples Test

	Paired Differences							
				95% Confidence Interval of the Difference				
Group	Mean	SD	SE Mean	Lower	Upper	t	df	p. (2-tailed)

OM	Digit Span F1 – Digit Span F2	-.11	1.62	.54	-1.35	1.13	-.21	8	.842
	VPA Immediate F1 – VPA Immediate F2	.22	2.44	.81	-1.65	2.10	.27	8	.791
	VPA Delayed F1 – VPA Delayed F2	.67	2.12	.71	-0.96	2.30	.94	8	.373
	ROCFT Copy F1 – ROCFT Copy F2	<.01	1.73	.58	-1.33	1.33	<0.01	8	>.999
	ROCFT Immediate F1 – ROCFT Immediate F2	1.17	4.50	1.50	-2.29	4.63	0.78	8	.459
	ROCFT Delay F1 – ROCFT Delay F2	-1.06	4.72	1.57	-4.68	2.57	-0.67	8	.521
MO	Digit Span F1 – Digit Span F2	-.56	1.51	.50	-1.72	0.60	-1.10	8	.302
	VPA Immediate F1 – VPA Immediate F2	-1.56	.88	.29	-2.23	-0.88	-5.29	8	.001
	VPA Delayed F1 – VPA Delayed F2	-.78	1.64	.55	-2.04	0.48	-1.42	8	.193
	ROCFT Copy F1 – ROCFT Copy F2	-.28	2.20	.73	-1.97	1.41	-0.38	8	.714
	ROCFT Immediate F1 – ROCFT Immediate F2	-2.17	5.39	1.80	-6.31	1.98	-1.21	8	.262
	ROCFT Delayed F1 – ROCFT Delayed F2	-3.22	3.99	1.33	-6.29	-0.15	-2.42	8	.042
Placebo	Digit Span F1 – Digit Span F2	-1.50	1.58	.50	-2.63	-0.37	-3.00	9	.015
	VPA Immediate F1 – VPA Immediate F2	-1.70	2.31	.73	-3.35	-0.05	-2.33	9	.045
	VPA Delayed F1 – VPA Delayed F2	-.70	1.06	.34	-1.46	0.06	-2.09	9	.066
	ROCFT Copy F1 – ROCFT Copy F2	-.40	3.09	.98	-2.61	1.81	-0.41	9	.692
	ROCFT Immediate F1 – ROCFT Immediate F2	-.85	4.24	1.34	-3.89	2.19	-0.63	9	.542
	ROCFT Delayed F1 – ROCFT Delayed F2	-.80	3.33	1.05	-3.18	1.58	-0.76	9	.466

Bootstrap for Paired Samples Test

			Bootstrap				
						BCa 95% Confidence Interval	
Group		Mean	Bias	SE	p. (2-tailed)	Lower	Upper
OM	Digit Span F1 – Digit Span F2	-.11	<.01	.51	.854	-1.11	0.89
	VPA Immediate F1 – VPA Immediate F2	.22	-.01	.79	.810	-1.56	1.78
	VPA Delayed F1 – VPA Delayed F2	.67	.01	.68	.382	-0.67	2.11
	ROCFT_Copy_F1 - ROCFT_Copy_F2	<.01	<-.01	.55	>.999	-0.89	0.89
	ROCFT Immediate F1 – ROCFT Immediate F2	1.17	.03	1.38	.462	-1.72	3.98

	ROCFT Delayed F1 – ROCFT Delayed F2	-1.06	.05	1.46	.530	-4.17	1.89
MO	Digit Span F1 – Digit Span F2	-.56	-.01	.47	.329	-1.44	0.22
	VPA Immediate F1 – VPA Immediate F2	-1.56	<-.01	.27	.001	-2.11	-1.00
	VPA Delayed F1 – VPA Delayed F2	-.78	<-.01	.51	.183	-1.89	0.33
	ROCFT Copy F1 – ROCFT Copy F2	-.28	<.01	.70	.728	-2.33	1.11
	ROCFT Immediate F1 – ROCFT Immediate F2	-2.17	-.07	1.70	.266	-5.90	1.12
	ROCFT Delayed F1 – ROCFT Delayed F2	-3.22	-.05	1.25	.048	-5.89	-0.67
Placebo	Digit Span F1 – Digit Span F2	-1.50	.02	.47	.013	-2.50	-0.60
	VPA Immediate F1 – VPA Immediate F2	-1.70	<.01	.70	.073	-3.20	-0.50
	VPA Delayed F1 – VPA Delayed F2	-.70	<-.01	.32	.055	-1.20	-0.30
	ROCFT Copy F1 – ROCFT Copy F2	-.40	-.02	.92	.668	-2.45	1.10
	ROCFT Immediate F1 – ROCFT Immediate F2	-.85	.02	1.27	.535	-2.90	1.76
	ROCFT_Delay_F1 - ROCFT_Delay_F2	-.80	.04	.99	.464	-2.85	1.30

Paired Samples Statistics

				Bootstrap			
						BCa 95% Confidence Interval	
Group			Statistic	Bias	SE	Lower	Upper
OM	Doors F1	Mean	9.89	.05	1.55	5.93	13.00
		N	9				
		SD	5.06	-.47	1.21	3.08	5.91
		SE Mean	1.68				
	Doors F2	Mean	10.11	.06	1.81	5.56	14.11
		N	9				
		SD	5.80	-.44	1.04	4.21	6.46
		SE Mean	1.93				
MO	Doors F1	Mean	10.38	.04	1.53	7.38	13.25
		N	8				
		Std. Deviation	4.57	-.43	1.11	2.64	5.54
		Std. Error Mean	1.61				
	Doors F2	Mean	11.75	.03	1.59	8.63	14.50
		N	8				
		Std. Deviation	4.71	-.55	1.43	1.95	5.90
		Std. Error Mean	1.67				
Placebo	Doors F1	Mean	9.56	-.02	.98	7.89	11.22
		N	9				
		SD	3.17	-.23	.57	2.20	3.66
		SE Mean	1.06				

	Doors F2	Mean	10.89	-.01	.69	9.53	12.22
		N	9				
		SD	2.20	-.16	.36	1.69	2.40
		SE Mean	.73				

Paired Samples Correlation[a]

					Bootstrap for Correlation			
							BCa 95% Confidence Interval	
Group		N	Correlation	p.	Bias	Std. Error	Lower	Upper
OM	Doors F1 & Doors F2	9	.94	<.001	-.01	.06	0.79	0.99
MO	Doors F1 & Doors F2	8	.89	.003	-.03	.13	0.64	0.99
Placebo	Doors F1 & Doors F2	9	.15	.694	.08	.45	-0.58	0.93

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	SD	SE Mean	Lower	Upper	t	df	p. (2-tailed)
OM	Doors F1 – Doors F2	-0.22	1.99	0.66	-1.75	1.30	-0.34	8	.746
MO	Doors F1 – Doors F2	-1.38	2.20	0.78	-3.21	0.46	-1.77	7	.120
Placebo	Doors F1 – Doors F2	-1.33	3.57	1.19	-4.08	1.41	-1.12	8	.295

Bootstrap for Paired Samples Test

			Bootstrap				
						BCa 95% Confidence Interval	
Group		Mean	Bias	Std. Error	p. (2-tailed)	Lower	Upper
OM	Doors F1 – Doors F2	-.22	-.02	.63	.751	-1.44	0.89
MO	Doors F1 – Doors F2	-1.38	<.01	.73	.123	-2.75	0.00
Placebo	Doors F1 – Doors F2	-1.33	-.01	1.11	.362	-3.67	0.44

Executive Functions

Paired Samples Statistics

				Bootstrap			
						BCa 95% Confidence Interval	
Group			Statistic	Bias	SE	Lower	Upper
OM	Trail Making Visual Scanning F1	Mean	9.00	.01	1.60	6.00	11.89
		N	9				
		SD	5.07	-.41	1.06	3.71	5.70
		SE Mean	1.69				
	Trail Making Visual Scanning F2	Mean	9.22	.01	1.52	5.86	12.11
		N	9				
		SD	4.89	-.45	1.24	2.12	5.68
		SE Mean	1.63				
	Trail Making Number Sequencing F1	Mean	9.00	-.01	1.77	5.56	12.33
		N	9				
		SD	5.52	-.43	.97	4.17	5.97
		SE Mean	1.84				
	Trail Making Number Sequencing F2	Mean	9.78	.01	1.52	6.56	12.78
		N	9				
		SD	4.82	-.42	1.14	2.64	5.62
		SE Mean	1.61				
	Trail Making Letter Sequencing F1	Mean	10.67	.01	1.47	6.48	13.44
		N	9				
		SD	4.74	-.53	1.46	.97	5.68
		SE Mean	1.58				
	Trail Making Letter Sequencing F2	Mean	11.11	<-.01	1.27	8.15	13.33
		N	9				
		SD	4.04	-.47	1.35	1.20	5.06
		SE Mean	1.35				
	Trail Making Switching F1	Mean	10.67	.01	1.00	8.33	12.78
		N	9				
		SD	3.20	-.25	0.63	2.40	3.54
		SE Mean	1.07				
	Trail Making Switching F2	Mean	10.67	<.01	1.00	8.45	12.67
		N	9				
		SD	3.20	-.28	0.75	2.22	3.66
		SE Mean	1.07				
	Trail Making Motor Speed F1	Mean	9.33	<.01	1.34	6.24	11.78
		N	9				
		SD	4.27	-.42	1.16	1.23	5.00
		SE Mean	1.42				
	Trail Making Motor Speed F2	Mean	9.89	.01	1.37	7.11	12.22
		N	9				
		SD	4.37	-.44	1.27	1.33	5.25
		SE Mean	1.46				
MO	Trail Making Visual Scanning F1	Mean	10.56	-.02	.93	8.73	12.00
		N	9				
		SD	2.96	-.28	.83	1.51	3.75
		SE Mean	.99				
		Mean	11.56	-.02	.52	10.67	12.33
		N	9				

	Trail Making Visual Scanning F2	SD	1.67	-.12	.27	1.32	1.79
		SE Mean	.56				
	Trail Making Number Sequencing F1	Mean	12.33	-.01	.63	11.33	13.22
		N	9				
		SD	2.06	-.14	.35	1.48	2.33
		SE Mean	.69				
	Trail Making Letter Sequencing F2	Mean	11.78	<-.01	.81	10.44	13.11
		N	9				
		SD	2.59	-.19	.39	2.07	2.74
		SE Mean	.86				
	Trail Making Letter Sequencing F1	Mean	11.00	<.01	.99	9.33	12.56
		N	9				
		SD	3.12	-.26	.67	2.06	3.61
		SE Mean	1.04				
	Trail Making Letter Sequencing F2	Mean	12.78	-.01	.41	12.22	13.33
		N	9				
		SD	1.30	-.10	.24	1.00	1.42
		SE Mean	.43				
	Trail Making Switching F1	Mean	11.22	-.01	.87	9.78	12.67
		N	9				
		SD	2.77	-.19	.43	2.18	2.99
		SE Mean	.92				
	Trail Making Switching F2	Mean	12.33	-.01	.64	11.00	13.56
		N	9				
		SD	2.00	-.15	.37	1.45	2.24
		SE Mean	.67				
	Trail Making Motor Speed F1	Mean	12.11	-.01	.29	11.78	12.44
		N	9				
		SD	.93	-.10	.24	0.60	1.05
		SE Mean	.31				
	Trail Making Motor Speed F2	Mean	12.11	-.01	.25	11.78	12.44
		N	9				
		SD	.78	-.06	.13	.67	.78
		SE Mean	.26				
Placebo	Trail Making Visual Scanning F1	Mean	8.40	-.03	1.52	5.80	10.90
		N	10				
		SD	5.21	-.29	.82	3.74	5.88
		SE Mean	1.65				
	Trail Making Visual Scanning F2	Mean	8.90	-.03	1.36	6.30	11.20
		N	10				
		SD	4.63	-.29	.86	3.20	5.36
		SE Mean	1.46				
	Trail Making Number Sequencing F1	Mean	10.30	-.02	1.28	7.70	12.50
		N	10				
		SD	4.30	-.36	1.13	2.13	5.30
		SE Mean	1.36				
	Trail Making Number Sequencing F2	Mean	10.70	-.01	1.19	8.00	12.80
		N	10				
		SD	4.00	-.39	1.24	1.89	5.34
		SE Mean	1.27				
		Mean	9.90	-.01	1.06	7.50	11.70
		N	10				

	Trail Making Letter Sequencing F1	SD	3.54	-.39	1.221	1.42	4.79
		SE Mean	1.12				
	Trail Making Letter Sequencing F2	Mean	11.00	-.02	1.26	8.10	13.30
		N	10				
		SD	4.22	-.40	1.28	1.90	5.38
		SE Mean	1.33				
	Trail Making Switching F1	Mean	10.40	-.01	1.17	7.70	12.60
		N	10				
		SD	3.95	-.37	1.19	1.95	5.23
		SE Mean	1.25				
	Trail Making Switching F2	Mean	10.90	-.01	1.17	8.00	13.08
		N	10				
		SD	3.93	-.44	1.36	1.57	5.27
		SE Mean	1.24				
	Trail Making Motor Speed F1	Mean	9.70	-.02	1.07	7.50	11.40
		N	10				
		SD	3.56	-.36	1.14	1.62	4.53
		SE Mean	1.13				
	Trail Making Motor Speed F2	Mean	10.20	-.01	1.04	7.50	11.90
		N	10				
		SD	3.49	-.46	1.37	1.15	4.67
		SE Mean	1.10				

Paired Samples Correlations

					Bootstrap for Correlation			
							BCa 95% Confidence Interval	
Group		N	Correlation	p.	Bias	SE	Lower	Upper
OM	Trail Making Visual Scan F1 Trail Making Visual Scan F2	9	.97	<.001	-.02	.11	0.88	0.99
	Trail Making Number Seq. F1 Trail Making Number Seq. F2	9	.85	.004	.02	.11	0.37	0.99
	Trail Making Letter Seq. F1 & Trail Making Letter Seq. F2	9	.84	.005	-.11	.46	-0.81	0.99
	Trail Making Switching F1 & Trail Making Switching F2	9	.95	<.001	.01	.03	0.73	1.00
	Trail Making Motor Speed F1 Trail Making Motor Speed F2	9	.96	<.001	-.04	.17	0.24	0.99
MO	Trail Making Visual Scan F1 Trail making Visual Scan F2	9	.89	.001	.02	.07	.	.
	Trail Making Number Seq. F1 Trail Making Number Seq. F2	9	.72	.029	.01	.18	0.24	0.99
	Trail Making Letter Seq. F1 & Trail Making Letter Seq. F2	9	.89	.001	.01	.04	0.46	1.00

	Trail Making Switching F1 & Trail Making Switching F2	9	.91	.001	-.01	.10	0.71	0.99
	Trail Making Motor Speed F1 Trail Making Motor Speed F2	9	.67	.048	-.02	.20	0.00	0.95
Placebo	Trail Making Visual Scan F1 & Trail Making Visual Scan F2	10	.84	.003	-.01	.13	0.51	0.98
	Trail Making Number Seq. F1 Trail Making Number Seq. F2	10	.94	<.001	-.01	.05	0.82	1.00
	Trail Making Letter Seq. F1 & Trail Making Letter Seq. F2	10	.92	<.001	-.04	.13	0.61	0.99
	Trail Making Switching F1 & Trail making Switching F2	10	.98	<.001	-.01	.02	0.92	1.00
	Trail Making Motor Speed F1 Trail Making Motor Speed F2	10	.91	<.001	-.10	.22	0.29	0.98

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	SD	SE Mean	Lower	Upper	t	df	p. (2-tailed)
OM	Trail Making Visual Scanning F1 Trail Making Visual Scanning F2	-.22	1.20	.40	-1.15	0.70	-0.56	8	.594
	Trail Making Number Seq. F1 – Trail Making Number Seq. F2	-.78	2.91	.97	-3.01	1.46	-0.80	8	.445
	Trail Making Letter Seq. F1 – Trail Making Letter Seq. F2	-.44	2.60	.87	-2.45	1.56	-0.51	8	.622
	Trail Making Switching F1 – Trail Making Switching F2	.00	1.00	.33	-.77	0.77	0.00	8	>.999
	Trail Making Motor Speed F1 – Trail Making Motor Speed F2	-.56	1.24	.41	-1.51	0.39	-1.35	8	.214
MO	DKEFS_TMT_VisScan_F1 - DKEFS_TMT_VisScan_F2	-1.00	1.66	.55	-2.27	0.27	-1.81	8	.108
	Trail Making Number Seq. F1 – Trail Making Number Seq. F2	.56	1.81	.60	-0.84	1.95	0.92	8	.384
	Trail Making Letter Seq. F1 – Trail Making Letter Seq. F2	-1.78	2.05	.68	-3.35	-0.20	-2.60	8	.031
	Trail Making Switching F1 – Trail Making Switching F2	-1.11	1.27	.42	-2.09	-0.14	-2.63	8	.030
	Trail Making Motor Speed F1 – Trail Making Motor Speed F2	0.00	0.71	.24	-0.54	0.54	0.00	8	>.999
Placebo	Trail Making Visual Scan F1 – Trail Making Visual Scan F2	-.50	2.88	.91	-2.56	1.56	-0.55	9	.596
	Trail Making Number Seq. F1 – Trail Making Number Seq. F2	-.40	1.51	.48	-1.48	0.68	-0.84	9	.423
	Trail Making Letter Seq. F1 – Trail Making Letter Seq. F2	-1.10	1.66	.53	-2.29	0.09	-2.09	9	.066
	Trail Making Switching F1 – Trail Making Switching F2	-.50	.71	.22	-1.01	.01	-2.24	9	.052
	Trail Making Motor Speed F1 – Trail Making Motor Speed F2	-.50	1.51	.48	-1.58	0.58	-1.05	9	.322

Bootstrap for Paired Samples Test

Group		Mean	Bootstrap Bias	Bootstrap Std. Error	Bootstrap p. (2-tailed)	Bootstrap BCa 95% Confidence Interval Lower	Bootstrap BCa 95% Confidence Interval Upper
OM	Trail Making Visual Scan F1 Trail making Visual Scan F2	-.22	-.01	.38	.572	-0.89	0.33
	Trail Making Number Seq. F1 Trail Making Number Seq. F2	-.78	-.02	.92	.476	-2.56	0.78
	Trail Making Letter Seq. F1 – Trail making Letter Seq. F2	-.44	.02	.82	.637	-2.36	1.14
	Trail Making Switching F1 – Trail Making Switching F2	.00	.01	.32	>.999	-0.44	0.56
	Trail Making Motor Speed F1 Trail Making Motor Speed F2	-.56	<-.01	.39	.223	-1.22	0.11
MO	Trail Making Visual Scan F1 Trail Making Visual Scan F2	-1.00	<-.01	.53	.263	-2.00	-0.22
	Trail Making Number Seq. F1 Trail Making Number Seq. F2	.56	<-.01	.57	.364	-0.67	1.78
	Trail Making Letter Seq. F1 – Trail Making Letter Seq. F2	-1.78	.01	.65	.044	-3.08	-0.67
	Trail Making Switching F1 – Trail Making Switching F2	-1.11	<-.01	.39	.035	-1.78	-0.44
	Trail Making Motor Speed F1 Trail Making Motor Speed F2	.00	<-.01	.22	>.999	-0.33	0.33
Placebo	Trail Making Visual Scan F1 Trail Making Visual Scan F2	-.50	-.01	.86	.624	-2.10	0.90
	Trail Making Number Seq. F1 Trail making Number Seq. F2	-.40	-.01	.46	.444	-1.50	0.40
	Trail Making Letter Seq. F1 – Trail Making Letter Seq. F2	-1.10	.01	.50	.135	-1.70	-0.40
	Trail Making Switching F1 – Trail Making Switching F2	-.50	<.01	.21	.106	-0.80	-0.20
	Trail Making Motor Speed F1 Trail Making Motor Speed F2	-.50	-.01	.45	.318	-1.20	0.10

Paired Samples Statistics

Group			Statistic	Bootstrap[b] Bias	Bootstrap[b] Std. Error	Bootstrap[b] BCa 95% Confidence Interval Lower	Bootstrap[b] BCa 95% Confidence Interval Upper
OM	Verbal Fluency Letter F1	Mean	9.78	-.04	1.06	7.89	11.67
		N	9				
		SD	3.35	-.30	.74	2.18	3.90
		SE Mean	1.12				
	Verbal Fluency Letter F2	Mean	9.56	-.04	1.08	7.78	11.22
		N	9				
		SD	3.40	-.29	.68	2.22	3.94
		SE Mean	1.13				

	Verbal Fluency Categories F1	Mean	10.56	-.09	2.04	7.11	14.00
		N	9				
		SD	6.35	-.46	.94	4.69	7.04
		SE Mean	2.12				
	Verbal Fluency Categories F2	Mean	10.33	-.07	1.66	7.44	13.11
		N	9				
		SD	5.20	-.44	1.03	3.27	6.15
		SE Mean	1.73				
	Verbal Fluency Switching F1	Mean	10.56	-.03	.91	8.93	12.22
		N	9				
		SD	2.79	-.30	.73	1.48	3.39
		SE Mean	.93				
	Verbal Fluency Switching F2	Mean	10.11	-.02	1.08	8.00	12.11
		N	9				
		SD	3.37	-.29	.61	2.35	3.77
		SE Mean	1.12				
MO	Verbal Fluency Letter F1	Mean	12.11	-.06	1.72	9.11	15.11
		N	9				
		SD	5.37	-.41	.93	4.13	5.85
		SE Mean	1.79				
	Verbal Fluency Letter F2	Mean	12.44	-.05	1.67	9.56	15.33
		N	9				
		SD	5.20	-.37	.80	4.11	5.61
		SE Mean	1.73				
	Verbal Fluency Categories F1	Mean	11.67	-.01	1.62	7.78	15.22
		N	9				
		SD	5.07	-.35	.93	3.74	5.70
		SE Mean	1.69				
	Verbal Fluency Categories F2	Mean	13.00	-.02	1.63	8.89	16.33
		N	9				
		SD	5.10	-.43	1.20	3.12	6.06
		SE Mean	1.70				
	Verbal Fluency Switching F1	Mean	9.3333	-.0234	1.1231	6.4553	11.4444
		N	9				
		SD	3.53553	-.32058	.89035	1.96497	4.28947
		SE Mean	1.17851				
	Verbal Fluency Switching F2	Mean	12.78	.02	1.31	9.71	15.67
		N	9				
		SD	4.21	-.33	.95	2.56	5.19
		SE Mean	1.40				
Placebo	Verbal Fluency Letter F1	Mean	10.70	.04	.98	8.80	12.70
		N	10				
		SD	3.27	-.19	.53	2.50	3.65
		SE Mean	1.03				
	Verbal Fluency Letter F2	Mean	12.20	.06	.99	10.59	14.20
		N	10				
		SD	3.29	-.21	.74	2.04	3.97
		SE Mean	1.04				
	Verbal Fluency Categories F1	Mean	10.60	.13	1.87	7.40	14.10
		N	10				
		SD	6.26	-.40	.94	4.65	7.03

		SE Mean	1.98				
	Verbal Fluency Categories F2	Mean	11.90	.11	1.19	9.70	14.20
		N	10				
		SD	3.98	-.29	.80	2.66	4.72
		SE Mean	1.26				
	Verbal Fluency Switching F1	Mean	11.30	.09	1.30	8.90	13.90
		N	10				
		SD	4.32	-.30	.87	2.57	5.36
		SE Mean	1.37				
	Verbal Fluency Switching F2	Mean	12.80	.06	.79	11.30	14.40
		N	10				
		SD	2.66	-.19	.54	1.65	3.24
		SE Mean	.84				

Paired Samples Correlations

					Bootstrap for Correlation			
							BCa 95% Confidence Interval	
Group		N	Correlation	p.	Bias	Std. Error	Lower	Upper
OM	Verbal Fluency Letter F1 Verbal Fluency Letter F2	9	.80	.009	-.05	.19	0.39	0.96
	Verbal Fluency Category F1 Verbal Fluency Category F2	9	.88	.002	-.02	.09	0.52	0.99
	Verbal Fluency Switch F1 Verbal Fluency Switch F2	9	.86	.003	-.03	.16	0.22	0.99
MO	Verbal Fluency Letter F1 & Verbal Fluency Letter F2	9	.85	.003	-.01	.11	0.58	0.98
	Verbal Fluency Category F1 Verbal Fluency Category F2	9	.93	.000	.01	.05	0.17	1.00
	Verbal Fluency Switch F1 Verbal Fluency Switch F2	9	.62	.075	-.11	.35	-0.17	0.89
Placebo	Verbal Fluency Letter F1 & Verbal Fluency Letter F2	10	.89	.000	<.01	.07	0.75	0.98
	Verbal Fluency Category F1 Verbal Fluency Category F2	10	.86	.001	<-.01	.09	0.64	0.98
	Verbal Fluency Switch F1 Verbal Fluency Switch F2	10	.93	.000	-.01	.07	0.73	0.99

Paired Samples Test

Group	Paired Differences	t	df

				SE	95% Confidence Interval of the Difference				p. (2-tailed)
		Mean	SD	Mean	Lower	Upper			
OM	Verbal Fluency Letter F1 -Verbal Fluency Letter F2	.22	2.11	.70	-1.40	1.84	.32	8	.760
	Verbal Fluency Cat. F1 - Verbal Fluency Cat. F2	.22	3.03	1.01	-2.11	2.55	.22	8	.831
	Verbal Fluency Switch F1 - Verbal Fluency Switch F2	.44	1.74	.58	-0.89	1.78	.77	8	.466
MO	Verbal Fluency Letter F1 - Verbal Fluency Letter F2	-.333	2.87	.96	-2.54	1.87	-.35	8	.737
	Verbal Fluency Cat. F1 - Verbal Fluency Cat. F2	-1.33	1.87	.62	-2.77	0.10	-2.14	8	.065
	Verbal Fluency Switch F1 - Verbal Fluency Switch F2	-3.44	3.43	1.14	-6.08	-0.81	-3.01	8	.017
Placebo	Verbal Fluency Letter F1 - Verbal Fluency Letter F2	-1.50	1.51	.48	-2.58	-0.42	-3.14	9	.012
	Verbal Fluency Cat. F1 - Verbal Fluency Cat F2	-1.30	3.47	1.10	-3.78	1.18	-1.19	9	.266
	Verbal Fluency Switch F1 - Verbal Fluency Switch F2	-1.50	2.07	.65	-2.98	-0.02	-2.29	9	.048

Bootstrap for Paired Samples Test

			Bootstrap				
						BCa 95% Confidence Interval	
Group		Mean	Bias	Std. Error	p. (2-tailed)	Lower	Upper
OM	Verbal Fluency Letter F1 Verbal Fluency Letter F2	.22	-.01	.67	.763	-1.22	1.56
	Verbal Fluency Cat. F1 - Verbal Fluency Cat. F2	.22	-.02	.97	.824	-2.00	2.55
	Verbal Fluency Switch F1 Verbal Fluency Switch F2	.44	-.013	.55	.490	-.56	1.56
MO	Verbal Fluency Letter F1 - Verbal Fluency Letter F2	-.33	<-.01	.91	.730	-2.22	1.24
	Verbal Fluency Cat. F1 - Verbal Fluency Cat. F2	-1.33	.01	.57	.066	-2.56	-0.11
	Verbal Fluency Switch F1 Verbal Fluency Switch F2	-3.44	-.04	1.07	.021	-5.22	-1.78
Placebo	Verbal Fluency Letter F1 - Verbal Fluency Letter F2	-1.50	-.02	.45	.033	-2.20	-0.80
	Verbal Fluency Cat. F1 - Verbal Fluency Cat. F2	-1.30	.03	1.02	.263	-3.265	0.90
	Verbal Fluency Switch F1 Verbal Fluency Switch F2	-1.50	.03	.63	.052	-2.80	-0.10

Paired Samples Statistics

				Bootstrap			
						BCa 95% Confidence Interval	
Group			Statistic	Bias	Std. Error	Lower	Upper
OM	Colour Word Interference Naming F1	Mean	9.00	<.01	1.24	6.50	11.00
		N	8				
		SD	3.78	-.46	1.21	1.51	4.75
		SE Mean	1.34				
	Colour Word Interference Naming F2	Mean	8.75	<.01	1.23	6.38	10.88
		N	8				
		SD	3.73	-.43	1.15	1.39	4.74
		SE Mean	1.32				
	Colour Word Interference Reading F1	Mean	9.75	<-.01	1.27	7.13	11.63
		N	8				
		SD	3.85	-.55	1.44	1.07	5.15
		SE Mean	1.36				
	Colour Word Interference Reading F2	Mean	9.00	<-.01	1.29	6.25	11.25
		N	8				
		SD	3.93	-.42	1.10	2.00	4.79
		SE Mean	1.39				
	Colour Word Interference Inhibition F1	Mean	10.63	-.01	1.42	7.63	12.88
		N	8				
		SD	4.31	-.57	1.49	1.64	5.62
		SE Mean	1.52				
	Colour Word Interference Inhibition F2	Mean	10.63	-.01	1.38	7.88	12.7500
		N	8				
		SD	4.17	-.61	1.60	1.39	5.52
		SE Mean	1.48				
	Colour Word Interference Switching F1	Mean	10.50	-.01	1.33	7.63	12.38
		N	8				
		SD	4.04	-.67	1.71	1.16	5.26
		SE Mean	1.43				
	Colour Word Interference Switching F2	Mean	10.38	-.01	1.47	7.38	12.75
		N	8				
		SD	4.44	-.52	1.37	2.14	5.52
		SE Mean	1.57				
MO	Colour Word Interference Naming F1	Mean	10.11	.02	.92	8.07	12.00
		N	9				
		SD	2.93	-.32	.86	1.22	3.69
		SE Mean	.98				
	Colour Word Interference Naming F2	Mean	9.78	.02	1.12	7.33	12.22
		N	9				
		SD	3.60	-.34	.92	2.04	4.37
		SE Mean	1.20				
	Colour Word Interference Reading F1	Mean	10.44	.0061	.68	9.11	11.78
		N	9				
		SD	2.13	-.16	.38	1.58	2.35

		SE Mean	.71				
	Colour Word Interference Reading F2	Mean	10.44	.02	1.04	8.11	12.67
		N	9				
		SD	3.32	-.32	.86	1.94	3.94
		SE	1.11				
	Colour Word Interference Inhibition F1	Mean	11.78	.01	.50	10.67	12.56
		N	9				
		SD	1.56	-.22	.58	.53	2.12
		SE	.52				
	Colour Word Interference Inhibition F2	Mean	11.22	.02	1.01	8.78	13.22
		N	9				
		SD	3.19	-.37	1.00	1.36	4.24
		SE Mean	1.06				
	Colour Word Interference Switching F1	Mean	11.44	.01	.77	9.67	13.11
		N	9				
		SD	2.46	-.17	.33	2.06	2.55
		SE Mean	.82				
	Colour Word Interference Switching F2	Mean	11.44	.03	.99	8.78	13.56
		N	9				
		SD	3.21	-.27	.63	2.35	3.56
		SE Mean	1.07				
Placebo	Colour Word Interference Naming F1	Mean	9.22	-.01	1.35	6.56	11.56
		N	9				
		SD	4.32	-.39	1.03	2.50	5.08
		SE Mean	1.44				
	Colour Word Interference Naming F2	Mean	9.67	-.01	1.19	7.22	11.67
		N	9				
		SD	3.81	-.43	1.21	1.58	4.89
		SE Mean	1.27				
	Colour Word Interference Reading F1	Mean	10.22	<-.01	1.41	7.11	12.78
		N	9				
		SD	4.49	-.44	1.21	2.05	5.47
		SE Mean	1.50				
	Colour Word Interference Reading F2	Mean	10.22	<-.01	1.20	7.78	12.43
		N	9				
		SD	3.80	-.32	.85	2.40	4.46
		SE Mean	1.27				
	Colour Word Interference Inhibition F1	Mean	10.56	<.01	1.55	6.89	13.67
		N	9				
		SD	4.95	-.46	1.24	2.24	5.93
		SE Mean	1.65				
	Colour Word Interference Inhibition F2	Mean	10.56	<-.01	1.05	8.44	12.56
		N	9				
		SD	3.36	-.26	.60	2.51	3.64
		SE Mean	1.12				
	Colour Word Interference Switching F1	Mean	9.44	.01	1.70	5.03	13.19
		N	9				
		SD	5.46	-.43	1.08	4.01	6.07
		SE Mean	1.82				
	Colour Word Interference Switching F2	Mean	11.44	<.01	.98	9.22	13.33
		N	9				
		SD	3.13	-.27	.69	2.12	3.53

		SE Mean	1.04					

Paired Samples Correlations

					Bootstrap for Correlation			
							BCa 95% Confidence Interval	
Group		N	Correlation	p.	Bias	SE	Lower	Upper
OM	Colour Word Interference Naming F1 & Colour Word Interference Naming F2	8	.96	<.001	-.04	.12	0.64	0.99
	Colour Word Interference Read F1 & Colour Word Interference Read F2	8	.94	.001	-.03	.09	0.73	1.00
	Colour Word Interference Inhib. F1 & Colour Word Interference Inhib. F2	8	.99	<.001	-.02	.11	0.86	1.00
	Colour Word Interference Switch. F1 & Colour Word Interference Switch. F2	8	.94	.001	-.10	.30	-0.05	0.99
MO	Colour Word Interference Naming F1 & Colour Word Interference Naming F2	9	.96	<.001	-.02	.09	0.71	0.99
	Colour Word Interference Read F1 & Colour Word Interference Read F2	9	.80	.010	-.01	.15	0.32	0.98
	Colour Word Interference Inhib. F1 & Colour Word Interference Inhib. F2	9	.96	<.001	-.03	.06	0.81	0.99
	Colour Word Interference Switch. F1 & Colour Word Interference Switch. F2	9	.86	.003	.02	.08	.	.
Placebo	Colour Word Interference Naming F1 & Colour Word Interference Naming F2	9	.96	<.001	<.01	.04	0.81	1.00
	Colour Word Interference Read F1 & Colour Word Interference Read F2	9	.97	<.001	-.01	.04	0.90	1.00
	Colour Word Interference Inhib. F1 & Colour Word Interference Inhib. F2	9	.87	.002	.01	.06	0.69	0.98

	Colour Word Interference Switch. F1 Colour Word Interference Switch. F2	9	.95	<.001	-.02	.08	0.76	0.99

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	SD	SE Mean	Lower	Upper	t	df	p. (2-tailed)
OM	Colour Word Interference Name F1 Colour Word Interference Name F2	.25	1.04	.37	-0.62	1.12	0.68	7	.516
	Colour Word Interference Read F1 - Colour Word Interference Read F2	.75	1.39	.49	-0.41	1.91	1.53	7	.170
	Colour Word Interference Inhib. F1 - Colour Word Interference Inhib.F2	.00	.76	.27	-0.63	0.63	0.00	7	>.999
	Colour Word Interference Switch F1 Colour Word Interference Switch F2	.13	1.55	.55	-1.17	1.42	0.23	7	.826
MO	Colour Word Interference Name F1 - Colour Word Interference Name F2	.33	1.12	.37	-0.53	1.19	0.89	8	.397
	Colour Word Interference Read F1 - Colour Word Interference Read F2	.00	2.06	.69	-1.58	1.58	0.00	8	>.999
	Colour Word Interference Inhib. F1 - Colour Word Interference Inhib. F2	.56	1.74	.58	-0.78	1.89	0.96	8	.366
	Colour Word Interference Switch. F1 Colour Word Interference Switch. F2	.00	1.66	.55	-1.27	1.27	0.00	8	>.999
Placebo	Colour Word Interference Name F1 - Colour Word Interference Name F2	-.44	1.24	.41	-1.40	0.51	-1.08	8	.312
	Colour Word Interference Read F1 - Colour Word Interference Read F2	.00	1.22	.41	-0.94	0.94	.000	8	>.999
	Colour Word Interference Inhib. F1 - Colour Word Interference Inhib. F2	.00	2.60	.87	-2.00	2.00	.000	8	>.999
	Colour Word Interference Switch. F1 Colour Word Interference Switch. F2	-2.00	2.69	.90	-4.07	0.07	-2.22	8	.056

Bootstrap for Paired Samples Test

		Bootstrap					
						BCa 95% Confidence Interval	
Group		Mean	Bias	Std. Error	p. (2-tailed)	Lower	Upper
OM	Colour Word Interference Name F1 Colour Word Interference Name F2	.25	<.01	.33	.486	-0.25	0.75
	Colour Word Interference Read F1 Colour Word Interference Read F2	.75	.02	.43	.279	0.25	1.38
	Colour Word Interference Inhib. F1 - Colour Word Interference Inhib. F2	.00	<-.01	.24	>.999	-0.38	0.38
	Colour Word Interference Switch F1 Colour Word Interference Switch F2	.13	<.01	.51	.821	-0.88	1.13
MO	Colour Word Interference Name F1 Colour Word Interference Name F2	.33	<-.01	.34	.376	-0.22	0.89
	Colour Word Interference Read F1 – Colour Word Interference Read F2	.00	-.02	.64	>.999	-1.11	1.11
	Colour Word Interference Inhib. F1 Colour Word Interference Inhib. F2	.56	-.01	.54	.368	-0.22	1.33

	Colour Word Interference Switch F1 Colour Word Interference Switch F2	.00	-.01	.52	>.999	-0.78	0.78
Placebo	Colour Word Interference Name F1 Colour Word Interference Name F2	-.44	<-.01	.39	.290	-1.11	0.22
	Colour Word Interference Read F1 – Colour Word Interference Read F2	.00	<-.01	.39	.999	-.56	0.56
	Colour Word Interference Inhib. F1 Colour Word Interference Inhib. F2	.00	<.01	.82	>.999	-1.76	1.33
	Colour Word Interference Switch F1 Colour Word Interference Switch F2	-2.00	.01	.83	.058	-3.78	-0.22

Symbol Search and SRT

Paired Samples Statistics

				Bootstrap			
						BCa 95% Confidence Interval	
Group			Statistic	Bias	Std. Error	Lower	Upper
OM	Symbol Search F1	Mean	11.86	<.01	.68	10.71	13.29
		N	7				
		SD	1.95	-.20	.45	1.51	2.00
		SE Mean	.74				
	Symbol Search F2	Mean	12.14	-.01	1.07	10.14	14.14
		N	7				
		SD	3.08	-.31	.68	2.08	3.41
		SE Mean	1.16				
	SRT Explicit F1	Mean	7.03	.01	1.37	4.57	9.77
		N	7				
		SD	3.85	-.40	.97	2.08	4.75
		SE Mean	1.45				
	SRT Explicit F2	Mean	6.57	.02	1.79	3.86	10.14
		N	7				
		SD	5.16	-.73	1.72	2.04	6.51
		SE Mean	1.95				
	SRT Implicit F1	Mean	38.90	-.80	16.42	14.50	62.38
		N	7				
		SD	48.50	-5.83	13.49	28.42	56.54
		SE Mean	18.33				
	SRT Implicit F2	Mean	44.16	-.27	12.88	21.77	68.65
		N	7				
		SD	36.87	-4.01	9.32	20.96	43.85
		SE Mean	13.93				
MO	Symbol Search F1	Mean	10.88	-.03	1.15	8.75	13.00
		N	8				
		SD	3.44	-.29	.61013	2.38	3.85
		SE Mean	1.22				
	Symbol Search F2	Mean	11.13	-.05	1.10	9.04	13.50
		N	8				
		SD	3.40	-.43	1.05	1.36	4.17
		SE Mean	1.20				
	SRT Explicit F1	Mean	7.31	-.01	.96	5.75	9.12
		N	8				

		SD	2.91	-.29	.70	2.02	3.29
		SE Mean	1.03				
	SRT Explicit F2	Mean	10.50	-.08	2.04	6.75	14.25
		N	8				
		SD	6.07	-.56	1.31	4.14	6.85
		SE Mean	2.15				
	SRT Implicit F1	Mean	9.16	.01	24.90	-40.53	57.14
		N	8				
		SD	74.60	-5.67	13.09	57.52	80.67
		SE Mean	26.37				
	SRT Implicit F2	Mean	60.68	.34	13.92	29.16	99.29
		N	8				
		SD	40.81	-4.15	10.37	24.25	48.74
		SE Mean	14.43				
Placebo	Symbol Search F1	Mean	9.56	.02	1.56	7.22	12.22
		N	9				
		SD	4.90	-.45	1.19	3.12	5.70
		SE Mean	1.63				
	Symbol Search F2	Mean	10.00	.024	1.89	7.11	13.11
		N	9				
		SD	5.94	-.46	1.07	4.50	6.44
		SE Mean	1.98				
	SRT Explicit F1	Mean	8.28	-.01	1.49	6.17	10.67
		N	9				
		SD	4.72	-.40	1.06	2.13	5.51
		SE Mean	1.57				
	SRT Explicit F2	Mean	8.33	.0094	1.45	6.22	10.56
		N	9				
		SD	4.64	-.45	1.18	2.49	5.74
		SE Mean	1.55				
	SRT Implicit F1	Mean	81.22	-2.12	44.52	8.63	161.15
		N	9				
		SD	146.08	-15.23	40.08	57.56	177.70
		SE Mean	48.69				
	SRT Implicit F2	Mean	129.24	-1.57	52.07	45.09	236.95
		N	9				
		SD	171.58	-24.85	64.37	59.99	233.25
		SE Mean	57.19				

Paired Samples Correlations

					Bootstrap for Correlation			
							BCa 95% Confidence Interval	
Group		N	Correlation	p.	Bias	Std. Error	Lower	Upper
OM	Symbol Search F1 & Symbol Search F2	7	.92	.003	-.02	.11	0.64	0.99
	SRT Explicit F1 & SRT Explicit F2	7	.41	.358	.03	.30	-0.48	0.98
	SRT Implicit F1 & SRT Implicit F2	7	.36	.431	.02	.36	-0.74	0.99

MO	Symbol Search F1 & Symbol Search F2	8	.84	.008	-.01	.12	0.42	0.98
	SRT Explicit F1 & SRT Explicit F2	8	.12	.786	<.01	.39	-0.73	0.93
	SRT Implicit F1 & SRT Implicit F2	8	-.57	.139	.08	.33	-0.92	0.40
Placebo	Symbol Search F1 & SymbolSearch F2	9	.95	.000	-.01	.06	0.85	0.99
	SRT Explicit F1 & SRT Explicit F2	9	.76	.018	-.06	.29	-0.10	0.96
	SRT Implicit F1 & SRT Implicit F2	9	.64	.061	-.26	.54	-0.54	0.94

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	SD	SE Mean	Lower	Upper	t	df	p. (2-tailed)
OM	Symbol Search F1 – Symbol Search F2	-.29	1.50	.57	-1.67	1.10	-0.51	6	.631
	SRT_Explicit_F1 - SRT_Explicit_F2	.46	5.01	1.89	-4.17	5.09	0.24	6	.817
	SRT_Implicit_F1 - SRT_Implicit_F2	-5.26	49.33	18.64	-50.88	40.36	-0.28	6	.787
MO	Symbol Search F1 – Symbol Search F2	-.25	1.91	.67	-1.85	1.35	-0.37	7	.722
	SRT Explicit F1 – SRT Explicit F2	-3.19	6.43	2.27	-8.56	2.18	-1.40	7	.203
	SRT Implicit F1 – SRT Implicit F2	-51.52	103.50	36.59	-138.04	35.01	-1.41	7	.202
Placebo	Symbol Search F1 – Symbol Search F2	-.44	2.01	.67	-1.99	1.10	-0.66	8	.525
	SRT Explicit F1 – SRT Explicit F2	-.06	3.24	1.08	-2.55	2.44	-.051	8	.960
	SRT Implicit F1 – SRT Implicit F2	-48.03	135.95	45.32	-152.53	56.48	-1.06	8	.320

Bootstrap for Paired Samples Test

			Bootstrap[a]				
						BCa 95% Confidence Interval	
Group		Mean	Bias	Std. Error	p. (2-tailed)	Lower	Upper
OM	Symbol SearchF1 Symbol Search F2	-.29	.01	.52	.608	-1.29	0.71
	SRT Explicit F1 – SRT Explicit F2	.46	-.01	1.76	.796	-4.21	4.71
	SRT Implicit F1 – SRT Implicit F2	-5.26	-.53	17.04	.775	-35.70	22.12
MO	Symbol Search F1 Symbol Search F2	-.25	.01844	.63917	.696	-1.38	.88

	SRT Explicit F1 – SRT Explicit F2	-3.19	.07	2.11	.183	-8.19	0.94
	SRT Implicit F1 – SRT Implicit F2	-51.52	-.33	34.91	.206	-114.76	7.16
Placebo	Symbol Search F1 Symbol Search F2	-.44	<-.01	.63643	.504	-1.89	.89
	SRT Explicit F1 SRT Explicit F2	-.06	-.02	1.00	.960	-1.83	2.00
	SRT Implicit F1 SRT Implicit F2	-48.03	-.55	42.63	.329	-113.97	24.84

NEADL and PANAS

Paired Samples Statistics

				Bootstrap			
						BCa 95% Confidence Interval	
Group			Statistic	Bias	Std. Error	Lower	Upper
OM	NEADL F1	Mean	50.11	<-.01	4.48	38.78	59.67
		N	9				
		SD	14.50	-1.25	3.11	9.43	16.83
		SE Mean	4.83				
	NEADL F2	Mean	53.11	.05	3.15	45.67	60.00
		N	9				
		SD	9.91	-.86	2.05	7.12	11.00
		SE Mean	3.30				
	PANAS PA F1	Mean	33.44	-.07	2.27	28.56	38.81
		N	9				
		SD	7.09	-.60	1.56	4.28	8.51
		SE Mean	2.36				
	PANAS PA F2	Mean	28.22	-.0181	2.1451	23.5556	33.5556
		N	9				
		SD	6.74	-.70288	1.99594	3.34581	8.13941
		SE Mean	2.25				
	PANAS NA F1	Mean	20.56	.01	3.18	16.56	25.33
		N	9				
		SD	10.33	-1.60	4.41	2.42	14.29
		SE Mean	3.44				
	PANAS NA F2	Mean	25.11	-.07	2.67	21.33	29.33[
		N	9				
		SD	8.65	-.75	2.15	5.05	10.38
		SE Mean	2.88				
MO	NEADL F1	Mean	52.67	.05	3.18	46.66	58.7778
		N	9				
		SD	9.91	-.67	1.42	7.66	10.77
		SE Mean	3.30				
	NEADL F2	Mean	51.44	.04	3.97	43.56	58.62
		N	9				
		SD	12.41	-1.20	3.08	6.73	16.03
		SE Mean	4.14				
	PANAS PA F1	Mean	32.11	.08	3.46	25.67	38.56
		N	9				
		SD	10.84	-.91	2.19	6.90	12.63

		SE Mean	3.61				
	PANAS PA F2	Mean	29.33	.10	3.39	22.87	36.35
		N	9				
		SD	10.57	-.85	2.11	6.68	12.83
		SE Mean	3.52				
	PANAS NA F1	Mean	23.72	-.03	2.93	16.17	31.64
		N	9				
		SD	9.33	-.69	1.67	6.21	10.94
		SE Mean	3.11				
	PANAS NA F2	Mean	22.06	<.01	3.16	15.87	29.50
		N	9				
		Std. Deviation	9.94	-.76	1.87	5.94	11.71
		Std. Error Mean	3.31				
Placebo	NEADL F1	Mean	51.10	-.06	5.76	37.30	61.80
		N	10				
		SD	19.40	-1.71	5.33	5.54	23.65
		SE Mean	6.14				
	NEADL F2	Mean	50.20	-.03	5.29	36.60	60.50
		N	10				
		Std. Deviation	17.74	-1.55	4.71	10.18	21.48
		Std. Error Mean	5.61				
	PANAS PA F1	Mean	31.90	.02	2.18	26.20	36.20
		N	10				
		SD	7.26	-.69	2.07	3.69	9.34
		SE Mean	2.30				
	PANAS PA F2	Mean	30.50	<.01	2.44	24.60	35.30
		N	10				
		SD	8.09	-.57	1.58	5.51	9.29
		SE Mean	2.56				
	PANAS NA F1	Mean	18.90	.03	2.24	15.70	22.80
		N	10				
		SD	7.56	-.71	2.15	3.74	9.32
		SE Mean	2.39				
	PANAS NA F2	Mean	18.60	-.02	1.66	16.10	21.40
		N	10				
		SD	5.52	-.49	1.48	2.87	6.96
		SE Mean	1.75				

Paired Samples Correlations

					Bootstrap for Correlation			
							BCa 95% Confidence Interval	
Group		N	Correlation	p.	Bias	Std. Error	Lower	Upper
OM	NEADL F1 & NEADL F2	9	.72	.027	-.06	.26	0.09	0.94

	PANAS PA F1 PANAS PA F2	9	.41	.275	-.15	.48	-0.63	0.88
	PANAS NA F1 PANAS NA F2	9	.74	.024	-.21	.49	-0.63	0.96
MO	NEADL F1 & NEADL F2	9	.58	.103	-.04	.28	-0.31	0.95
	PANAS PA F1 PANAS_PA F2	9	.94	.000	-.01	.09	0.53	1.00
	PANAS NA F1 PANAS NA F2	9	.84	.005	-.03	.15	0.18	0.98
Placebo	NEADL F1 & NEADL F2	10	.97	.000	-.03	.12	0.67	0.99
	PANAS PA F1 PANAS PA F2	10	.85	.002	-.03	.12	0.57	0.96
	PANAS NA F1 PANAS NA F2	10	.67	.035	-.13	.34	-0.09	0.91

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	p. (2-tailed)
OM	NEADL F1 – NEADL F2	-3.00	10.01	3.34	-10.70	4.70	-0.90	8	.395
	PANAS PA F1 PANAS PA F2	5.22	7.53	2.51	-0.57	11.01	2.08	8	.071
	PANAS NA F1 PANAS NA F2	-4.56	7.09	2.36	-10.01	0.89	-1.93	8	.090
MO	NEADL F1 – NEADL F2	1.22	10.49	3.50	-6.84	9.28	0.35	8	.736
	PANAS PA F1 PANAS PA F2	2.78	3.80	1.27	-.141	5.70	2.19	8	.060
	PANAS NA F1 PANAS NA F2	1.67	5.57	1.86	-2.61	5.95	0.90	8	.395
Placebo	NEADL F1 – NEADL F2	.90	5.04	1.59	-2.71	4.51	0.56	9	.586
	PANAS PA F1 PANAS PA F2	1.40	4.27	1.35	-1.66	4.46	1.04	9	.327
	PANAS NA F1 PANAS NA F2	.30	5.66	1.79	-3.75	4.35	0.17	9	.871

Bootstrap for Paired Samples Test

			Bootstrap				
						BCa 95% Confidence Interval	
Group		Mean	Bias	Std. Error	p. (2-tailed)	Lower	Upper
OM	NEADL_F1 - NEADL_F2	-3.00	-.05	3.13	.383	-11.00	3.89
	PANAS_PA_F1 - PANAS_F2	5.22	-.05	2.38	.103	0.67	10.33
	PANAS_NA_F1 - PANAS_NA2	-4.56	.07	2.21	.117	-9.11	-0.31

MO	Pair 1	NEADL F1 – NEADL F2	1.22	.02	3.25	.727	-5.22	8.33
	Pair 2	PANAS PA F1 – PANAS PA F2	2.78	-.03	1.21	.103	1.11	4.56
	Pair 3	PANAS NA F1 – PANAS NA F2	1.67	-.03	1.73	.376	-1.44	4.67
Placebo	Pair 1	NEADL F1 – NEADL F2	.90	-.03	1.52	.615	-1.20	3.20
	Pair 2	PANAS PA F1 – PANAS PA F2	1.40	.02	1.30	.324	-0.90	3.90
	Pair 3	PANAS NA F1 – PANAS NA F2	.30	.05	1.70	.860	-3.93	4.60

RME

Paired Samples Statistics

				Bootstrap			
						BCa 95% Confidence Interval	
Group			Statistic	Bias	Std. Error	Lower	Upper
OM	RME F1	Mean	22.78	<-.01	1.73	19.67	25.55
		N	9				
		SD	5.43	-.43	1.14	3.42	6.54
		SE Mean	1.81				
	RME F2	Mean	23.22	<.01	1.82	19.78	26.11
		N	9				
		SD	5.76	-.55	1.54	2.68	7.30
		SE Mean	1.92				
MO	RME F1	Mean	23.38	<.01	1.79	19.75	26.75
		N	8				
		SD	5.45	-.48	1.12	3.77	6.02
		SE Mean	1.93				
	RME F2	Mean	25.00	.04	1.65	22.25	27.88
		N	8				
		SD	5.01	-.42	.93	3.80	5.45
		SE Mean	1.77				
Placebo	RME F1	Mean	23.67	.01	1.88	20.44	26.96
		N	9				
		SD	6.06	-.41	1.06	4.58	6.74
		SE Mean	2.02				
	RME F2	Mean	23.78	.02	1.63	21.00	26.67
		N	9				
		SD	5.19	-.33	.71	4.15	5.57
		SE Mean	1.73				

Paired Samples Correlations

					Bootstrap for Correlation			
							BCa 95% Confidence Interval	
Group		N	Correlation	Sig.	Bias	Std. Error	Lower	Upper
OM	RME F1 & RME F2	9	.87	.002	-.03	.15	0.57	0.99

MO	RME F1 & RME F2	8	.70	.056	-.01	.18	0.29	0.93
Placebo	RME F1 & RME F2	9	.90	.001	<-.01	.07	0.71	0.99

Paired Samples Test

		Paired Differences							
					95% Confidence Interval of the Difference				
Group		Mean	SD	SE Mean	Lower	Upper	t	df	p. (2-tailed)
OM	RME_F1 - RME_F2	-.44	2.83	.94	-2.62	1.73	-0.47	8	.650
MO	RME_F1 - RME_F2	-1.63	4.10	1.45	-5.06	1.81	-1.12	7	.300
Placebo	RME_F1 - RME_F2	-.11	2.67	.89	-2.16	1.94	-0.13	8	.904

Bootstrap for Paired Samples Test

		Bootstrap[a]					
						BCa 95% Confidence Interval	
Group		Mean	Bias	SE	p. (2-tailed)	Lower	Upper
OM	RME_F1 - RME_F2	-.44	-.01	.90	.630	-2.33	1.00
MO	RME_F1 - RME_F2	-1.63	-.04	1.35	.286	-4.38	1.25
Placebo	RME_F1 - RME_F2	-.11	-.01	.83	.911	-1.44	1.33

E.14 Non-parametric analyses (Wilcoxon Signed Ranks) Period 2

Ranks

Group			N	Mean Rank	Sum of Ranks
OM	Digit Span F2 – Digit Span F1	Negative Ranks	3	4.50	13.50
		Positive Ranks	4	3.63	14.50
		Ties	2		
		Total	9		
	VPA Immediate Recall F2 VPA Immediate Recall F1	Negative Ranks	4	3.25	13.00
		Positive Ranks	2	4.00	8.00
		Ties	3		
		Total	9		
	VPA Delayed Recall F2 – VPA Delayed Recall F1	Negative Ranks	3	5.00	15.00
		Positive Ranks	3	2.00	6.00
		Ties	3		
		Total	9		
	Doors F2 – Doors F1	Negative Ranks	3	3.00	9.00
		Positive Ranks	3	4.00	12.00
		Ties	3		

		Total	9		
	ROCFT Copy F2 – ROCFT Copy F1	Negative Ranks	3	5.00	15.00
		Positive Ranks	4	3.25	13.00
		Ties	2		
		Total	9		
	ROCFT Immediate F2 – ROCFT Immediate F1	Negative Ranks	7	4.64	32.50
		Positive Ranks	2	6.25	12.50
		Ties	0		
		Total	9		
	ROCFT Delay F2 – ROCFT Delay F1	Negative Ranks	2	4.75	9.50
		Positive Ranks	5	3.70	18.50
		Ties	2		
		Total	9		
MO	Digit Span F2 – Digit Span F1	Negative Ranks	2	3.00	6.00
		Positive Ranks	4	3.75	15.00
		Ties	3		
		Total	9		
	VPA Immediate F2 – VPA Immediate F1	Negative Ranks	0	.00	.00
		Positive Ranks	8	4.50	36.00
		Ties	1		
		Total	9		
	VPA Delayed F2 – VPA Delayed F1	Negative Ranks	1	2.50	2.50
		Positive Ranks	4	3.13	12.50
		Ties	4		
		Total	9		
	Doors F2 – Doors F1	Negative Ranks	1	3.00	3.00
		Positive Ranks	5	3.60	18.00
		Ties	2		
		Total	8		
	ROCFT Copy F2 – ROCFT Copy F1	Negative Ranks	2	2.50	5.00
		Positive Ranks	2	2.50	5.00
		Ties	5		
		Total	9		
	ROCFT Immediate F2 – ROCFT Immediate F1	Negative Ranks	4	3.00	12.00
		Positive Ranks	5	6.60	33.00
		Ties	0		
		Total	9		
	ROCFT Delayed F2 – ROCFT Delayed F1	Negative Ranks	2	1.75	3.50
		Positive Ranks	6	5.42	32.50
		Ties	1		
		Total	9		
Placebo	Digit Span F2 – Digit Span F1	Negative Ranks	1	2.50	2.50
		Positive Ranks	8	5.31	42.50
		Ties	1		
		Total	10		
	VPA Immediate F2 – VPA Immediate F1	Negative Ranks	2	3.50	7.00
		Positive Ranks	8	6.00	48.00
		Ties	0		
		Total	10		
	VPA Delayed F2 – VPA Delayed F1	Negative Ranks	1	3.50	3.50
		Positive Ranks	6	4.08	24.50
		Ties	3		

	Total	10		
Doors F2 – Doors F1	Negative Ranks	2	1.75	3.50
	Positive Ranks	3	3.83	11.50
	Ties	4		
	Total	9		
ROCFT Copy F2 – ROCFT Copy F1	Negative Ranks	3	3.83	11.50
	Positive Ranks	3	3.17	9.50
	Ties	4		
	Total	10		
ROCFT Immediate F2 – ROCFT Immediate F1	Negative Ranks	3	5.67	17.00
	Positive Ranks	7	5.43	38.00
	Ties	0		
	Total	10		
ROCFT Delay F2 – ROCFT Delay F1	Negative Ranks	4	5.38	21.50
	Positive Ranks	6	5.58	33.50
	Ties	0		
	Total	10		

Group		Digit Span F2 – Digit Span F1	VPA Imm. F2 – VPA Imm F1	VPA Delay F2 – VPA Delay_F1	Doors F2 - Doors F1	ROCFT Copy F2 – ROCFT Copy F1	ROCFT Imm. F2 ROCFT Imm._F1	ROCFT Delay F2 ROCFT Delay F1
OM	Z	-0.09	-0.53	-0.95	-0.32	-0.17	-1.19	-0.76
	Asymp. p. (2-tailed)	.931	.596	.343	.750	.864	.234	.446
MO	Z	-1.00	-2.57	-1.36	-1.58	<0.01	-1.25	-2.04
	Asymp. p. (2-tailed)	.317	.010	.174	.114	1.000	.212	.042
Placebo	Z	-2.41	-2.14	-1.90	-1.08	-0.21	-1.08	-0.61
	Asymp. p. (2-tailed)	.016	.032	.058	.279	.833	.282	.540

Executive Function

Ranks

Group			N	Mean Rank	Sum of Ranks
OM	Trail Making Vis. Scan F2 Trail Making Vis. Scan F1	Negative Ranks	3	2.50	7.50
		Positive Ranks	3	4.50	13.50
		Ties	3		
		Total	9		
	Trail Making Number Seq. F2 Trail Making Number Seq. F1	Negative Ranks	3	4.67	14.00
		Positive Ranks	5	4.40	22.00
		Ties	1		
		Total	9		
	Trail Making Letter Seq. F2 Trail Making Letter Seq. F1	Negative Ranks	3	4.17	12.50
		Positive Ranks	4	3.88	15.50

		Ties	2		
		Total	9		
	Trail Making Switch. F2 – Trail Making Switch. F1	Negative Ranks	2	3.75	7.50
		Positive Ranks	3	2.50	7.50
		Ties	4		
		Total	9		
	Trail Making Motor Sp. F2 – Trail Making Motor Sp. F1	Negative Ranks	2	2.00	4.00
		Positive Ranks	4	4.25	17.00
		Ties	3		
		Total	9		
MO	Trail Making Vis. Scan F2 Trail Making Vis. Scan F1	Negative Ranks	1	3.50	3.50
		Positive Ranks	6	4.08	24.50
		Ties	2		
		Total	9		
	Trail Making Number Seq. F2 – Trail Making Number Seq._F1	Negative Ranks	4	4.88	19.50
		Positive Ranks	3	2.83	8.50
		Ties	2		
		Total	9		
	Trail Making Letter Seq. F2 Trail Making Letter Seq. F1	Negative Ranks	1	2.50	2.50
		Positive Ranks	7	4.79	33.50
		Ties	1		
		Total	9		
	Trail Making Switch F2 – Trail Making Switch F1	Negative Ranks	1	2.00	2.00
		Positive Ranks	6	4.33	26.00
		Ties	2		
		Total	9		
	Trail Making Motor Sp. F2 Trail Making Motor Sp. F1	Negative Ranks	2	2.50	5.00
		Positive Ranks	2	2.50	5.00
		Ties	5		
		Total	9		
Placebo	Trail Making Vis. Scan F2 – Trail Making Vis. Scan F1	Negative Ranks	2	3.00	6.00
		Positive Ranks	3	3.00	9.00
		Ties	5		
		Total	10		
	Trail Making Number Seq. F2 Trail Making Number Seq. F1	Negative Ranks	2	1.50	3.00
		Positive Ranks	2	3.50	7.00
		Ties	6		
		Total	10		
	Trail Making Letter Seq. F2 – Trail Making Letter Seq. F1	Negative Ranks	1	8.50	8.50
		Positive Ranks	8	4.56	36.50
		Ties	1		
		Total	10		
	Trail Making Switch F2 – Trail Making Switch F1	Negative Ranks	0	.00	.00
		Positive Ranks	4	2.50	10.00
		Ties	6		
		Total	10		
	Trail Making Motor Sp. F2 – Trail Making Motor Sp. F1	Negative Ranks	2	2.75	5.50
		Positive Ranks	4	3.88	15.50
		Ties	4		
		Total	10		

Test Statistics

Group		Trail Making Vis. Scan F2 – Trail Making Vis. Scan F1	Trail Making Num. Seq. F2 – Trail Making Num. Seq. F1	Trail Making Lett. Seq. F2 – Trail Making Lett. Seq. F1	Trail Making Switch F2 – Trail Making Switch F1	Trail Making Motor Sp. F2 – Trail Making Motor Sp F1
OM	Z	-0.65	-0.57	-0.26	<0.01	-1.39
	Asymp. Sig (2-tailed)	.516	.572	.798	1.000	.163
MO	Z	-1.90	-0.94	-2.20	-2.06	<0.01
	Asymp. Sig (2-tailed)	.058	.347	.028	.040	1.000
Placebo	Z	-0.41	-0.74	-1.68	-1.89	-1.06
	Asymp. Sig. (2-tailed)	.680	.461	.093	.059	.288

Ranks

Group			N	Mean Rank	Sum of Ranks
OM	Verbal Fluency Letters F2 Verbal Fluency Letters F1	Negative Ranks	6	4.33	26.00
		Positive Ranks	3	6.33	19.00
		Ties	0		
		Total	9		
	Verbal Fluency Cat. F2 – Verbal Fluency Cat. F1	Negative Ranks	4	4.88	19.50
		Positive Ranks	4	4.13	16.50
		Ties	1		
		Total	9		
	Verbal Fluency Switch F2 Verbal Fluency Switch F1	Negative Ranks	4	5.50	22.00
		Positive Ranks	4	3.50	14.00
		Ties	1		
		Total	9		
MO	Verbal Fluency Letters F2 Verbal Fluency Letters F1	Negative Ranks	3	3.17	9.50
		Positive Ranks	3	3.83	11.50
		Ties	3		
		Total	9		
	Verbal Fluency Cat. F2 - Verbal Fluency Cat. F1	Negative Ranks	1	5.50	5.50
		Positive Ranks	7	4.36	30.50
		Ties	1		
		Total	9		
	Verbal Fluency Switch F2 Verbal Fluency Switch F1	Negative Ranks	1	2.00	2.00
		Positive Ranks	7	4.86	34.00
		Ties	1		
		Total	9		
Placebo	Verbal Fluency Letters F2 Verbal Fluency Letters F1	Negative Ranks	2	2.50	5.00
		Positive Ranks	8	6.25	50.00
		Ties	0		
		Total	10		
	Verbal Fluency Cat. F2 - Verbal Fluency Cat. F1	Negative Ranks	3	4.83	14.50
		Positive Ranks	7	5.79	40.50
		Ties	0		
		Total	10		
	Verbal Fluency Switch F2 Verbal Fluency Switch F1	Negative Ranks	1	3.00	3.00
		Positive Ranks	6	4.17	25.00
		Ties	3		
		Total	10		

Test Statistic

Group		Verbal Fluency Letters F2 - Verbal Fluency Letters F1	Verbal Fluency Cat. F2 - Verbal Fluency Cat. F1	Verbal Fluency Switch F2 - Verbal Fluency Switch F1
OM	Z	-0.42	-0.21	-0.59
	Asymp. Sig. (2-tailed)	.672	.833	.558
MO	Z	-0.21	-1.78	-2.25
	Asymp. Sig. (2-tailed)	.833	.076	.025
Placebo	Z	-2.32	-1.34	-1.89
	Asymp. Sig. (2-tailed)	.020	.182	.059

Ranks

Group			N	Mean Rank	Sum of Ranks
OM	Colour Word Naming F2 - Colour Word NamingF1	Negative Ranks	3	3.33	10.00
		Positive Ranks	2	2.50	5.00
		Ties	3		
		Total	8		
	Colour Word Reading F2 - Colour Word Reading F1	Negative Ranks	3	2.00	6.00
		Positive Ranks	0	.00	.00
		Ties	5		
		Total	8		
	Colour Word Inhibition F2 - Colour Word Inhibition F1	Negative Ranks	2	2.50	5.00
		Positive Ranks	2	2.50	5.00
		Ties	4		
		Total	8		
	Colour Word Switching F2 - Colour Word Switching F1	Negative Ranks	3	2.67	8.00
		Positive Ranks	2	3.50	7.00
		Ties	3		
		Total	8		
MO	Colour Word Naming F2 - Colour Word Naming F1	Negative Ranks	5	4.80	24.00
		Positive Ranks	3	4.00	12.00
		Ties	1		
		Total	9		
	Colour Word Reading F2 - Colour Word Reading F1	Negative Ranks	4	4.25	17.00
		Positive Ranks	4	4.75	19.00
		Ties	1		
		Total	9		
	Colour Word InhibitionF2 - Colour Word Inhibition F1	Negative Ranks	4	3.63	14.50
		Positive Ranks	2	3.25	6.50
		Ties	3		
		Total	9		
	Colour Word Switching F2 - Colour Word Switching F1	Negative Ranks	3	5.83	17.50
		Positive Ranks	5	3.70	18.50
		Ties	1		
		Total	9		
Placebo	Colour Word Naming F2 - Colour Word Naming F1	Negative Ranks	2	3.00	6.00
		Positive Ranks	4	3.75	15.00
		Ties	4		
		Total	10		
		Negative Ranks	3	3.50	10.50

Colour Word ReadingF2 - Colour Word Reading F1	Positive Ranks	3	3.50	10.50
	Ties	3		
	Total	9		
Colour Word Inhibition F2 - Colour Word Inhibition F1	Negative Ranks	5	4.40	22.00
	Positive Ranks	3	4.67	14.00
	Ties	1		
	Total	9		
Colour Word Switching F2 - Colour Word Switching F1	Negative Ranks	2	2.50	5.00
	Positive Ranks	6	5.17	31.00
	Ties	1		
	Total	9		

Test Statistics

Group		Colour Word Naming F2 - Colour Word Naming F1	Colour Word Reading F2 - Colour Word Reading F1	Colour Word Inhibition F2 - Colour Word Inhibition F1	Colour Word Switching F2 - Colour Word Switching F1
OM	Z	-0.71	-1.63	0.00	-0.14
	Asymp. Sig. (2-tailed)	.480	.102	1.000	.888
MO	Z	-0.91	-0.14	-0.85	-0.07
	Asymp. Sig. (2-tailed)	.366	.886	.395	.943
Placebo	Z	-1.00	0.00	-0.57	-1.85
	Asymp. Sig. (2-tailed)	.317	1.000	.566	.065

Ranks

Group			N	Mean Rank	Sum of Ranks
OM	Symbol Search F2 – Symbol Search F1	Negative Ranks	2	2.75	5.50
		Positive Ranks	3	3.17	9.50
		Ties	4		
		Total	9		
	SRT Explicit F2 – SRT Explicit F1	Negative Ranks	3	3.83	11.50
		Positive Ranks	3	3.17	9.50
		Ties	1		
		Total	7		
	SRT Implicit F2 – SRT Implicit F1	Negative Ranks	4	3.25	13.00
		Positive Ranks	3	5.00	15.00
		Ties	0		
		Total	7		
MO	Symbol Search F2 – Symbol Search F1	Negative Ranks	3	3.00	9.00
		Positive Ranks	4	4.75	19.00
		Ties	2		
		Total	9		
	SRT Explicit F2 – SRT Explicit F1	Negative Ranks	3	3.67	11.00
		Positive Ranks	5	5.00	25.00
		Ties	0		

		Total	8		
	SRT Implicit F2 – SRT Implicit F1	Negative Ranks	1	6.00	6.00
		Positive Ranks	7	4.29	30.00
		Ties	0		
		Total	8		
Placebo	Symbol Search F2 – Symbol Search F1	Negative Ranks	5	3.00	15.00
		Positive Ranks	3	7.00	21.00
		Ties	2		
		Total	10		
	SRT Explicit F2 – SRT Explicit F1	Negative Ranks	3	5.33	16.00
		Positive Ranks	5	4.00	20.00
		Ties	1		
		Total	9		
	SRT Implicit F2 – SRT Implicit F1	Negative Ranks	2	6.00	12.00
		Positive Ranks	7	4.71	33.00
		Ties	0		
		Total	9		

Test Statistic[a]

Group		Symbol Search F2 – Symbol Search F1	SRT Explicit F2 SRT Explicit F1	SRT Implicit F2 SRT Implicit F1
OM	Z	-0.55	-0.21	-0.17
	Asymp. Sig. (2-tailed)	.581	.833	.866
MO	Z	-.88	-0.98	-1.68
	Asymp. Sig. (2-tailed)	.380	.326	.093
Placebo	Z	-0.43	-0.28	-1.24
	Asymp. Sig. (2-tailed)	.671	.779	.214

Ranks

Group			N	Mean Rank	Sum of Ranks
OM	NEADL F2 – NEADL F1	Negative Ranks	4	2.50	10.00
		Positive Ranks	3	6.00	18.00
		Ties	2		
		Total	9		
	PANAS PA F2 – PANAS PA F1	Negative Ranks	7	5.36	37.50
		Positive Ranks	2	3.75	7.50
		Ties	0		
		Total	9		
	PANAS NA F2 – PANAS NA F1	Negative Ranks	2	2.50	5.00
		Positive Ranks	6	5.17	31.00
		Ties	1		
		Total	9		
	RME F2 – RME F1	Negative Ranks	5	4.60	23.00
		Positive Ranks	4	5.50	22.00

		Ties	0		
		Total	9		
MO	NEADL F2 – NEADL F1	Negative Ranks	3	5.50	16.50
		Positive Ranks	4	2.88	11.50
		Ties	2		
		Total	9		
	PANAS PA F2 – PANAS PA F1	Negative Ranks	6	5.50	33.00
		Positive Ranks	2	1.50	3.00
		Ties	1		
		Total	9		
	PANAS NA F2 – PANAS NA F1	Negative Ranks	4	4.88	19.50
		Positive Ranks	3	2.83	8.50
		Ties	2		
		Total	9		
	RME F2 – RME F1	Negative Ranks	2	3.50	7.00
		Positive Ranks	5	4.20	21.00
		Ties	1		
		Total	8		
Placebo	NEADL F2 – NEADL F1	Negative Ranks	5	4.30	21.50
		Positive Ranks	3	4.83	14.50
		Ties	2		
		Total	10		
	PANAS PA F2 – PANAS PA F1	Negative Ranks	5	4.90	24.50
		Positive Ranks	3	3.83	11.50
		Ties	2		
		Total	10		
	PANAS NA F2 – PANAS NA F1	Negative Ranks	4	4.88	19.50
		Positive Ranks	4	4.13	16.50
		Ties	2		
		Total	10		
	RME F2 – RME F1	Negative Ranks	4	3.25	13.00
		Positive Ranks	3	5.00	15.00
		Ties	2		
		Total	9		

Test Statistics

Group		NEADL F2 – NEADL F1	PANAS PA F2 PANAS PA F1	PANAS NA F2 PANAS NA F1	RME F2 – RME F1
OM	Z	-0.68	-1.78	-1.82	-0.06
	Asymp. Sig. (2-tailed)	.498	.075	.068	.952
MO	Z	-0.42	-2.12	-0.93	-1.21
	Asymp. Sig. (2-tailed)	.672	.034	.352	.228
Placebo	Z	-0.49	-0.92	-0.21	-0.17
	Asymp. Sig. (2-tailed)	.622	.360	.833	.865

E.15 Effect of Period

Memory

Box's Test

Box's M	170.36
F	1.74
df1	56
df2	1747.35
p.	.001

Multivariate Tests

Effect		Value	F	Hypothesis df	Error df	p.	Partial Eta Squared	Noncent. Parameter	Observed Power
Intercept	Pillai's Trace	.26	.94	7.00	19.00	.499	.26	6.58	.30
	Wilks' Lambda	.74	.94	7.00	19.00	.499	.26	6.58	.30
	Hotelling's Trace	.35	.94	7.00	19.00	.499	.26	6.58	.30
	Roy's Largest Root	.35	.94	7.00	19.00	.499	.26	6.58	.30
Group	Pillai's Trace	.74	1.68	14.00	40.00	.101	.37	23.46	.79
	Wilks' Lambda	.37	1.76	14.00	38.00	.084	.39	24.58	.81
	Hotelling's Trace	1.42	1.83	14.00	36.00	.073	.42	25.54	.82
	Roy's Largest Root	1.17	3.34	7.00	20.00	.016	.54	23.37	.87

Trail Making

Box's Test

Box's M	43.94
F	1.02
df1	30
df2	1937.23
Sig.	.43

Multivariate Tests

Effect		Value	F	Hypothesis df	Error df	p.	Partial Eta Squared	Noncent. Parameter	Observed Power
Intercept	Pillai's Trace	.279	1.63	5.00	21.00	.197	.28	8.13	.46
	Wilks' Lambda	.721	1.63	5.00	21.00	.197	. 28	8.13	.46
	Hotelling's Trace	.387	1.63	5.00	21.00	.197	. 28	8.13	. .46
	Roy's Largest Root	.387	1.63	5.00	21.00	.197	. 28	8.13	.46
Group	Pillai's Trace	.503	1.48	10.00	44.00	.180	.25	14.78	.65
	Wilks' Lambda	.507	1.70	10.00	42.00	.113	.29	17.00	.72
	Hotelling's Trace	.954	1.91	10.00	40.00	.073	.32	19.09	.77

	Roy's Largest Root	.934	4.11	5.00	22.00	.009	.48	20.55	.89

Verbal Fluency

Box's

Box's M	24.21
F	1.66
df1	12
df2	2951.75
p.	.07

Multivariate Tests

Effect		Value	F	Hypothesis df	Error df	p.	Partial Eta Squared	Noncent. Parameter	Observed Power
Intercept	Pillai's Trace	.12	1.02	3.00	23.00	.403	.12	3.05	.24
	Wilks' Lambda	.88	1.01	3.00	23.00	.403	.12	3.05	.24
	Hotelling's Trace	.13	1.02	3.00	23.00	.403	.12	3.05	.24
	Roy's Largest Root	.13	1.02	3.00	23.00	.403	.12	3.05	.24
Group	Pillai's Trace	.59	3.38	6.00	48.00	.007	.30	20.26	.91
	Wilks' Lambda	.42	4.13	6.00	46.00	.002	.35	24.78	.96
	Hotelling's Trace	1.33	4.87	6.00	44.00	.001	.40	29.25	.98
	Roy's Largest Root	1.30	10.40	3.00	24.00	<.001	.57	31.20	1.00

Colour Word Interference

Box's Test

Box's M	45.31
F	1.67
df1	20
df2	1839.86
Sig.	.031

Multivariate Tests

Effect		Value	F	Hypothesis df	Error df	p.	Partial Eta Squared	Noncent. Parameter	Observed Power
Intercept	Pillai's Trace	.215	1.37	4.00	20.00	.280	.22	5.48	.35
	Wilks' Lambda	.785	1.37	4.00	20.00	.280	.22	5.48	.35
	Hotelling's Trace	.274	1.37	4.00	20.00	.280	.22	5.48	.35
	Roy's Largest Root	.274	1.37	4.00	20.00	.280	.22	5.48	.35
Group	Pillai's Trace	.419	1.39	8.00	42.00	.229	.21	11.13	.55

	Wilks' Lambda	.606	1.42	8.00	40.00	.217	.22	11.38	.56
	Hotelling's Trace	.609	1.45	8.00	38.00	.210	.23	11.57	.56
	Roy's Largest Root	.532	2.79	4.00	21.00	.053	.35	11.16	.66

Symbol Search and SRT

Box's Test

Box's M	13.72
F	0.90
df1	12
df2	1900.85
p.	.550

Multivariate Tests

Effect		Value	F	Hypothesis df	Error df	p.	Partial Eta Squared	Noncent. Parameter	Observed Power
Intercept	Pillai's Trace	.11	0.75	3.00	19.00	.538	.11	2.24	.18
	Wilks' Lambda	.90	0.75	3.00	19.00	.538	.11	2.24	.18
	Hotelling's Trace	.12	0.75	3.00	19.00	.538	.11	2.24	.18
	Roy's Largest Root	.12	0.75	3.00	19.00	.538	.11	2.24	.18
OverallGroup	Pillai's Trace	.24	0.91	6.00	40.00	.501	.12	5.43	.31
	Wilks' Lambda	.76	0.92	6.00	38.00	.492	.13	5.51	.32
	Hotelling's Trace	.31	0.93	6.00	36.00	.487	.13	5.56	.32
	Roy's Largest Root	.30	2.01	3.00	20.00	.145	.23	6.04	.44

NEADL, PANAS and RME

Box's Test

Box's M	37.75
F	1.39
df1	20
df2	1839.86
p.	.114

Multivariate Tests

Effect		Value	F	Hypothesis df	Error df	p.	Partial Eta Squared	Noncent. Parameter	Observed Power
Intercept	Pillai's Trace	.18	1.11	4.00	20.00	.378	.18	4.45	.29
	Wilks' Lambda	.82	1.11	4.00	20.00	.378	.18	4.45	.29
	Hotelling's Trace	.22	1.11	4.00	20.00	.378	.18	4.45	.29
	Roy's Largest Root	.22	1.11	4.00	20.00	.378	.18	4.45	.29
Group	Pillai's Trace	.48	1.65	8.00	42.00	.140	.24	13.19	.64
	Wilks' Lambda	.57	1.60	8.00	40.00	.156	.24	12.79	.62

Hotelling's Trace	.65	1.55	8.00	38.00	.175	.25	12.36	.60
Roy's Largest Root	.45	2.35	4.00	21.00	.088	.31	9.38	.58