The Age of Onset of Cannabis Use and Executive Function

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Candidate's Statement

This is to certify that the research described in this thesis is solely my own work.

Signed:..... James Reynolds

Acknowledgements

I would like to thank all the people who were involved with each project including all participants and organisations involved helping me data collect. The time and effort taken out of their busy schedules to help me complete my PhD was highly appreciated.

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Abstract

This thesis explored the association between cannabis use and executive function, with a specific focus on the age of onset of cannabis use. Previous research has provided some preliminary evidence that early onset cannabis use, namely cannabis initiation during the early teenage years or younger, is associated with greater cognitive deficits than later onset use. The first study within this thesis included a large battery of validated neuropsychological tasks administered to cannabis users, controls and tobacco using controls to compare executive function performance. This approach found several cognitive domains in which cannabis users performed at significantly lower levels than the two controls groups. Further analyses showed that the early onset cannabis users ($\leq$15 years) were performing at lower levels on some of these tests than late onset users ($\geq$16 years) when compared to the control groups. While the early onset hypothesis did not explain all of the deficits in the cannabis using groups there was a clear pattern for early onset users to be impaired at a greater level on some tests. In particular, it appeared that the cannabis-related deficits were more pronounced on tests which required visual scanning, set switching abilities and visuo-motor coordination. While the visuo-motor deficits were quite clear, it could not be determined if visual scanning deficits were explaining the performance deficits on the set switching task.

Subsequently an eye-tracking study was conducted to investigate the age of onset of cannabis use effects on visual scanning and set switching processes. This study suggested that visual scanning was impaired while set switching processes remained intact in cannabis users. Furthermore, this study found some support of an age of onset effect; two of the dependent variables showed evidence of greater impairments among early onset cannabis users relative to the other groups.

In addition this thesis includes a large scale survey which assessed lifestyle predictors of the age of onset of cannabis use. Two lifestyle factors were highly associated with executive function abilities - other drug use and educational achievement - were predictors of the age of onset of cannabis use. As the two quasi-experimental studies controlled for these two variables, in addition to other confounding variables, it is unlikely they were explaining the pattern of deficits reported.

Based on data presented here and supported by existing multidisciplinary research, it is argued that the relationship between cannabis use and cognition reported in this thesis is causal. While cannabis may have a causal impact on cognitive performance, such as visual search and visuo-motor coordination, the cannabis users still performed at a "normal" level. The severity of cognitive impairments does appear to be mediated by early onset cannabis use, however not all cognitive processes appear to be at risk for these greater impairments. Findings may indicate a developmental vulnerability to cannabis use.

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Chapter One. Literature Review

1.1. Cannabis

1.1.1. Terminology

The use of cannabis is so ubiquitous that countless terms have been created to describe the drug and the means by which it is used. Jacquette (2010) attempted to collate some of these terms in his book on the philosophy of cannabis by alphabetically naming over two pages worth of cannabis-related synonyms. Although such an audacious task will not be attempted here, the terminology used in the current thesis will briefly be described.

For the purposes of this thesis the term *cannabis* will be used to describe the drug derived from the plant cannabis *sativa.* This term will be used in place of the American synonym *marijuana* and the colloquialisms *weed, hash,* and *skunk*, although these are not in the strictest sense the same substances. The name of the drug sometimes varies dependent on the different growing and manufacturing processes of the plant. The term *spliff* is used to describe a common method of smoking cannabis. A spliff typically consists of a cigarette paper filled with cannabis, occasionally tobacco, and rolled into a cone shaped 'cigarette' to then smoke. For a full description of the various devices used to consume cannabis see Appendix A.1.1.

Regarding cannabis *use*, the term *acute* refers to the stage of cannabis use at which physiological and psychological effects are occurring shortly after consuming the drug and this term can be used interchangeably with the synonym *intoxication*. The term *withdrawal* refers to the stage of cannabis use during which deleterious physiological and psychological effects are associated with the decline in levels of the drug within the blood or tissue. The term *chronic* is used to describe long term drug use, such that chronic cannabis use related damage, refers to the damage done by long term cannabis use rather than the acute or withdrawal stages.

Other recreational drug use, not including cannabis use, tobacco use or alcohol use, will be referred to as *other drug use.* Examples include ecstasy and amphetamines.

1.1.2. Cannabinoids

Among the numerous chemical compounds discovered in the cannabis plant, 70 types of cannabinoids have been identified (Turner, 1980; Elsohly & Slade, 2005). The main groups of cannabinoids include: Δ^9-TetraHydroCannabinol (Δ^9-THC), Δ^8-THC, cannabinol, and cannabidiol.

1.1.2.1. Psychoactive Cannabinoids

Δ^9-THC is the primary psychoactive component of cannabis and the central focus of numerous studies investigating the many properties of the drug (Kalant, 2001). Additional psychoactive cannabinoids include Δ^8-THC and cannabinol. The two strongest psychoactive cannabinoids, Δ^9-THC and Δ^8-THC, have a much stronger affinity to bind with CB_1 receptors than the weaker psychoactive cannabinoid, cannabinol.

1.1.2.2. Cannabidiol (CBD)

The other salient cannabinoid is CBD, and although it is not psychotropic (Grotenhermen, 2003), nor does it bind with CB_1 receptors, it appears to reduce the effects of Δ^9-THC. CBD has been shown to reduce anxiety and subjective intoxication induced by Δ^9-THC (Niesink & van Laar, 2013; Zuardi, Shirakawa, Finkelfarb & Karniol, 1982) and acute injections of both of these cannabinoids have been shown to have opposite functional effects on regional brain activity, namely hypo- vs. hyperactivity during cognitive tasks across a range of brain regions (Bhattacharyya et al., 2009).

1.1.3. Cannabis Use

1.1.3.1. Recreational Use

Cannabis is the most commonly used illegal drug in the World (United Nations Office on Drugs and Crime, 2011). Cannabis use in 2009/10 was reported at 6.6% of the population for England and Wales, this figure rises to 7.4% in Northern Ireland and 8.4% in Scotland (Home Office, 2010). Elsewhere in the world these rates increase for the United States of America (USA; 13.4%) and go as high as 24.2% for Palau (United Nations Office on Drugs and Crime, 2011). Figure 1.1 highlights several groups at

higher risk for the use of cannabis such as males, younger individuals, students, the unemployed, and mixed-race ethnicities.

While these figures suggest that cannabis use is quite high this does not describe the rate at which people become addicted to the drug. Epidemiological data has helped answer this question by showing that approximately 9% of individuals who use cannabis become addicted based on a nationally representative sample located within America (Anthony, Warner & Kessler, 1994). This diagnosis was made by use of the DSM-III (American Psychiatric Association, 1980) and as the diagnostic criteria has changed over the updated DSM versions, any newer findings need to be compared while considering the method used to assess addiction or "cannabis use disorder", as it is currently called (DSM-V; American Psychiatric Association, 2013). While these estimates typically deal with the percentage of individuals who have used cannabis in the year prior to testing or the percentage of individuals who have used cannabis once in their lifetimes, this does not differentiate between those who have tried the drug once and those who are regular users. In contrast, Compton, Grant, Colliver, Glantz and Stinson (2004) also analysed data from two large cohorts of individuals from the USA and found that dependence rates were much higher at approximately 30-35%. These differences could be due to that Compton et al (2004) used the less strict DSM-IV (American Psychiatric Association, 1994) to determine abuse and dependence.

Three main types of cannabis are used within the UK based on police seizures: cannabis resin, herbal cannabis, and *sinsemilla* (Potter, Clark & Brown, 2008). There are varying effects of acute cannabis use which are partially dependent on the type of cannabis used; as the production, the sex, and the part of the plant which is selected will dictate the level of cannabinoids consumed. Within the UK the most popularly consumed variety of cannabis is *sinsemilla*, accounting for 55% of the cannabis seized in 2004/5. Colloquially referred to as 'skunk', this variety of cannabis refers to the female plant grown without contact to the male's pollen thus leading to a complete lack of seeds. This variety of the plant boasts high levels of Δ^9-THC and relatively low levels of CBD in contrast to its frequently consumed relatives. Seized sinsemilla within the UK has shown a Δ^9-THC content of 13.3% whilst its nearest competitor, cannabis resin, contains low Δ^9-THC levels at around 3.7%. Additionally, CBD, which has been shown to ameliorate some of the effects of THC (Niesink & van Laar, 2013; Zuardi et al, 1982) and produces no psychotropic effects of its own, is much more prevalent in resin (4.2%) compared to sinsemilla in which the levels are below the detectable threshold of 0.1%.

Not all cannabis use is illegal as several regions have decriminalised or legalised the recreational use of cannabis. At this point in time the regions which have legalised recreational cannabis use are two USA states, Colorado (Amendment 64, 2012) and Washington (Initiative 502, 2012), in addition to two countries, Uruguay (Room, 2014) and the Netherlands (Caulkins et al., 2011). This is worth considering as the levels of cannabinoids in the finished plant and the products used during the manufacturing process are likely to differ between the illegal and legal/regulated growing procedures.

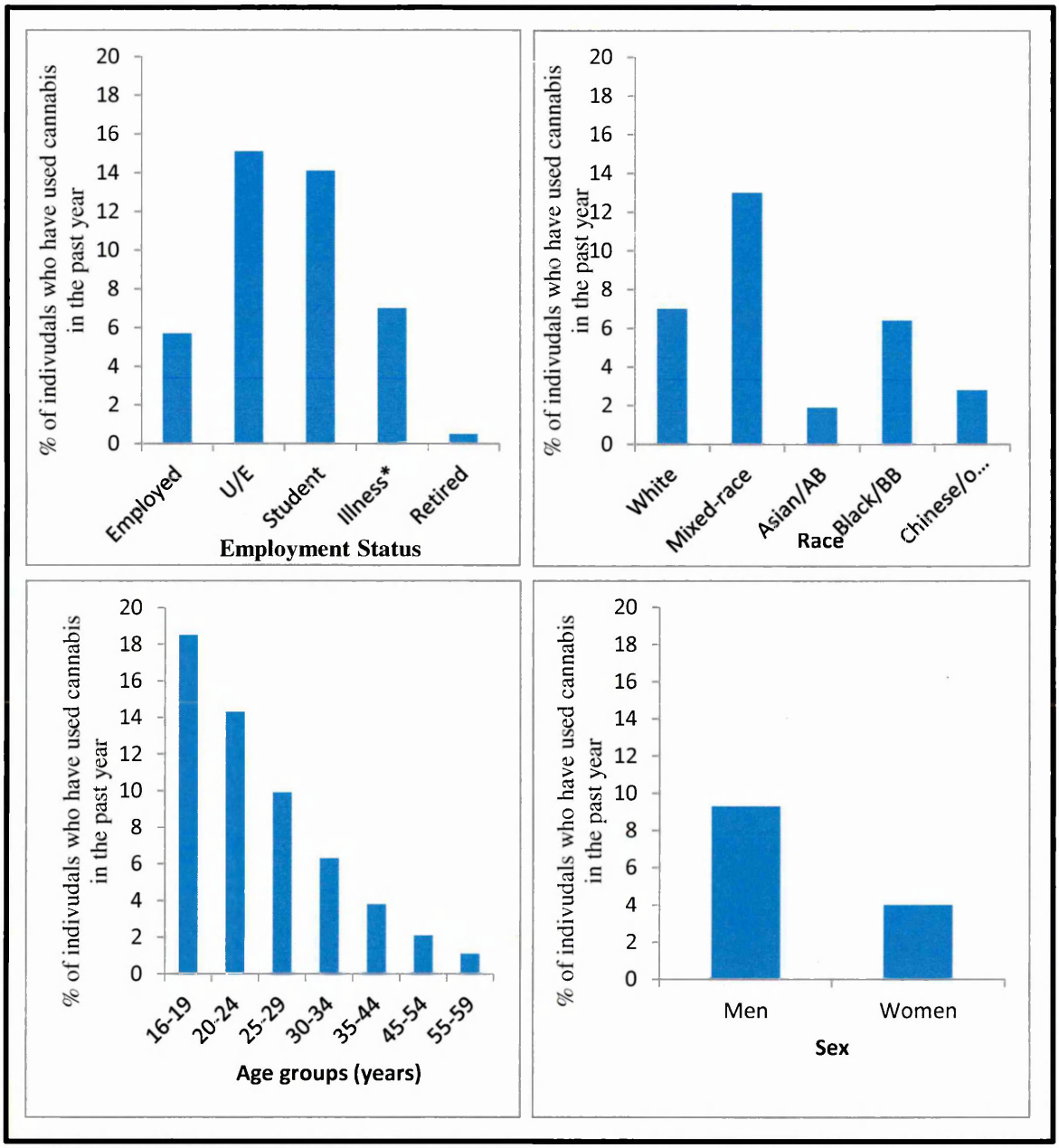


Figure 1.1. A series of graphs displaying the varying percentages of individuals with the UK who have used cannabis in the past year among different groups. Data taken from

British Crime Survey, Home Office Statistics (2010). AB = Asian-British; BB = Black British; U/E = Unemployed; *long term or temporarily ill and unable to work.

1.1.3.2. Cannabis as a Medicine

Medical grade cannabis is now available for prescription in several countries throughout the world to treat various ailments. Clinical studies show promising results for the analgesic effects of varying cannabis derivatives on a variety of different pains (Holdcroft et al., 1997). There is also evidence suggesting it can reduce vomiting and nausea symptoms induced from chemotherapy (Tramer et al., 2001), can help reduce convulsions associated with epilepsy (Cunha et al., 1980) and help reduce symptoms associated with multiple sclerosis (Baker, Jackson & Pryce, 2007). The current research programme focussed on recreational cannabis users as opposed to those with prescribed medicinal cannabis and therefore this will not be discussed any further.

1.1.3.3. Summary

The recreational and medicinal based use of the drug highlights the prevalence of cannabis use throughout the world. This necessitates an investigation into the possible adverse effects of chronic cannabis use.

1.1.4. Cannabis and the Brain

1.1.4.1. Cannabinoid receptor sites

The two known binding sites for cannabinoids are the CB_1 and CB_2 receptors. The highest densities of CB_1 receptors are found in the basal ganglia and cerebellum. High densities are also found in the hippocampus and throughout the cerebral cortex (Herkenham et al., 1990). Eggan and Lewis (2007) examined how CB_1 receptors are distributed throughout the macaque neocortex. Their primary finding was that prefrontal cortex CB_1 density was much greater than sensory or motor cortices. More specifically, the DLPFC was the area of the prefrontal cortex with the highest density. Secondary findings show support for Herkenham et al. (1990) by displaying the highest densities of CB_1 receptors in the basal ganglia structures, the molecular layer of the cerebellum, the dendate gyrus and amygdala. Although there are clear interspecies differences as seen in Figure 1.2, Eggan and Lewis (2007) show that prefrontal cortex regions have the highest levels of CB_1 receptors throughout the cortex.

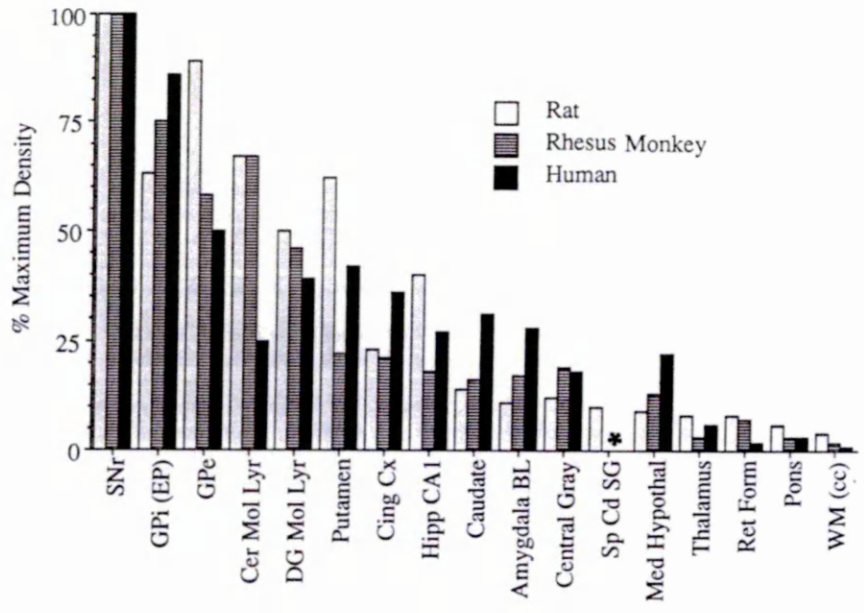


Figure 1.2. A graph reproduced from Herkenham et al (1990), displaying the varying density of CB1 receptors in different brain regions. SNr = substantia nigra; GPi = interntal segment of the globus pallidus; EP = entopendulcular nucleus; GPe = external segment of the globus pallidus; Cer Mol Lyr = cerebellum molecular layer; DG Mol Lyr = dendate gyrus molecular layer; Cing Cx = cingulate cortex; Hipp CA1 = hippocampal field CA1; BL = this abbreviation was not defined by the authors but likely refers to either basal lateral or basal regions of the amygdala; Sp Cd SG = substantia gelatinosa of spinal cord* only rat measured; Med Hypothal = medial hypothalamus; Ret Form = reticular formation; WM(cc) = white matter of the corpus callosum.

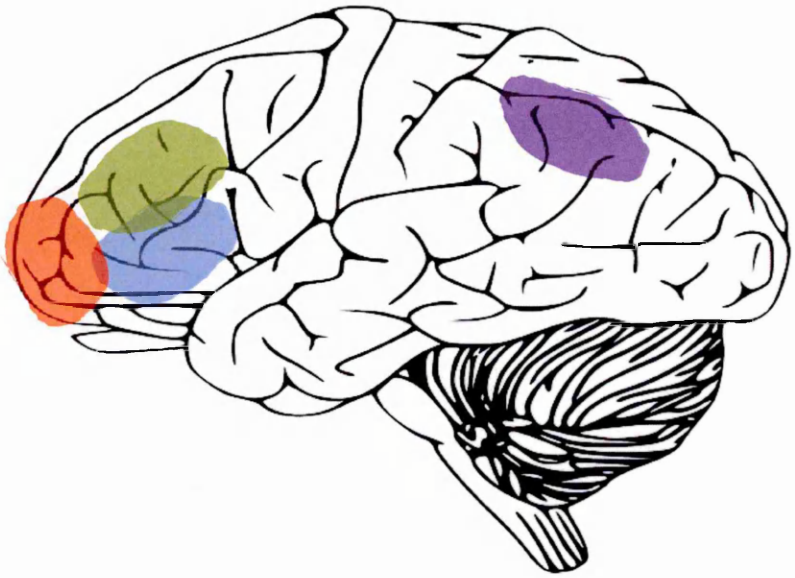


Figure 1.3. A lateral view of the left hemisphere of the brain. The red shaded area represents the ventromedial prefrontal cortex; the blue represents the inferior frontal cortex/gyrus; the olive represents the dorsolateral prefrontal cortex; the purple represents the intraparietal sulcus.

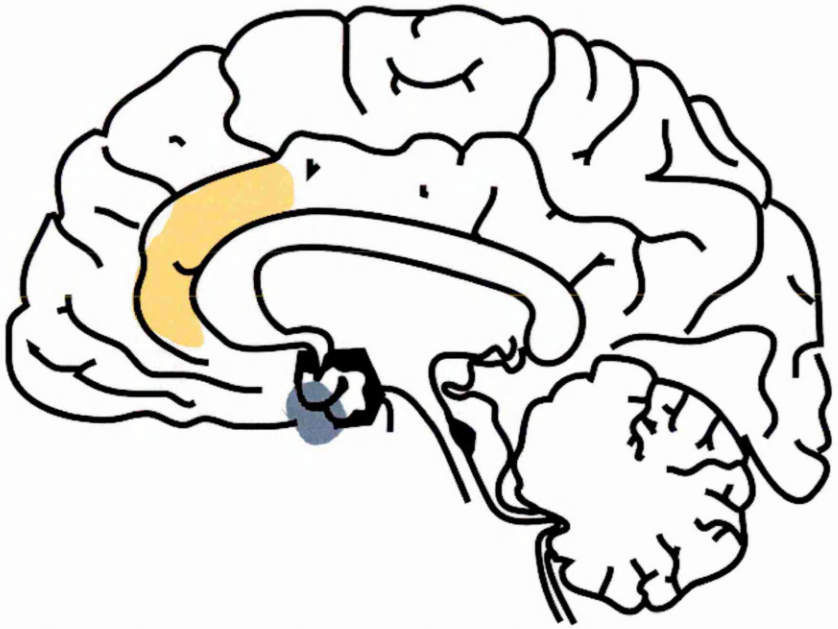


Figure 1.4. A sagittal view of the brain. The orange shaded area represents the anterior cingulate cortex; the teal represents the approximate area of the amygdala.

1.1.5. The Effects of Cannabis on the Brain

The current thesis is investigating whether cannabis use has long term detrimental effects on cognition. In order to examine a possible mechanism for these effects, the impact of cannabinoids on the brain will be discussed here.

1.1.5.1. The Neurotoxic Effects of Cannabinoids

Animal studies have provided strong evidence for the neurotoxic properties of cannabis. Administration of Δ^9-THC to rats over a long timescale was found to cause decreased neuronal density in hippocampal neurons (Landfield, Cadwallader & Vinsant, 1988; Scallet et al., 1987). These findings have been partially supported by the detection of markers of apoptosis in cortical neurons following the administration of similar doses of Δ^9-THC to neonatal rats (Downer, Gowran & Campbell, 2007). These findings have also been supported by in vitro studies of rat neurons in which Δ^9-THC was associated with cell damage (Campbell, 2001; Chan, Hinds, Impey & Storm, 1998; Downer, Fogarty & Campbell, 2003).

Potentially contradictory findings have been ever present in this field which suggest that cannabinoids, including Δ^9-THC, can also be neuroprotective (e.g. van der Stelt et al., 2001a; van der Stelt et al., 2001b; Carroll, Zeissler, Hanemann & Zajicek, 2012). Sarne et al (2011) suggest one viable explanation for the apparent contradiction is that cannabinoids are neurotoxic to the brain cells, however this damage triggers a conditioning mechanism which can help protect against future damage.

The potential toxicity of cannabis in humans is far less clear. Lorenzetti, Lubman, Whittle, Solowij and Yucel (2010) provided a review of the literature on the relationship between cannabis use and brain structure in humans.

The review showed largely mixed findings with some evidence of volumetric differences across cannabis users and controls in specific regions (e.g. Matochik, Eldreth, Cadet & Bolla, 2005; Medina et al., 2007; Yucel et al., 2008), some evidence of early onset use being associated with greater group differences (Wilson et al., 2000), and some which show no differences or even greater regional volumes in cannabis users (Block et al. 2000; Medina et al., 2007; Tzilos et al., 2005; Jager et al., 2007). Among the studies which did find differences there was a distinct lack of regional consensus such that some studies found reductions in hippocampal volume (Matochik et al., 2005; Yucel et al., 2008) while another found an increase in hippocampal volume (Medina et

al., 2007), and three showed no effect of cannabis on hippocample volume (Block et al., 2000; Medina et al., 2007; Wilson et al., 2000). Lorenzetti et al (2010) suggest that as these studies are so few in number, and that the effects of cannabis on certain brain regions are yet to be replicated, it is too early to interpret the findings regarding whether or not cannabis leads to morphological changes.

One more recent study used a longitudinal methodology to test whether brain volumes which predate cannabis use will later predict cannabis use onset (Cheetham et al., 2012). The authors found that orbitofrontal cortex (OPFC) volume at age 12 predicted later cannabis use onset, yet regions such as the hippocampus and amygdala which were found to have reduced volumes in earlier research (Matochik et al., 2005; Yucel et al., 2008), were not predictive of later cannabis onset. As this was the first study to address the question longitudinally (Cheetham et al., 2012), it cannot be stated as to how brain volume and cannabis use are linked and whether there is a more complex and dynamic, transactional interplay. A more recent study using a non-longitudinal study confirmed this association between cannabis use and OPFC volume (Filbey et al. 2014). In particular the authors found that the age of cannabis onset was related to such volume in a manner previously reported by Wilson et al (2000). Filbey et al (2014) argue that the consensus in the animal literature suggests toxicity is a viable explanation however they also highlight that the previous results by Cheetham et al (2012) point to neurological differences explaining cannabis use, as opposed to vice versa. Due to the quasi-experimental nature of this research it is also possible that a third variable was explaining the association.

1.1.5.2. Dopaminergic Dysregulation

Recently Bloomfield et al (2014) used Positron Emission Tomography (PET) to examine dopamine synthesis in cannabis users and controls. The authors found that dopamine synthesis was reduced within the corpus striatum of cannabis users, and the "heavy" cannabis users, users with diagnoses of dependence, and early onset cannabis users had the lowest dopamine synthesis. As each of these correlations - cannabis use & age of onset with dopamine synthesis – did not control for the other cannabis use variables it is not clear if the early onset relationship is due to greater cannabis use, or vice versa. Despite this limitation, this research provides clear findings for a reduction in dopamine synthesis among human cannabis users. These findings partially contradict earlier research which suggests that dopamine function in the striatum does not differ

between cannabis users and controls (Urban et al., 2012). There were substantial sample differences between the two studies, including cannabis use behaviours, which could explain the lack of concordance. Bloomfield et al (2014) suggested the findings reported by Urban et al (2012) could be due to a return to normal functioning given the large period of abstinence from cannabis; approximately four weeks. Although Urban et al (2012) did not find group differences they did also find a relationship between lower dopamine release and an early age of cannabis onset, similar to Bloomfield et al's findings. These mixed results suggest that it is not clear how long term cannabis use affects dopaminergic function in humans.

Due to the quasi-experimental approach used by these two studies (Bloomfield et al., 2014; Urban et al., 2012) a causal role of cannabis on dopaminergic function is hard to determine however among animal studies, experimental approaches increase the ability to infer a causal role of cannabis on such effects. Doses of THC comparable with previous studies examining toxicity (e.g. Landfield et al., 1988) were administered over 14 days to rats which led to significant reductions in prefrontal cortex dopamine transmission after a week's abstinence from the drug (Verrico, Jentsch & Roth, 2003). This builds on previous work identifying similar dopaminergic deficits in the prefrontal cortex (Jentsch, Verrico, Le & Roth, 1998). The authors suggested that these reductions in dopaminergic functioning could be explaining previously found deficits in cognitive function in human cannabis users (e.g. Pope & Yurgellun-Todd, 1995).

1.1.5.3. Summary

While there is strong evidence of cannabis induced neurotoxicity in rats the results are not clear in human research. The quasi-experimental nature of these studies combined with small sample sizes and lack of consistent results make it too early to conclude that cannabis causes brain damage in human cannabis users.

There is also a clear effect of dopaminergic dysfunction after long term cannabis administration in rats and tentatively in humans. While it is not clear if putative neurotoxicity or dopaminergic dysfunction is explaining the cognitive deficits found in human cannabis users, it presents a possible mechanism to explain the effects given the role of dopamine and neurons in cognitive functioning (e.g. Buckholtz et al., 2010).

1.1.6. Cannabis Summary

In this section it is clear that cannabis is a widely used substance despite its predominantly illegal nature. The exact consequences of using these drugs are unclear, yet there is preliminary evidence for neurotoxic effects which could explain reports of cognitive deficits in cannabis users. Given that the levels of Δ^9-THC have been increasing over the past 20 years within the UK (Potter et al., 2008), the potential risk for adverse effects to develop is increasing as time goes by. As the primary binding site for Δ^9-THC, CB_1 receptors, are densely packed in regions involved in executive functions, it is these cognitive processes which are at increased risk of damage, and the focus of this research.

1.2. Executive Function

The term executive function describes a series of higher order cognitive processes involved in the control of behaviour to reach a certain goal (Banich, 2009; Koechlin, 2014; Miyake et al., 2000). Such behaviours are so crucial for normal functioning in society that deficits in executive functioning following trauma predict the likelihood of the ability to live independently (Hanks, Rapport, Millis, & Deshpande, 1999).

1.2.1. Theories of Executive Function

The following section describes some influential, theoretical approaches of executive function. While the terminology has changed over time, the underlying processes which have been described represent early attempts to conceptualise what is now referred to as executive function.

1.2.1.1. Attentional Control Model

The model of attention control (Norman & Shallice, 1986) suggests the existence of one system which selects between conflicting routine actions (the contention scheduling mechanism) and a second which intervenes when dealing with a complex or novel situation that requires conscious processing (Supervisory Activating System; SAS). This has been criticised by assuming that the distinction between executive and other cognitive processes is merely a control-automatic distinction (Stuss & Alexander, 2000). A direct test of the model by Bayliss and Roodenrys (2000) on individuals with ADHD found that this dichotomy between control and automatic is insufficient to explain the pattern of deficits among their participants and concluded that the fractionation of executive function was necessary.

1.2.1.2. Working Memory Model

Baddeley & Hitch (1974) proposed a model of working memory, a temporary information storage system which contained the first description of "executive" processes. The model originally included three components but was subsequently updated to include the episodic buffer, in addition to the original visuo-spatial sketchpad, the phonological loop, and the central executive (Baddeley & Hitch, 2000). This modality-free central executive was suggested to be an attentional control system involved in the coordination of the 'slave' systems. Baddeley et al (1986) incorporated the supervisory activating system (SAS) from the model of attentional control into the theory (Baddeley, 1996; Norman & Shallice, 1980). Following a seminal publication by Stuss and Benson (1984) which reviewed the structure and function of the frontal lobes, Baddeley and Wilson (1988) began to link *dysexecutive syndrome* with the frontal lobes and thus argue for the importance of the frontal lobes in central executive functioning. After Parkin's criticisms of the central executive concept (Parkin, 1988), Baddeley developed the explanation of the central executive to include a number of components which constitute individual executive functions (Baddeley, 1998). These suggested functions were: the capacity to coordinate performance on two different tasks, switch between strategies, attend to a stimulus while inhibiting a second, the ability to access and manipulate information from long-term memory, and hold information within working memory.

1.2.1.3. Hierarchical Feedback-Feedforward Model

Stuss (1992) took the distinction between 'lower' and 'higher' processes and elaborated on this in his three level, Hierarchical Feedback-Feedforward model. The second of three levels includes the supervisory or executive processes such as plan formulation and does not specify that executive function is unitary, unlike earlier models. The model highlights that the novel situations which demand executive processes take longer and more effort than automatic processes completed on level one. The model links these two levels with the third which is involved in metacognition and consciousness. Considerations regarding the development of executive function components along with biological maturational processes are incorporated into the model. It is also stated that executive processes need to be considered more by the hierarchical nature of the cognitive processes than by whether or not the process itself is subserved by the frontal lobes (Stuss, 1992; Stuss & Alexander, 2000). This is a departure from those who

suggest that executive function is the cognitive analogue to the prefrontal cortex (e.g. Koechlin & Summerfield, 2007). Given the many prefrontal cortex networks with cortical and sub-cortical regions of the brain (Middleton & Strick, 2001) there is an inherent problem with ascribing executive function to one specific region.

1.2.1.4. Information Processing Model of Executive Function

By using information processing theory, Koechlin and Summerfield (2007) attempted to quantify executive function. They propose that the key tenet of executive function is the selection of action which is determined by information gathered from stimuli. The model also includes the division of executive function into sensorimotor (stimuli-motor responses), contextual (external context accompany stimuli), and episodic control (involving memory & goals). This assertion is supported by fMRI and behavioural data taken during a variation of the GO/NO-GO paradigm in which sensorimotor, contextual and episodic information was varied (Koechlin, Ody & Kouneiher, 2003). These data suggested that each of these three stages map onto separate regions of the frontal lobes, the rostral Lateral Prefrontal Cortex (LPFC), the caudal LPFC and the premotor cortex are involved in episodic control, context, and sensorimotor responses, respectively. Similar to Stuss (1992), Koechlin and Summerfield (2007) present a hierarchical model of executive function, which they refer to as the cascade model. This cascade model

receives support from the time based activation of each brain region during the task, with activation moving in an anterior-posterior direction (Koechlin et al., 2003).

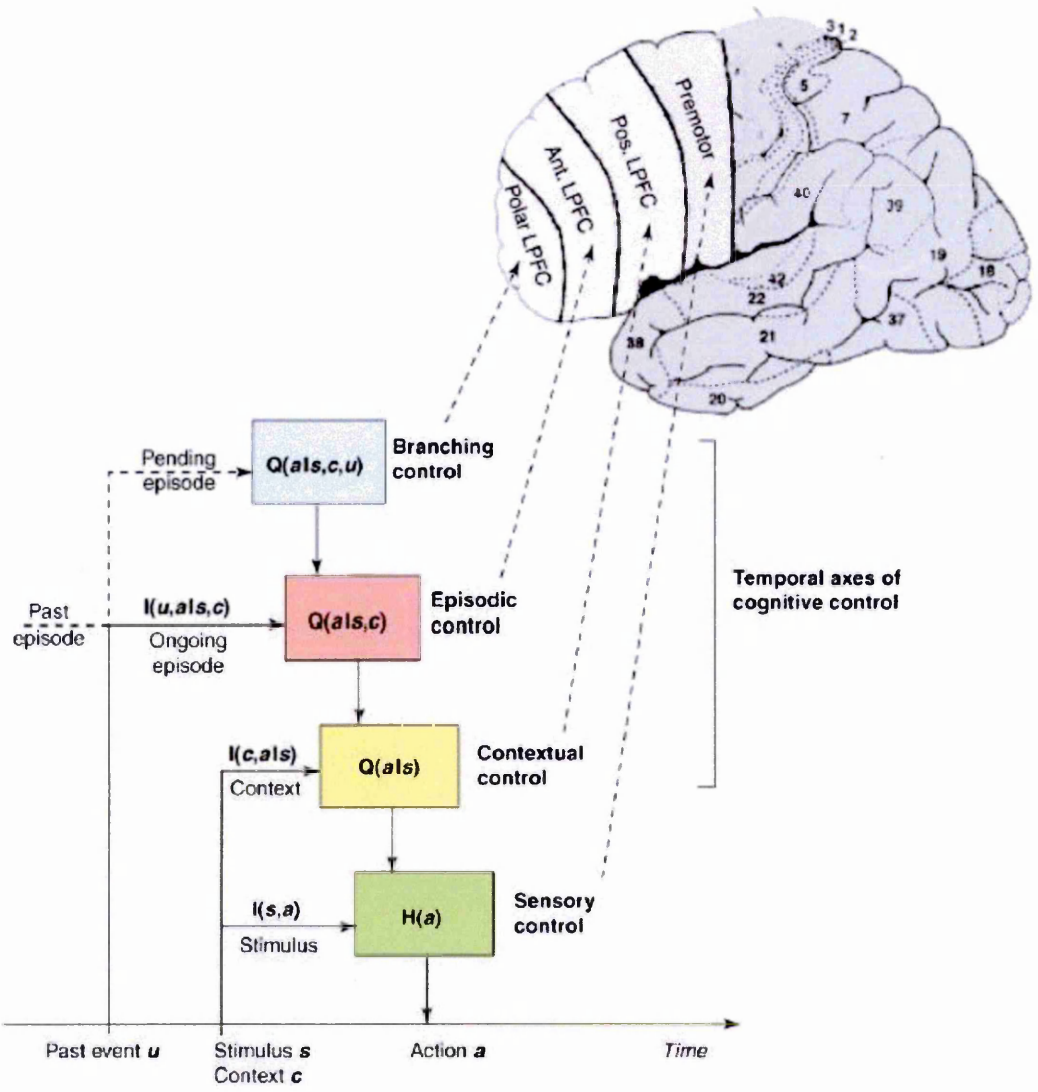


Figure 1.5. An image reproduced from Koechlin & Summerfield (2007) which highlights the various stages of the cascade model and the associated neurological correlates.

1.2.1.5. The Monoaminergic Modulation of Executive Function

One aspect of executive function frequently postulated is that it controls other processes (e.g. Baddeley & Hitch, 1974; Miller & Cohen, 2001; Norman & Shalice, 1986). It is proposed that this 'control' by the prefrontal cortex (PFC) is based on the PFC's ability to prolong, alter or diminish neural firing in other brain regions by use of a monoamine system (Robbins & Arnsten, 2009). This builds on work on identifying neural networks

from the PFC to the basal ganglia (Middleton & Strick, 2001), to sensory cortices, and to the amygdala (Barbas, Zikiopoulos & Timbie, 2011) highlighting the role of the frontal lobes in downstream coordination of emotions, selection of sensory information, and the initiation of actions.

This monoaminergic modulation theory also places an emphasis on the projections *to* the PFC, particularly from the amygdala. This explains previous results identifying that either insufficient or excessive dopamine or noradrenaline in the PFC, such as that which happens during stress, can impair working memory (Birnbaum, Gobeske, Auerbach, Taylor & Arnsten, 1999; Zarht, Taylor, Mathew & Arnsten, 1997).

Although much of the work in this area is with rodents and therefore extrapolations to humans must be treated cautiously, this theory links cognitive and neurological data with neurotransmitter systems and therefore is a crucial part of any potential unified theory of executive function.

1.2.1.6. Executive Function as an Emergent Property

A frequently used conceptualisation of executive function is that it is a property which accounts for the association between executive function task performance in a manner similar to general intelligence (*g*; Banich, 2009). Early factor analysis research within this field found evidence that individual differences in executive function as measured by the tasks selected were actually best explained by a three factor model of shifting, updating, and inhibition (Miyake et al., 2000). If executive function was unitary then it would be expected that a single latent variable would best fit the data however this has not occurred. Despite the clear fractionation of executive function identified by these methods, the latent variables still are associated with each other which leaves a role of executive function (Adrover-Roig, Sesé, Barceló & Palmer, 2012; Friedman et al., 2006; Miyake et al., 2000; Royall, Chiodo & Polk, 2003; Testa, Bennet & Ponsford, 2012).

Despite these findings (e.g. Miyake et al., 2000) there have been suggestions that the general concept of executive function can be abandoned (e.g. Royall & Palmer, 2014). The authors also used a factor analytic approach and suggested that there is no evidence of executive function beyond the role of *g* and memory which therefore implies that any previously tested association between tests of "executive function" are merely an artefact representing *g* and/or memory. This is supported by other work identifying that

fluid intelligence accounts for dementia or schizophrenia related impairments in a number of frequently used executive function tests (Roca et al., 2013; 2014). In contrast, the authors found that fluid intelligence did not account for deficits in multitasking and decision making. Furthermore, Friedmann et al (2006) used similar methods and found that other executive processes are not related to fluid or crystallised intelligence and therefore associations between executive function tasks cannot be completely ascribed to intelligence, based on current methods of assessing IQ, and therefore there still exists a role for "executive function" to explain the association between "executive" tasks.

1.2.1.7. Summary

There is still a considerable amount of controversy surrounding executive function despite attempts to develop a unified theory (Banich, 2009). When discussing what counts as an "executive subcomponent" or an "executive task", there is a distinct lack of clarity and evidence-based protocol for a conclusion to be made. While Figure 1.6 suggests a number of executive processes, the authors rarely give evidence for the executive name-tag (e.g. Powell et al., 2004) and therefore it is difficult to come to a conclusion without appealing to authority. Banich (2009) suggests that the only area of agreement is that damage to the prefrontal cortex impairs executive function. However the support of this proposition is somewhat reminiscent of circular reasoning as Banich states that executive function tasks show prefrontal cortex activity during imaging studies.

An additional classification for an executive process appears to require certain characteristics of the cognitive construct to determine if it can be called "executive". The problem with this approach is that the characteristics are hard to define (Stuss, 2000) or lacking evidence for why that specific definition is "executive". Two examples are that: executive processes are involved in control processes (e.g. Norman & Shallice, 1986) or executive processes are "higher" cognitive processes (e.g. Stuss, 1992). While the division of cognitive processes into distinct levels of a hierarchical model has been suggested to be based on separate prefrontal regions (Banich, 2009; Koechlin & Summerfield, 2007) this does not help define why different levels of these models are more or less "executive". Unlike the term "higher" cognitive functioning; the term "control" processes is easier to operationalise and may be a more testable candidate for describing executive function (Miller & Cohen, 2001). This would mean that any

cognitive process which can be described as having a controlling influence on other processes would be a candidate for being "executive".

Another approach to classifying executive function is that it is an emergent function which explains the correlations between "executive" tasks much in the same way that *g* does (Banich, 2009). This approach has the benefit of being clearly testable by factor analysis methods. Studies have found that performance on "executive" tasks are related to each other even if they are fractionable (Miyake et al., 2001) and these associations exist after controlling for *g* (Friedman et al., 2006; Roca et al., 2013: 2014). In this scenario, any putative executive function could be tested by determining if it is related to other existing executive functions beyond the effects of *g*.

While there may not be a clear definition, the theoretical approaches to executive function suggest that any cognitive process could be tentatively called "executive" if it recruits prefrontal cortex activity, is involved in higher/control processes, and is related to other executive processes.

1.2.2. Executive Function Components

There have been a vast number of suggestions concerning which cognitive processes are executive in nature, below is a figure summarising some of the perspectives.

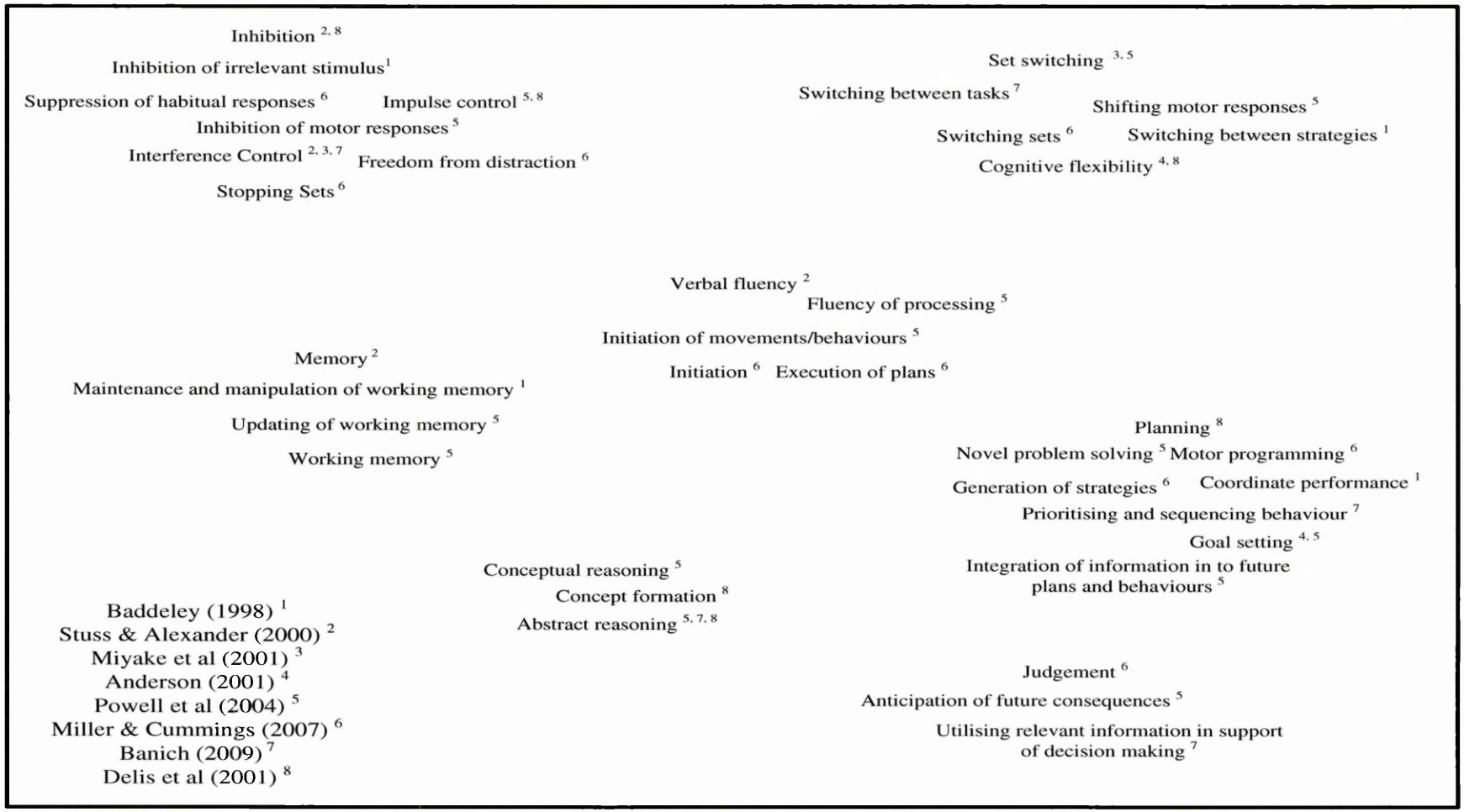


Figure 1.6. An image showing seven clusters of executive function components.

The figure above presents theoretically and experimentally focussed papers describing a large number of executive components. As many of these suggested processes are similar or identical in nature (i.e. attention switching and set switching refer to overlapping concepts) they were grouped into seven separate components which will be discussed here. These components of executive function are inhibition, set switching, working memory, strategic planning, initiation, decision making, and finally, abstract and conceptual reasoning. Although there are potentially more suggested components of executive function than the limited selection presented here, some of the other processes are grouped into these seven categories. For example, a commonly suggested component of executive function is attention, attentional control or regulation of attention (Stuss & Alexander, 2000; Anderson, 2001; Powell et al., 2004) however these were not included as they could be included in either the inhibition category (the suppression of attention) or set switching category (the shifting of attention).

In order to determine the neural substrates which subserve these processes the use of functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) will be discussed. These two methods both indirectly assess brain activity by measuring the 'fuel' use and by-products of active neurons within the brain. The early device, PET, typically monitors the physiological activity of glucose, oxygen or neurotransmitters, while fMRI typically measures blood oxygenation or blood flow (Banich, 2004). The spatial and temporal resolution is much more precise in fMRI and has thus become more frequently used since its later inception.

1.2.2.1. Inhibition

The first component to be considered is inhibition, one of the most commonly examined executive function components (Miyake et al., 2000), however it is described in a number of different ways. Nigg (2000) suggested eight separate forms of inhibition, two of which are automatic, two of which are motivational and four which are effortful and relate to executive processes. These last four classes of executive inhibition are interference control, cognitive inhibition, response inhibition and occulomotor inhibition. Confirmatory factor analysis suggests that interference control, behavioural inhibition and occulomotor inhibition are all closely related (Miyake et al., 2000; Friedman & Miyake, 2004). The focus of this section will be on the two most frequently described and well understood types, interference control and behavioural inhibition. A further suggested form of inhibition is task set inhibition (Aron, Robbins & Poldrack,

2004) which refers to the inhibition of one task set response during a set switching paradigm. In a switching task in which two tasks are alternated every trial (ABA format) the B response is only initiated once after inhibition of the A response, comparable to the dictum "an object in motion continues in motion until a force acts upon it". This will be discussed further in the set switching section (see section 1.2.2.2.).

From the three methods of classification described in Section 1.2.1.7, inhibition is arguably one of the key constructs of executive function. Neuroimaging methods highlight a clear role of the prefrontal cortex in inhibitory processes, in particular the Inferior Frontal Cortex (IFC) during tasks and behaviours which require the "braking" of an action (Aron, Robbins & Poldrack, 2004; Aron, Robbins & Poldrack, 2014). Behaviourally, inhibition exhibits a controlling influence on other cognitive processes by means of slowing them down or stopping them completely (Nigg, 2000). Furthermore, there are clear associations between tasks which reportedly measure inhibitory processes and other putatively executive function tasks (Miyake et al., 2000; Friedman et al. 2006).

1.2.2.2. Set Switching

Set switching, also known as 'attention switching' or 'set shifting', refers to the control and configuration of multiple *task sets*, operations or schemas. The main phenomenon and behavioural measure of set switching studies is the concept of a switch cost. This concept is measurable when a switch from one task to another results in a greater cost than a repeat trial. This cost is observable by greater reaction times and a greater number of errors. These switch costs have been observed in both of the two main subtypes of switching tasks: alternating runs paradigms (ARPs) and task cueing paradigms (TCPs; see Figure 1.7; Altman, 2007). A third paradigm within switching tasks is the prespecified task sequence, which involves a switch every trial. Although the prespecified task sequence (PTS) paradigm does not allow a direct evaluation of switch costs, as every trial is a switch trial, pure repetition trials administered alongside it allow a comparison of switch trials with repeat trials and this analysis also yields evidence of a switch cost (Arbuthnott & Frank, 2000). This switch cost typically encapsulates every additional cognitive process which might aid the task-set reconfiguration from response A to response B. Task-set reconfiguration, referred to as

"- *a sort of mental 'gear changing'* - " (Monsell, 2003; p.135), will largely depend on the task, the paradigm and the switch type.

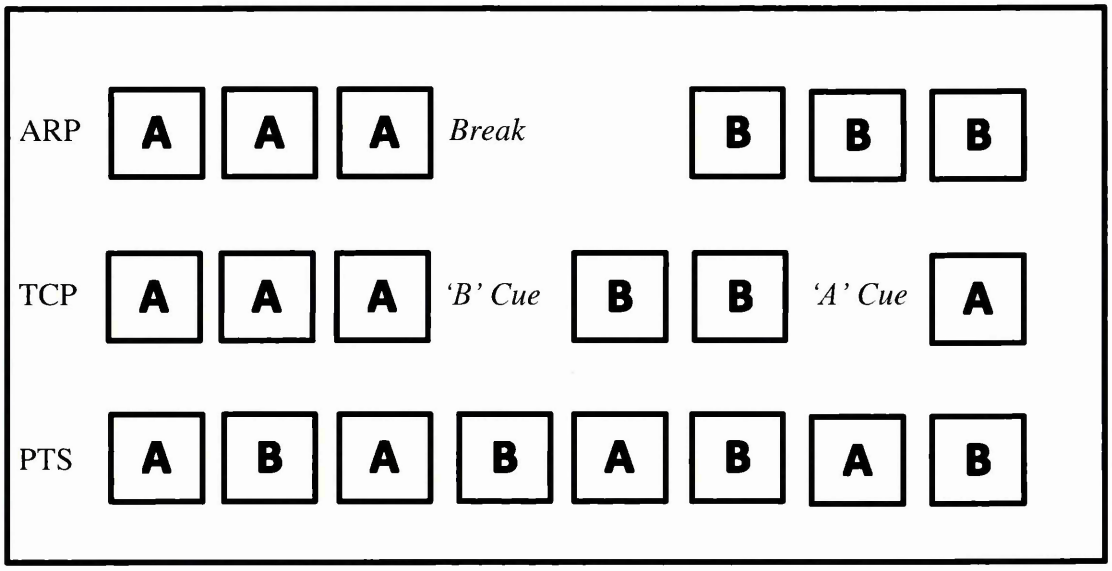


Figure 1.7: An illustration of the three major switching paradigms using a double task (A & B) example. ARP=Alternating Runs Paradigm; TCP= Task Cueing Procedure; PTS= Prespecified Task Sequence.

One factor influencing the scale of the switch cost is advance reconfiguration, in which knowledge of an upcoming switch allows for preparation – to start the 'gear change'- and thus reducing the switch cost. Supporting evidence for advance reconfiguration comes from ARP tasks in which the time between the response in the previous trial and the presentation of the next task stimulus is manipulated (Rogers & Monsell, 1995) and from TCP tasks in which the time between the cue and the stimulus is manipulated (Meiran, 1996). In both cases, larger intervals of time were associated with reductions in switch costs, supporting the advance reconfiguration hypothesis.

Task set inhibition, usually described as contributing towards switch costs, is a vague phenomenon as different switch costs are dependent on the type of switching task (Koch, Gade, Schuch & Philipp, 2010). Therefore Nigg's (2000) theories on inhibitory components cannot be directly applied as the nature of the inhibition varies along with task and paradigm. In tasks which follow a task-cueing paradigm, where the switch is unpredictable, there can be expected to be greater demands on behavioural inhibition. For tasks in which all the stimuli are visually presented on one page (e.g. The Trail Making Test; TMT), and the individual must select the correct response, the authors

suggest that interference control is involved (Delis et al., 2001), however when stimuli appear sequentially on a screen and no distracters are present there is likely to be a greater behavioural inhibition effect (Mayr & Keele, 2000). The evidence for an inhibitory effect in set switching studies comes from two primary sources. Correlational studies show that relationships exist between performance on inhibition tasks and set switching tasks (Langenecker, Zubieta, Young, Akil & Nielson, 2007; Sanchez-Cubillo et al., 2009), yet the strongest evidence for an inhibitory effect comes from n-2 repetition paradigms. Tests which require the switching between three task sets results in higher switch costs when there is a n-2 repetition (ABA) than when there is a n-2 switch (ABC; Mayr & Keele, 2000). If task set reconfiguration was the only contributor to switch costs then it would be expected that the 'ABC' would lead to greater switch costs as there are three separate reconfiguration processes. This higher switch cost for 'ABA' tests has been referred to as backward inhibition, the notion that residual inhibitory effects from previous sets carries over when the reconfiguration process is required to reinitiate.

Arguments for set switching to be an executive process are largely supported by meta-analyses of neuroimaging research (Wager et al., 2004). Although there are inconsistencies between studies which appear to be at least partially mediated by the switching paradigm (e.g. PTS vs TCP) and the switch type (e.g. rule switch vs task switch), there still appears to be a role of prefrontal cortex. These regions include the DorsoLateral PreFrontal Cortex (DLPFC) and the medial PFC, in addition to parietal sulci regions (Wager et al., 2004; Wager et al., 2005; Hyafil, Summerfield & Koechlin, 2009). If set switching, or its constituent processes, can be conceptualised as a gear changing process (Monsell, 2003) then it can be said to influence and control other processes, providing evidence that it could be an executive process. Finally, there is also a clear role for set switching to be related to other "executive tasks" as determined by factor analysis methods (Miyake et al., 2000; Friedman et al., 2006).

1.2.2.3. Working Memory

As discussed in section 1.2.1., one of the early models of working memory (Baddeley, 1998) incorporated executive function components into the theory. Since these original suggestions of executive function being part of the working memory model, there have been suggestions that working memory is a component of executive function (e.g. Brandt et al., 2009). A third perspective suggests that working memory in its

maintenance capacity is not an executive process, yet that constant updating and manipulation of information in working memory requires executive control (Miyake et al., 2000). Despite these varying positions there is an established link between the two phenomena from psychometric studies (McCabe, Roediger III, McDaniel, Balota & Hambrick, 2010) and neuroimaging data (Osaka et al., 2004). It is clear that working memory resources play a key role in the completion of executive function tasks and for this reason is becomes essential to describe it within this section. The current description will differentiate between updating and maintenance, as well as verbal- and visuo-spatial working memory.

Maintenance of working memory representations is the process which limits the decay of information held within working memory. Evidence suggests that maintenance of verbal information is accomplished primarily through articulatory rehearsal, the process of rehearsing verbal information, and attentional refreshing, the process of refreshing memory traces through the focussing of attention (Camos, Lagner & Barrouillet, 2009). With regards to maintenance of working memory representations within the spatial domain, the most commonly suggested mechanism is the attention-based rehearsal hypothesis (Awh, Vogel & Oh, 2006) which suggests that such representations are maintained through a sustained shift in attention to a memorised location. These assumptions have since been refuted by a set of experiments suggesting that a break in spatial attention does not impact spatial working memory and instead the authors suggest a role of the occulomotor system in the coding of spatial information (Belopolsky & Theeuwes, 2009).

Updating involves determining which new items of information are of importance and then revising the list of items held in working memory, by replacing the old with the new, more relevant, pieces of information (Morris & Jones, 1990). Depending on the task situations, whether it be experimental or in a real-world situation, the updating of working memory representations may or may not be dependent on three components: retrieval, transformation and substitution (Ecker, Lewandowsky, Oberauer & Chee, 2010). The specific components which are evoked are dependent on the nature of the task itself. Retrieval of previous information is not always necessary during the updating process if the information is merely substituted with new information, however if information is to be transformed, the existing information must be retrieved and then manipulated into a new piece of information. Ecker et al (2010; p.171)

describe a restaurant scene which elucidates how the three components contribute to the updating of working memory.

While a role of the prefrontal cortex in working memory has been identified there is largely mixed findings when considering working memory as a solitary process. However, when considering the maintenance and updating of working memory as two separate processes there appears to be more consistency (D'Esposito, Postle & Rympa, 2000; Veltman, Rombouts & Dolan, 2003). There also appears to be a modality effect, with the left PFC involved in verbal and the right PFC involved in spatial working memory (D'Esposito, Aguirre, Zarahn, Ballard, Shin & Lease, 1998; Reuter-Lorenz et al., 2000). Based solely on the neuroimaging data, there is a case for updating and maintenance of working memory to be executive processes, even though they recruit different regions of the PFC. When considering the role these processes play, it is not clear that the maintenance of information has any role in the control of other processes, in contrast to updating which is described as having an active role in influencing representations of information maintained in working memory (Baddeley, 1986). Although there is considerably less focus in factor analysis studies on working memory maintenance, one study that used a single measure of this construct found that it was highly related to a latent variable within multiple models of executive function (Adrover-Roig et al., 2012). The role of updating has repeatedly been shown to form a key part of such models (Adrover-Roig et al., 2012; Friedman et al., 2006; Miyake et al., 2000).

1.2.2.4. Strategic Planning

Strategic planning is the ability to make predictions about the future and organise behaviour to achieve a goal. This is an increasingly complex and multidimensional process that requires a broad range of cognitive skills (Hayes-Roth & Hayes-Roth, 1979; Anderson, Dewhurst & Nash, 2012).

One of the earliest perspectives on planning was discussed by Miller et al (1960) who described planning as "any hierarchical process in the organism that can control the order in which a sequence of operations can be performed" (p.16). It was argued that all plans involve one, or multiple paths named TOTE (test-operate-test-exit). Firstly it is tested whether a goal has been completed, if not an operation is carried out to complete that goal, the operation is then tested to determine success and if the goal is then met, the plan exits. This occurs in a feedback loop where if an operation is unsuccessful a

new operation is selected and tested, until the goal is ultimately reached. A second key aspect of Miller et al's work is the contribution of a temporary working memory store for the maintenance and manipulation of plan representations. Working memory allowed a conscious organisation of the TOTE status, regarding the maintenance of the end goal state, the operations chosen to reach that goal and the replacement of a new operator when a previous one was judged to be unsuccessful. This TOTE perspective has even been employed as a theoretical explanation for a holistic executive function, rather than the fractionated account which is presented in this thesis (Kopp, 2012).

When attempting to determine the cognitive processes involved in planning, Burgess, Simons, Coates and Channon (2005) pondered several possible processes. One example which was suggested was the ability to look forward in time. A key development in the field of planning was that future thinking or this ability to look ahead in time shares a neural network with episodic memory; primarily temporal, prefrontal, hippocampal, cingulate, and parietal regions (Addis, Wong & Schacter, 2007). The future events were specifically those which were novel and therefore this overlap was not due to the participant just remembering a previous event, and thinking about doing it again. Although there was a large overlap between these two putatively separate processes there were also several regions unique to each one. These findings build on previous work with brain injured patients, such as N.N (Tulving, 1985) who cannot remember episodic events or imagine future events suggesting that the processes are intimately related. Furthermore, other neuroimaging (Szpunar, Watson, & McDermott, 2007) and cognitive experiments (Anderson et al., 2012) have supported these findings. However, as these future thinking tasks involve imagining a specific event it is not clear if this episodic overlap will extend to all forms of future planning and imagination.

Using a neuropsychological approach to planning, the Tower of Hanoi (TOH)/London(TOL) tests, it has been demonstrated that working memory and inhibition are correlated with planning abilities although these variables were less related to the TOL than the TOH (Welsh, Satterlee-Cartmell & Stine, 1999). While this suggests working memory and inhibition contribute to planning, the correlational approach cannot prove this as the correlation might represent another shared cognitive construct such as processing speed. These findings were extended by Zook, Davalos, DeLosh and Davis (2004) who found that working memory and inhibition were predictors of the TOH after controlling for fluid intelligence, although this same model did not significantly explain performance on the TOL. While both studies suggest that

the TOL and TOH differ, the results suggest a role of working memory and inhibition in planning abilities as determined by the TOH. Specifically it appears that spatial working memory and not verbal working memory is involved in the TOH (Handley, Capon, Copp & Harper, 2002). This suggests that planning several moves ahead on the TOH takes up spatial working memory resources and the role of inhibition could be to suppress distractions during the task performance. These findings are limited to planning within the TOH and may not be applicable to planning in real world situations however they do provide some support for the recruitment of a short term memory store during planning as described by Miller et al (1960).

A bilateral prefrontal-parietal network has been frequently found to be recruited during strategic planning tasks such as the TOH (Newman, Carpenter, Varma & Just, 2003; Anderson, Albert & Finch, 2005; Boghi et al., 2006; Newman, Grecco & Lee, 2009) which makes this construct a viable candidate for "executive" status. Strategic planning is at the core of executive function definitions, as both concepts have been described as the organisation of behaviour in order to reach a goal (e.g. Miyake et al., 2000; Banich, 2009; Koechlin, 2014). Strategic planning is so central to accounts of executive function that Kopp (2012) proposed a TOTE conceptualisation of executive function. Furthermore, factor analysis methods have found that strategy generation and planning are key parts of executive function (Testa et al., 2012) although this model suggested they contributed to three separate but related parts of executive function.

1.2.2.5. Decision Making

Decision making is the ability to assess different options, predict the outcomes, and select the option which is most beneficial, a process which is undertaken countless times in everyday life. The processes by which individuals make decisions are largely influenced by a myriad of factors which potentially lead to biases, poor judgement, and costly outcomes. One of the major theoretical distinctions in decision making is the two-system view (Kahneman & Klein, 2009). This theory suggests that intuitive decision making (otherwise known as system one; Stanovich & West, 2000) is fast, effortless, emotionally charged, and often influenced greatly by habit (Kahneman & Klein, 2009). In contrast, reasoned decision making (system two) is slow, effortful and thought out. While system one is often implicit, in which motivations are not always clear, system two processing is often clearly explicit. The paradigmatic example which defines the two systems is the individual walking across the road with a car speeding

towards him. The use of the intuitive system would see him jump to safety while a reasoned decision making processes would most likely not end well.

Even during system two there is a clear role of emotions which can influence the supposedly rational decision making processes. Evidence for this is apparent within the *framing bias*. This cognitive bias is commonly observed when a participant is given £50 in fake money. They then are given the option as to whether they would like to keep £20 or lose £30, both responses resulting in the same outcome. Typically individuals are loss aversive with a larger percentage choosing the 'keep £20' option (e.g. De Martino, Kumaran, Seymour & Dolan, 2006). Just by framing the question in a different manner can have a large effect on the decisions people make, potentially to their detriment.

A development of the role of emotions in decision making was the somatic marker hypothesis (Damasio, 1996; Bechara, Damasio & Damasio, 1999; Bechara, Damsio, Tramel & Damsio, 2005). Somatic makers refer to bio-regulatory states of the body elicited by emotions and can influence decision making consciously or non-consciously. Evidence in support of this has come from observing Skin Conductance Responses (SCRs) in patients with amygdala damage, VMPFC damage, and normal controls (Bechara et al., 1999). Both brain damaged groups displayed significantly reduced anticipatory SCRs which was associated with the more disadvantageous card selection. In addition amygdala patients failed to develop SCRs in response to reward and punishment following card selection. This suggests that in healthy controls the repeated exposure to reward and punishment after choosing cards leads to a conditioned SCR response which influences subsequent decision making however in individuals with amygdala damage this process does not occur. While these findings support the somatic marker hypothesis, this type of methodology cannot prove a causal association as the SCRs – or lack thereof - which precede deck selection may not be influencing performance and may just be an unrelated artifact of the brain damage.

Neuroimaging data supports the lesions studies with the VMPFC and also the OPFC, DLPFC, and amygdala being recruited during decision making processes (De Martino et al., 2006; Li, Lu, D'Argembeau, Ng & Bechara, 2010). Conceptually, decision making processes are not described as controlling other cognitive processes of behaviours (Kahneman & Klein, 2009) although other cognitive processes are recruited to aid decision making such as information held in working memory (Li et al., 2010). As system two is a top-down, controlled and willed process, there is a line of reasoning

which suggests it could be classed as executive (e.g. Miller & Cohen, 2001). Factor analysis studies have not included tests of decision making to determine if it would form part of a latent variable within an executive function model. These findings suggest that system two – the reasoned decision making system - could be classed as executive.

1.2.2.6. Initiation

Initiation is the commencement of a volitional cognitive action usually facilitated behaviourally through a motor or verbal response. Dysfunction of initiation was first described as psychological inertia which is the body's propensity to remain in a constant state, an aversion to change (Luria, 1976). Although the severest form of inertia tends to occur in extreme scenarios such as a symptom of Huntington's disease in which initiating movements becomes an increasingly difficult task (akinesia; Wahlin & Byrne, 2012), much more mild forms of inertia can be very common. The cognitive analogue to akinesia has been described in patients with Parkinson's disease and schizophrenia, a term referred to as *cognitive-akinesia* in which a cognitive process cannot be initiated or *bradyphrenia* in which cognitive processes are markedly slowed (Higginson et al., 2003; Pantellis et al., 1999). Duffy and Campbell's (2001) tripartite theory of executive function links initiation with apathy. Their apathetic syndrome includes behavioural and cognitive impairments such as diminished spontaneity, diminished verbal output, diminished motor behaviour, diminished spontaneous prosody and delayed response latency. This is apparent in Powell & Voeller's (2004) review of executive function in children, in which initiation is described in terms of procrastination. The suggestion of emotion being tied to initiation is supported by a study demonstrating that positive mood boosted performance on a verbal fluency test, a class of tests suggested to involve initiation (Phillips, Bull, Adams & Fraser, 2002). No such research has been conducted observing the effects of motivation of initiation tasks.

While patients with severe cases of neurodegenerative conditions (e.g. Wahlin & Byrne, 2012) may have trouble initiating cognitive acts (e.g. plans), motor acts (e.g. hand movements), or verbal acts (e.g. speech), individual differences in healthy individuals cannot be measured in such ways due to the ceiling effects that would arise from testing whether an individual (for example) can move their hand . Due to this problem, many tests of initiation examine the extent to which an individual can repeatedly initiate acts at a fast rate (e.g. verbal fluency tests).

The definition of initiation is quite vague and has not received the same level of theoretical or empirical attention as some of the other executive function components (e.g. Anderson, 2002; Powell & Voeller, 2004) and thus it becomes difficult to determine which initiated behavioural actions can be classed as "executive". A differentiation in neural correlates for volition vs. reflexive responses has been discovered using a saccade task and an eye-tracking methodology (Mort et al., 2003). These top-down, willed initiated acts could be classified as executive while automatic initiated acts (i.e. reflexes) which can be differentiated are not executive. Tests of fluency also recruit PFC regions included the left IFC (Costafreda et al., 2006) and these tests also form central parts of factor analysis-derived executive function models (Testa et al., 2012).

1.2.2.7. Abstract Reasoning and Conceptual Thought

Abstract reasoning and conceptual thought are regularly cited as executive functions although are often just described as a process which contributes towards performance on the Wisconsin Card Sorting Task (WCST; Lysaker, Bell, Bryson & Kaplan, 1998; Powell & Voeller, 2004). The nature of concept formation and abstract reasoning is generally applicable to the ability to form concepts about objects and being able to group them into categories based on visual, tactile, semantic or abstract rules. The Dysexecutive Questionnaire (DEX; Wilson, Alderman, Burgess, Emslie & Evans, 1996) contains a single item which measures abstract reasoning: "S/he has problems understanding what other people mean unless they keep things simple and straightforward". This highlights the real-world applications of abstract reasoning, the requirement for an individual to infer meaning where limited concrete information is provided.

Two categories of tasks involve a particular type of abstract reasoning - inductive reasoning- and these are the WCST and matrix reasoning tests (Primi, 2001; Specht, Lie, Shah & Fink, 2009). Primi (2001) describes the three stages of the reasoning process; 1) perceptual and conceptual analysis of the available stimuli in order to infer the rules; 2) the recognition of the parallels between these rules and a new analogous situation; 3) inferring the correct sorting structure (i.e. WCST) or pattern (i.e. Matrix Reasoning) based on these rules. The author also concluded that abstraction complexity is highly related to the central executive (Baddeley & Hitch, 1974).

Looking at a complex task such as the WCST during fMRI poses a number of problems when trying to dissociate the different process involved and determine which neural activity which underpins abstraction and concept formation. Lie, Specht, Marshall and Fink (2006) used three different versions of the WCST varying in task complexity and a baseline condition with multiple contrast measures available, providing the basis to partial out different processes recruited during the tasks. These authors suggest that the number of sorting dimensions completed on task 'A', the most difficult of the tasks and comparable with the traditional WCST, provides a measure of concept formation and goal-directed behaviour. This measure was correlated with activity within the right DLPFC, the left inferior temporal gyrus and the left superior parietal cortex. A meta-analysis of WCST performance in general, without the decomposition of individual cognitive components shows a wide pattern of brain activation, with key areas being identified as the inferior parietal lobule (IPL), the ACC, the bilateral IFG and the cerebellum (Buchsbaum, Greer, Chang & Berman, 2005). This suggests that the PFC has a role in abstract reasoning and concept formation, indicative of executive functioning. While this process does is not directly involved in the control of other processes, the reasoning process is a willed and top-down process (Primi, 2001), also indicative of executive functioning. Factor analysis studies using the WCST found that task analysis, which is similar to Primi's (2001) first reasoning stage: perceptual and conceptual analysis of the available stimuli in order to infer the rules, was one of the latent variables within a six factor model of executive function (Testa et al., 2012). It is not clear if the other stages of Primi's account of reasoning are central to executive function based on factor analysis, however it does appear that abstract reasoning and conceptual thought processes are executive in nature.

1.2.3. Summary

Although defining executive function is a controversial task there are several areas of agreement. A large body of evidence now suggests that executive function is fractionable and made up of multiple components. This section has identified a series of seven dissociable, albeit highly interlinked, executive function components. These executive function processes appear to recruit prefrontal and cingulate cortical areas, in addition to supplementary regions like the basal ganglia and amygdala. These brain regions contain moderate-to-high levels of CB_1 receptors (see Figures 1.3 and 1.4), which present the potential for the influence of cannabis on executive function (Herkenham et al., 1990). These findings highlight that prefrontal regions and networks

involved in executive function could be more at risk to the effects of cannabis than other processes and behaviours, given that cannabis primarily interacts with the brain through CB_1 receptors (Grotenhermen, 2003).

1.3. The Age of Onset of Cannabis Use

At birth the brain weighs approximately one-third of its adult weight and continues to grow and mature through childhood and adolescence, synaptic connections are created and pruned, axons are myelinated, neurotransmitter levels and their receptors undergo large changes (see Figure 1.8; Rice & Barone, 2000). All of these changes create a potential for vulnerability to exogenous factors such as drugs, "Much of the potential and many of the vulnerabilities of the brain might, in part, depend on the first two decades of life" (Toga, Thompson & Sowell, 2006; p.148). The following sections will discuss the development of the brain in terms of structural, functional and cognitive changes, and will then address how environmental factors, such as exposure to cannabis, can alter the developmental trajectory depending on the age at which the individual is exposed.

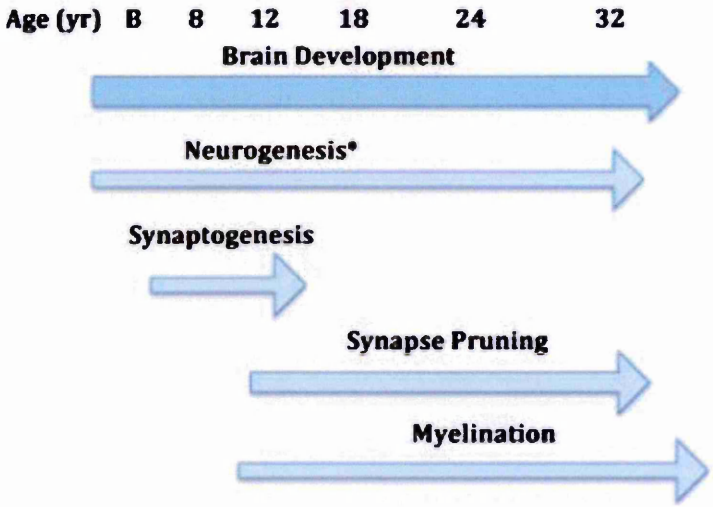


Figure 1.8. A timeline of brain development reproduced from Kolb, Mychasiuk & Gibb (2013; p.2)."* Neurogenesis is largely complete by 6 months gestation but continues in the cerebellum up to the eighth postnatal month and in the hippocampus and subventricular zone throughout life."

1.3.1. Structural Development

Postnatal neuromaturation studies of grey and white matter have found a developmental trajectory which continues throughout childhood and well into the third decade of life. A number of studies show that white matter, which serves as a communication platform between brain structures, continues to increase in volume into the second and third decade (Reiss et al., 1996; Giedd et al., 1999; Paus et al., 1999). The exact nature of these changes is clarified due to studies examining fractional anisotropy (FA). FA describes the extent to which a substance (typically water) diffuses equally in all directions (isotropic diffusion) or just along one axis (anisotropic diffusion). The interactions between the protons within the water and white matter within a singular image voxel can describe fibre density, fibre diameter and myelin sheath diameter (Pierpaoli & Basser, 1996; Barnea-Goraly et al., 2005). Studies show age-related increases in FA in a diverse number of brain areas including prefrontal, temporal, basal ganglia and thalamic pathways (Barnea-Goraly et al., 2005; Ashtari et al., 2007). Ashtari et al (2007) describe their findings of age-related increases in FA, along with increased axial diffusivity and no changes in radial diffusivity, as improved white matter organisation due to a reduction in tortuosity, which is a product of adolescent development. One study which increased the maximum age beyond the 20s to 76 years found that white matter changes within the frontal and temporal lobes peak around the middle of the fifth decade, suggesting that development does not stop at adolescence (Bartzokis et al., 2001).

Unlike white matter, grey matter structures do not develop linearly throughout adolescence (Giedd et al., 1999). Giedd et al (1999) report that grey matter across three of the four lobes reaches peak volume in the second decade and then begins to decline. Frontal, parietal and temporal lobes reach their respective peak volumes between ages 11.0-12.1 years, 10.2-12.1 years and 16.5-16.7 years, which then all decline in volume until the maximum age tested at 22 years. Conversely, the occipital lobe's volume increased linearly between the tested ages of 4 and 22 years. Many grey matter structures follow the three most anterior of the lobes in this typical developmental pattern, with dendritic arborisation and subsequent synaptogenesis leading to peak volumes at an early age. Dendritic and synaptic pruning then takes over to enhance the efficiency of the surviving neural connections. Post mortem examination of a section of the prefrontal cortex, the left middle frontal gyrus (lMFG), and a section of the auditory cortex, the left Heschl's gyrus, was conducted to examine the time course of

development from conceptual age 192 - 22300 days (Huttenlocher & Dabholkar, 1997). These two different grey matter structures show different rates of development, yet both following the same pattern. The auditory cortex reached peak synaptic density at age 3, while the MFG reached peak synaptic density at age 3.5. Synaptic elimination was over by age 12 for the auditory cortex but the MFG displayed a much more protracted development, with synaptic elimination appearing to continue into mid-adolescence. This relatively protracted development of the frontal lobes compared with other lobes is well supported (Gogtay et al., 2004; Sowell, Thompson, Holmes, Jernigan & Toga, 1999; Sowell, Trauner, Gamst & Jernigan, 2002). Within the frontal lobes there is evidence for different prefrontal cortical gyri to mature at different rates (Gogtay et al., 2004). This study examined the developmental trajectories of the DLPFC, the VMPFC and the OFC. The authors found that the DLPFC matures last in terms of grey matter volume reductions, preceded by the VMPFC, while the OFC matures earlier. This heterogeneous pattern of development was reflected throughout the cortex, with other gyri following separate developmental paths.

1.3.2. Functional Development

Positron emission tomography (PET) is a method of determining functional brain activity via glucose metabolism using radioactive isotopes (Banich, 2004). A review of the PET studies shows a vast amount of evidence for the development of functional brain activity throughout the first two decades of life (Chugani, 1998). This review found that functional activity was similar to that of structural brain development and cognitive development. Glucose metabolism within the first few years is highest in areas which are necessary for survival (i.e. heart rate, breathing, & homeostasis) and experience (i.e. movement & sensory input); the brain stem, the thalamus, the primary motor cortex and primary sensory cortex. Conversely, within this time period, other cerebral activity is relatively low. Cerebral activity follows a sharp incline in baseline activity levels throughout the first decade in life and reaches its peak between ages four and nine, and similar to the structural findings - the frontal lobes mature latest (Gogtay et al., 2004). This peak in functional activity is followed by a slow decline throughout the second decade of life to around ages 16-18 when glucose metabolism reaches an adult level.

1.3.3. Cognitive development

Developmental methods such as longitudinal and cross-sectional designs have been applied to cognitive development and produced varying degrees of clarity dependent on the specific function being measured. A meta-analysis by Romine & Reynolds (2006) grouped tasks into planning, verbal fluency, design fluency, inhibition of perseveration, and set maintenance. The findings displayed large increases in ability between ages five and 11, medium increases between 11 and 14 years, and mixed changes between 14 and years and adulthood dependent on the specific functions (see Figure 1.9).

Additional work on other areas of inhibition such as behavioural and interference control has shown that maturation occurs in the late teens to early twenties (Brocki & Bohlin, 2004; Hooper et al., 2004; Huizinga, Dolan & van der Molan, 2006; Taylor, Barker, Reidy & McHale, 2012). It appears that development of the set switching construct continues to develop throughout the second decade of life yet the rate of this maturation process is too slow to detect differences over small periods of time (Huizinga et al., 2006; Anderson, Anderson, Northam, Jacobs & Catroppa, 2001). Working memory appears to mature a little earlier, around age 15, for both spatial and verbal working memory tasks (Anderson et al., 2001; Huizinga et al., 2006). The development of planning abilities differed across different outcome measures from the same task with some suggesting a late teen maturation point, and other finding that performance increased to the eldest age tested, at 22 (Anderson et al., 2001; Huizinga et al., 2006; Taylor et al., 2012; Romine & Reynolds, 2005). Like planning, decision making and abstract reasoning also increased in performance to the eldest age group tested, suggesting that these processes also continue to mature into the twenties (Hooper, Luciana, Conklin & Yarger, 2004; Huizinga et al., 2006; Taylor et al., 2012). Verbal fluency gives the most inconsistent results out of all of these processes with no age differences being detected between 11-17 (Anderson et al., 2006) and performance decreasing between 17 and 18 (Taylor et al., 2012). As the tasks used to measure these processes are not process pure (e.g. Sanchez-Cubillo et al., 2009) it is difficult to determine development especially if two different cognitive processes which are recruited by one task mature at different rates. This needs to be considered when inferring a developmental path.

Although there are non-parallel developmental trajectories between executive function components, there exists a clear trend for these abilities to improve from childhood

throughout adolescents towards adulthood. This trend may not be linear over short periods of time, and some temporal fluctuations may appear around age 18 in particular (Taylor et al., 2012), yet it is clear that overall, executive function continues to mature late into the second decade of life, and even into the third (Hooper et al., 2004; Anderson et al., 2006; Huizinga et al., 2006).

In the table and figure below there is a summary of the developmental data discussed in this section. It is worth highlighting that the state of the research has not progressed to a point where the stages of development are clear and uncontroversial. The information below should represent an estimate rather than a final conclusion. Furthermore, the years at which development reaches a maturation point is taken from the average age across samples and it should also be noted that individual differences, such as sex, will influence when a specific individual reaches their own maturation point.

Table 1.1.

A summary of the estimated age at which each component of executive function reaches maturation.

EF Components	**Age of Maturation**
Inhibition	
Behavioural Inhibition	14-17
Interference Control	15-21
Perseveration	14
Set Switching	16-17
Working Memory	15
Strategic Planning	17-22*
Verbal Fluency	NC
Decision Making	14-17*
Abstract and Conceptual Thought	15-21*

Note. NC = Not clear based on the available data; * = performance improved up to the eldest group in respective study, therefore it is unclear whether performance would continue to improve beyond this point.

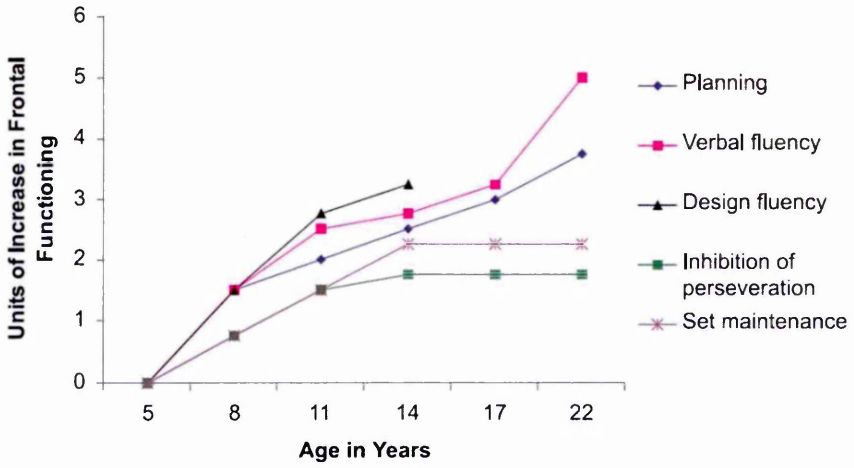


Figure 1.9. A graph reproduced from Romine & Reynolds (2005) showing the developmental trajectory of various executive function components.

1.3.4. A Vulnerable Period?

This section looks at some of the evidence for the claim presented by Toga et al seen in at the beginning of section 1.3. "Much of the potential and many of the vulnerabilities of the brain might, in part, depend on the first two decades of life" (Toga, Thompson & Sowell, 2006; p.148). While evidence for earlier onset brain damage conferring greater cognitive consequences has been discovered in patients with brain trauma (Barker, Andrade, Morton, Romanowski & Bowles, 2010), the claim will be examined in relation to whether this period of development is vulnerable to drug use.

1.3.4.1. Structural evidence

Given that the endocannabinoid system has a role in brain development (Lubman, Cheetham & Yucel, 2014) it has been suggested that exposure to exogenous cannabinoids could interfere with normal development via a CB_1 receptor mechanism. The changing regional dependent availability of CB_1 receptors throughout development may mediate the level of interference by such cannabinoids (Romero et al., 1997).

Studies examining rats have provided some of the most in depth findings regarding the impact of cannabis on the structural integrity of the brain. Rubino et al (2009) administered THC to adolescent rats and then examined them again at adulthood. Results showed lower synaptic density, dendritic length and number within the

hippocampus, in addition to decreases in pre and post synaptic proteins (VAMP2; PSD95) crucial for intra-neuronal communications such as synaptic vesicle transportation and fusion with the cell membrane. The authors concluded that these abnormalities will reduce synaptic numbers and efficiency of synaptic transmissions. This study did not include an appropriate non-adolescent THC administered control group but instead cited papers which suggest that THC administered later in life has no long lasting effects (Schneider & Kock, 2003). Therefore it could be argued that this study only provides evidence for the toxicity of cannabis, rather than providing evidence that it interferes with development. In comparison to human studies, this study of cannabis on rats was truly experimental, and thus causation was easier to infer.

In humans there is also evidence to suggest a vulnerable period to cannabis use (Wilson et al., 2000). A group who started using cannabis before the age of 17 was compared to those who started using after the age of 17 and under went MRI examination in search of morphological differences. The key findings included lower grey matter volume in the early users and this reduction was most marked within the frontal lobes. There was no relationship between volume and duration of use, suggesting that the early group did not present with volume reduction simply due to extended periods of cannabis use, but because of a vulnerability to the drug during a developmentally crucial period. Unlike the studies previously discussed involving rats (i.e. Rubino et al., 2009) this study was cross-sectional and therefore the causal nature of the interaction cannot be determined.

1.3.4.2. Cognitive evidence

There exists several pieces of evidence derived from studies on cognition; however these are discussed in section 1.4 under the title of executive function deficits in cannabis users.

1.3.5. Age of Onset Summary

The frontal lobes, and in particular, regions of the prefrontal cortex mature late into the second and even third decade of life. Although there is not a clear parallel with morphological development, executive function development also continues to mature throughout the second and occasionally into the third decade of life. Studies on humans and rodents have highlighted preliminary evidence for a risk of damage within this developmental period, with early onset exposure to cannabis leading to greater structural, functional, and cognitive abnormalities than later onset exposure.

1.4. Executive Function Deficits in Cannabis Users

The aim of this section is to provide an update on the current state of the research on chronic cannabis use and cognition, and present a case for the investigation into the effects of the age of onset of cannabis use and executive function. Furthermore, as there is a lack of process-pure tasks it is acknowledged that performance deficits discovered in previous research may not be due to the specific theoretical cognitive constructs suggested here, however based on task reviews and individual author interpretations it is aimed to best attribute task deficits into an appropriate cognitive domain. Within each cognitive domain several areas will be discussed: the differences between cannabis users and controls, the quantity and duration of cannabis use, the effect of the age of onset, and neuroimaging findings.

The papers discussed in the following section were chosen based on criteria set out by Gonzalez et al (2003). Each study must include 1) a group with a history of "primarily" cannabis use; 2) includes an appropriate control group (this is not always the case for studies looking at dose-related responses); 3) outcome measures using valid neuropsychological tests (un-validated tests are common with neuroimaging devices and therefore this does not apply to the neuroimaging discussions); 4) cannabis group is drug free on day of testing; 5) study addresses other potential substance use; 6) study addresses potential history of neurological or psychiatric problems.

1.4.1. Inhibition

The impact of cannabis has been primarily explored on two inhibitory processes: interference control (e.g. the Stroop test) and behavioural inhibition (e.g. Go-No/Go tests).

1.4.1.1. Cannabis users vs. controls

Pope, Gruber, Hudson, Huestis and Yurgelun-Todd (2001) along with Gruber et al (2011) tested abstinent cannabis users' performance on the same version the Stroop task and compared the results with control groups, yet found no marked differences in errors made or time taken between the groups. A comparable study with a different version of the Stroop task also failed to uncover performance differences between the two groups (Solowij et al., 2002). Thames, Arbid and Sayegh (2014) found that recent cannabis users (use in the past month) and past cannabis users (no use in the past month) both presented with deficits in "executive function". This variable was a composite score of

two tests, the Trail Making Test (B-A) and the Stroop test (interference condition). Although attributing the deficits to one task or the other becomes problematic, it is possible that the impairments detected could be at least part due to interference control, as measured by the Stroop test.

1.4.1.2. Quantity of cannabis use

Although no differences in performance were found between controls and cannabis users on the Stroop task (Solowij et al., 2002) there did appear to be a negative relationship between years spent smoking cannabis and performance on two outcome measures of the task. Bolla et al (2002) also found that the number of spliffs consumed per week predicted worse Stroop performance. Contrary results were obtained by Pope and Yurgelun-Todd (1996) who administered a version of the Stroop task to heavy cannabis users and light cannabis users. This comparison failed to find a direct dose-related response between heavy and light using cannabis groups. When the two groups were divided into same sex groups, the authors found that the male heavy users took significantly longer to complete the task than male light users while no differences were present for the females. The authors pointed out that males did not differ greatly from females in terms of recent or lifetime cannabis use, but suggest that males may consume more cannabis on an individual session than females, thus explaining the discrepancy. This suggestion was untested however, and remains speculative.

1.4.1.3. The age of onset of cannabis use

There have been two studies which have examined the effect of the age of onset of cannabis use on inhibition. Pope et al (2003) recruited a number of cannabis users into their study and divided them into early and late onset cannabis users (<17 & ≥ 17 years old, respectively) while Gruber et al (2011) chose a slightly different age criterion for their early and late onset groups (<16 & ≥ 16 years, respectively). Both studies administered the Stroop task however only Gruber et al found an effect of the age of onset. The findings showed that controls outperformed the early group but no differences were detected between controls and the late onset cannabis users. A further approach using a correlational analysis found that the age of onset was correlated with performance on three separate outcome measures from the interference condition of the Stroop task: omission errors, commission errors and performance accuracy.

1.4.1.4. Neuroimaging data

Battisti et al (2010) used a computerised version of the Stroop task paradigm with cannabis users and controls while EEG examination was conducted. Contrary to earlier findings, the cannabis users presented with behavioural deficits, making a greater number of errors on the incongruent condition and showing normal performance on the congruent tasks. Furthermore, the users presented with altered electrophysiological readings as determined by ERP analysis, in which levels of activation for a conflict resolution marker, varied between conditions. Similar findings have been discovered under PET and fMRI examination. Eldreth et al (2004) used a Stroop paradigm during PET and found that cannabis users showed no behavioural deficits, yet presented with underlying metabolic abnormalities. During the incongruent task the cannabis users presented with hypoactivity within the ACC and hyperactivity within the left lateral PFC relative to controls. Gruber and Yurgellun-Todd (2005) used fMRI during a Stroop task and found that overall there were no differences in task performance between users and controls. Imaging data also supported the findings of Eldreth et al (2004), as cannabis users presented with lower ACC activity and increased bilateral dorsolateral PFC activity compared to controls during the incongruent condition. These findings suggest that although behavioural deficits may not always be present on interference tasks such as the Stroop, there are underlying functional abnormalities that can be detected using EEG, PET and fMRI techniques.

Hester, Nestor and Garavan (2009) found no performance differences on a go/no-go task between abstinent cannabis users and controls, however cannabis users presented with increased activity during the inhibition part of the task within the right putamen, IPL and middle cingulate gyrus. Tapert et al (2007) also found no differences in performance on the go/no-go task between users and controls. Imaging data also showed increased activity in the cannabis users during the inhibition section of the task, specific to the right dorsolateral PFC and occipital gyri, and bilaterally in the medial frontal cortex, IPL and SPL. These findings suggest that cannabis affects behavioural inhibition as measured by the Go/No-Go tasks in the same manner as interference control as measured by the Stroop task. Specifically, it means that even though group differences are not always found on the behavioural data there tends to be different levels of regional brain activity during these tasks between cannabis users and controls.

1.4.1.5. Summary

The studies which are reviewed here regarding the effects of chronic cannabis use on inhibitory processes suggest the impairments are mild, very rarely reaching the behavioural level and are unlikely to be picked up by current cognitive assessment tools. Despite differences between controls and cannabis users not being detectable there is now evidence for an effect of quantity of cannabis use effecting inhibitory processes with several studies reporting similar results (Pope & Yurgellun-Todd, 1996; Bolla et al., 2002; Solowij et al., 2002). It is not clear whether recruiting a sample of more heavy cannabis users would result in differences between cannabis users and controls becoming visible as Solowij et al (2002) recruited a cannabis using group which had a greater frequency of use (days *per* month) than Pope and Yurgellun-Todd's (1996) 'heavy' cannabis users, and found no such between group differences. Furthermore, Solowij et al's (2002) cannabis sample reported a very long duration of use (23.9 years). It is therefore possible that cannabis use does affect inhibitory processes at a minor level, with behavioural tasks struggling to detect differences between cannabis users and controls. This is supported by neuroimaging studies which consistently find abnormalities at electrophysiological and metabolic levels, with neuroimaging tools such as EEG, PET and fMRI picking up abnormal activity during the task processes, while the less sensitive behavioural data rarely picks up on abnormalities present in cannabis users. This highlights the need for more sensitive behavioural measures for detecting mild impairments in cognitive and neural functioning.

A further explanation for the mixed findings between controls and cannabis users is highlighted by Gruber et al (2011) who found no differences in the Stroop task between controls and cannabis users, however when dividing the group into early and late onset users, differences in performance emerged between controls and early users. It is possible that if other studies had also made such a distinction they would have detected similar deficits.

A third explanation for the findings is that cannabis use is not a causal factor in the mild impairments in inhibitory processing, but rather individual differences in inhibitory processes are a causal factor which led to the onset of cannabis use. It has been argued that one of the key explanatory factors behind drug use and abuse is a maladapted impulse system which has failed to be controlled by higher order cognitive processes

(Bechara, 2005). It appears that there is support for cannabis use leading to impaired inhibition, inhibition deficits leading to cannabis use and also support for a third variable explaining both occurrences (Perry & Carroll, 2008). Although it is not clear at this stage, it could be that the impairments in neural functioning relating to behavioural inhibition found in cannabis users (e.g. Hester et al., 2009) could reflect the cause of their cannabis use rather than a product of it, while a dual causation explanation is also viable.

1.4.2. Set Switching

Set switching is the ability to switch between multiple cognitive tasks or 'sets'. Tasks which fall under the prespecified task sequence structure, in which the switch occurs consistently and predictably, include the TMT/Trails B (e.g. Delis et al., 2001). The second group are tasks which use a task-cueing (or cognitive flexibility) paradigm, in which the switch cue occurs on the task itself and the participant must respond to the new information by making a switch to an alternative response. A classic example of this paradigm is the WCST (e.g. Berg, 1948).

1.4.2.1. Cannabis users vs. controls

The effects of cannabis on TMT performance are inconclusive as one study examining performance between cannabis users and controls showed that users took longer and committed more errors on the switching component of the TMT (Medina et al., 2007). One study found no significant differences between cannabis users and controls on the TMT B (switching component) however the authors do report a trend towards cannabis users taking longer to complete the task (Gruber et al., 2011).

This contradicts an earlier, comparable study by Pope et al (2001) which did not find this trend. As discussed in the section on inhibition (1.4.1.1), Thames et al (2014) found that current and past cannabis users were impaired on a measure of "executive function" which combined the TMT (B-A) and the Stroop test. It is possible that the deficits were at least partly due to impairments in set switching, as measured by the TMT (B-A). It is possible that methodological differences influence these mixed results as Medina et al (2007) used the Delis Kaplan Executive Function System (D-KEFS; Delis et al., 2001) version whereas the remaining studies used the Trails A and B version (e.g. Lezak et al., 2004). These two tests have the same rules and requirements but the stimuli are set out in different ways perhaps yielding varying degrees of sensitivity.

A study by Solowij et al (2002) did find deficits on the WCST, confined to the measure 'maintaining the set' which is interpreted as attentional dysfunction, while perseverative errors are more indicative of cognitive flexibility. These findings were replicated by Gruber et al (2011) who also found deficits on the WCST which could be explained by cognitive inflexibility.

1.4.2.2. Quantity/duration of cannabis use

Pope and Yurgelun-Todd (1996) found that heavy cannabis users produced more perseverative errors in the WCST and completed fewer categories on the WCST than light users. These two differences could potentially be attributed to impaired set switching processes. These findings were replicated by Bolla, Brown, Eldreth, Tate and Cadet (2002) who also examined the dose-related effects of cannabis and found the heavy users completed fewer categories than light users. This was the only outcome measure from the WCST discussed, and it is possible that although perseverations influenced the number of categories completed in the study by Pope and Yurgellun-Todd, this may not be the case with Bolla et al as another cognitive process such as concept formation could contribute to the underlying deficit. Furthermore, Bolla et al., (2002) examined the dose related effects of cannabis and did not find a significant effect on TMT performance.

1.4.2.3. The age of onset of cannabis use

There is further evidence of dissociation between the two separate forms of switching tasks. Cognitive flexibility as determined by total perseverations was impaired in early cannabis users compared to controls and interestingly, also compared to late cannabis users (Gruber et al., 2011). Across other cognitive domains, early onset users' performance were frequently impaired to controls, but this occurrence of early onset users being impaired relative to late users highlights quite a substantial effect of the age of onset of cannabis use. Performance as measured by 'total categories' was also impaired in early cannabis users compared to controls, while there was no difference between late cannabis users and controls. This measure (total categories) is less related to cognitive flexibility and could be more easily attributed to concept formation. The same study reported no differences between controls, early cannabis users and late cannabis users on any of the measures of the TMT (Gruber et al., 2011) suggesting that cognitive flexibility may be more vulnerable to long term cannabis use than predictable

task switching. It is also possible that the difference reflects other contributory processes which contribute towards task performance as both tasks are not process pure.

Pope et al (2003) found evidence on impaired performance on the WCST, however these effects disappeared when controlling for verbal IQ. As verbal IQ was impaired in the cannabis using group it is possible that cannabis also had a causal impact of verbal IQ rather than just representing a bias in the recruitment method leading to group differences. If the problem of causation is disregarded the use of the covariate still suggests that the deficits on the WCST were not due to cognitive flexibility but could be explained by a common cognitive process between the WCST and verbal IQ although it is not clear what this could have been.

1.4.2.4. Neuroimaging data

There are many studies which have adapted standard set switching measures into versions which are complementary with the methods employed during various neuroimaging devices (e.g. Dove, Pollmann, Schubert, Wiggins & Cramon, 2000; Swainson et al., 2003) however a study looking at performance on these tasks combined with PET or fMRI data on a sample of cannabis users has not been discovered (last searched on 13/03/15). This is an area worthy of further investigation.

1.4.2.5. Summary

When observing the two forms of set switching (prespecified & task-cueing) it is clear the latter is impaired in cannabis users, an effect which appears to be related to both the quantity of cannabis used and the age of onset of cannabis use. The evidence suggesting prespecified task sequence impairment, as measured by performance on the TMT, is much more equivocal and needs further research to clarify the inconsistencies. Unlike inhibition research, the effects of cannabis on the neural underpinnings of set switching have not been examined and thus it cannot be concluded if abnormal activation in a manner similar to that with the Stroop task, mediate the performance on the TMT or WCST.

1.4.3. Working Memory

The focus of working memory performance in chronic cannabis users will be discussed in both verbal (VWM) and visuospatial (VSWM) modalities, and with regards to the maintenance or updating of this information. For the purposes of this section only 'pure'

tasks will be discussed, this refers to tasks which have a primary outcome measure that can be attributed to working memory over other processes. Tasks such as the verbal fluency test, which partially rely on verbal working memory, will be discussed in a different section.

1.4.3.1. Cannabis users vs. controls

From the three studies employing working memory tasks which did not include a neuroimaging component, the Cambridge Neuropsychological Test Automated Battery (CANTAB; Fray, Robbins & Sahakian, 1996) was used in all instances. The first study reported that chronic cannabis use impairs spatial working memory as determined by two outcome measures, number of errors made and spatial working memory strategy (Harvey, Sellman, Porter & Frampton, 2007). A second study, also employing the CANTAB, found that spatial working memory was intact (Grant, Chamberlain, Schreiber & Odlaug, 2012). Becker, Collins and Luciana (2014) administered four separate assessments of spatial working memory. The two spatial working memory subtests from the CANTAB were used (Self-Ordered Search and Spatial Recognition) in addition to a computerised version of the Corsi-Blocks task and the Spatial Delayed Response Task (DRT). Three of the four tasks did not uncover performance differences between cannabis users and controls however the DRT did show that cannabis users spatial working memory was impaired after varying levels of time delays. It is not clear why only one task was impaired as the DRT shares many similar features with the other tasks administered. The authors did not comment on this discordance.

A common assessment of verbal working memory, the digit span task, has not uncovered any deficits in cannabis users on either of the forward or backward conditions across multiple studies (Gruber et al., 2011; Becker et al., 2014). A different assessment of verbal working memory, the letter-number sequencing test from the WAIS-III, did uncover performance deficits in cannabis users at two out of three occasions after abstinence was initiated (Hanson et al., 2010). The first testing occurred at 3.3 days since last use, the second testing at 13.3 days since last use and the final testing at 21.0 days (mean-average times). This longitudinal approach not only provides evidence of impairment in verbal working memory but also shows that performance reaches levels comparable with controls after three weeks. This perhaps suggests the impairments are only the residual effects of the cannabinoids in the body rather than evidence for the neurotoxicity of cannabis.

1.4.3.2. Quantity/Duration of cannabis use

The previous studies discussed which have looked at cannabis users and controls on various measures of verbal and spatial working memory did not conduct analyses observing the quantity or duration of cannabis use. Solowij et al (2002) did use the Omitted Numbers working memory test, however they found no performance differences between groups when testing controls, short-term cannabis users (10 years of use) and long term cannabis users (23 years of use).

1.4.3.3. The age of onset of cannabis use

As with a number of other cognitive domains, Gruber et al (2011) looked at the effect of the age of onset of cannabis use on verbal working memory. As with their prior analysis on cannabis users and controls, their age of onset analysis failed to show any performance differences on either the forward or backwards conditions of the digit span task. This suggests that the age that one commences cannabis use does not have an effect on verbal working memory, however due to the lack of research on verbal working memory and the complete absence of evidence regarding spatial working memory it is too soon to come to a conclusion.

1.4.3.4. Neuroimaging data

Evidence suggests that cannabis users are not impaired on tasks which require the maintenance of spatial working memory representations (Kanayama, Rogowska, Pope, Gruber & Yurgelun-Todd, 2004) however fMRI data from the same study showed that the cannabis users had increased activation in regions commonly associated with spatial working memory including the DLPFC, in addition to more widespread activation when compared to controls. These findings were supported by a study using a spatial *n*-back paradigm (Schweinsburg et al., 2008), however due to the participants being required to simply determine whether any space had been occupied before in a block of 10 randomly appearing shapes, as opposed to a given number of preceding stimuli (e.g. three shapes before) this task does not tap into the same executive processes of spatial working memory manipulation that the normal *n*-back task does. The findings showed no behavioural differences between groups on the tasks however fMRI data indicated that cannabis users had abnormal activation patterns during the task located to the right DLPFC and right posterior parietal cortex in addition to the inferior and superior medial occipital cortex.

The maintenance of verbal working memory representations as measured by the Sternberg task also appears to be unaffected by chronic cannabis use (Jager, Kahn, Brink, Ree & Ramsey, 2006). The task resulted in expected activation in both groups in common regions associated with verbal working memory including the DLPFC and superior parietal cortex, however the latter of these two regions displayed different activation levels in cannabis users relative to controls, within activity failing to decrease as working memory load was reduced. In contrast, controls displayed activation levels which were commensurate with task complexity.

1.4.3.5. Summary

The non-neuroimaging studies and the neuroimaging studies' behavioural data suggest that both verbal and spatial working memory are largely unaffected in cannabis users. A wide range of tasks were administered in the spatial domain and only limited evidence supported the proposition that cannabis users are impaired in these cognitive domains. Although fewer studies have ventured into the study of verbal working memory a similar pattern emerges, that performance is unaffected in cannabis users. Despite these behavioural findings, there is consistent evidence that functional activity within the DLPFC is different in chronic cannabis users across both domains of working memory. As with the inhibition component, it appears that altered working memory functioning at the neuronal level is yet to manifest itself at a behavioural level which therefore is undetectable by cognitive test performance. This could be due to a compensatory mechanism highlighted by the regional hyperactivity and more widespread network activation.

Regarding the contribution of quantity and the age of onset of cannabis use, there is too little research to ascertain whether or not these factors play a role in the cognitive or functional differences between cannabis users and controls.

1.4.4. Planning

Planning and strategy formation are commonly measured by a series of similar tasks known as 'towers'. Common examples include the Tower of London (Shallice, 1982), Stockings of Cambridge (Fray et al., 1996), the Tower of Hanoi (e.g. Goel & Grafman, 1995) and the D-KEFS' Towers test (Delis et al., 2001). In fact, as Goel & Grafman (1995) point out, many authors mistakenly cite the wrong towers test when reporting their own data. Although the tests are similar, there are some clear differences. An

additional test is the Jansari-Agnew-Akesson-Murphy (JAAM; Janasari, Agnew, Akesson & Murphy, 2004) test which is an ecologically valid virtual reality test which involves organising a diary and other office based tasks which involve planning.

1.4.4.1. Cannabis users vs. controls

Cannabis related deficits have been found on the planning subscale of the JAAM (Montgomery et al., 2012) and on the strategic working memory component (also known as the Self-Ordered Search test) of the CANTAB (Harvey et al., 2007). All of these studies using measures of planning and strategy formation have discovered evidence of cannabis induced impairments. Becker et al (2014) administered the Towers of London test to cannabis users and controls (see Figure 1.10).

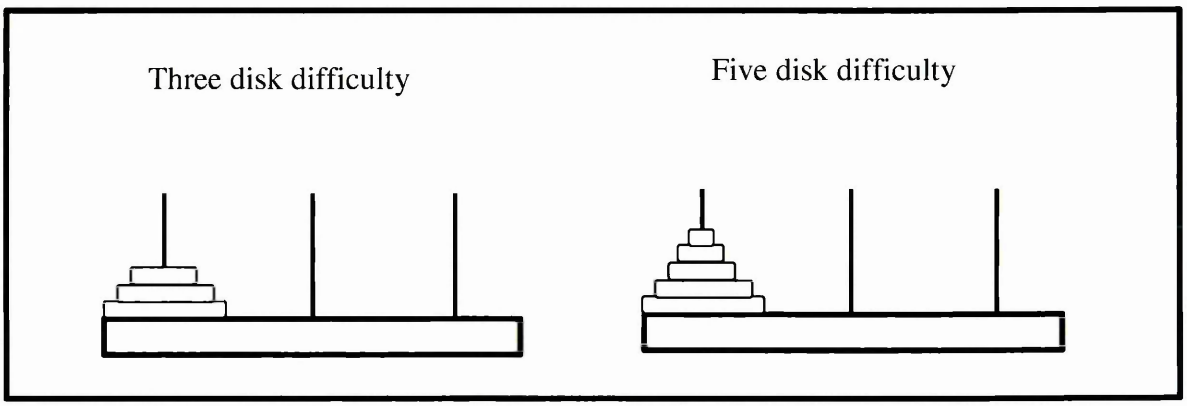


Figure 1.10. A figure displaying two possible difficulties of the Tower of London Test.

The study showed that for one of the difficulties (three disks) cannabis users took significantly more moves to complete the task while no other performance differences emerged on the other three difficulties. Furthermore, on the most difficult task (five disks) cannabis users displayed significantly faster initiation times, perhaps suggestive of impulsivity, however as there were no performance differences on this difficulty it appears this faster initiation was not detrimental to performance.

1.4.4.2. Quantity/duration of cannabis use

Medina et al (2007) found that although performance on the Towers Test (D-KEFS) did not predict group allocation with a cannabis using and control group, quantity of cannabis use was significantly negatively correlated with the Towers total score, final item score and accuracy score. This suggests that if Medina et al (2007) recruited a heavier cannabis using sample then between group differences may have appeared.

Alternatively, the correlation between quantity of cannabis use and the dependent variables could be explained by an untested confound.

1.4.4.3. The age of onset of cannabis use

Studies describing the effect of the age of onset of cannabis use on measures of strategic planning have not been found (last search on 13/03/15).

1.4.4.4. Neuroimaging data

To date the use of neuroimaging devices to examine the neural underpinnings of performance on strategic planning tasks has not been conducted on cannabis users despite fMRI compatible versions of Towers tests being made available, such as the Tower of London (Newman, Greco & Lee, 2009). As with the age of onset this area should be explored in more detail (last search on 13/03/15).

1.4.4.5. Summary

Despite often being described as a key component of executive function (e.g. Lezak et al., 2004; Delis et al., 2001) the impact of cannabis on planning and strategy formation is rarely examined. Several pieces of evidence shows that these processes are vulnerable to the effects of chronic cannabis use (Harvey et al., 2007; Montgomery et al., 2012; Becker et al., 2014) and therefore the effects of the duration and quantity of cannabis use, the age of onset of cannabis use and the functional brain activity which mediates performance should all be examined in further detail.

1.4.5. Verbal fluency

In section 1.2.2.7. it was discussed that verbal fluency should be described by the underlying processes (i.e. working memory, strategy formation, initiation, inhibition) however determining which process is impaired is not easily done. Therefore cognitive deficits on verbal fluency tasks will just be described as verbal fluency deficits within this section. If deficits are detected on the verbal fluency tasks (VFTs) it is not clear where the deficits occurred and therefore deficits on the VFT will be discussed as verbal fluency deficits and if further interpretations are possible it will be elaborated on where appropriate.

1.4.5.1. Cannabis users vs. controls

Only one study using a VFT found that cannabis users produced significantly fewer words in a given time frame than controls (McHale & Hunt, 2008) while the remaining studies found no differences between cannabis users and controls (Pope et al., 2001; Medina et al., 2007; Gruber et al., 2011). A key difference between these studies is that McHale and Hunt used only one trial, whereas the remaining three studies which found no deficits employed variations of the 'FAS' test, in which the average scores across all three trials was taken as an indicator of performance. A second difference is that McHale and Hunt (2008) instructed participants to write down their responses, while the remaining three studies produced words orally. It is possible that these differences contributed towards McHale and Hunt detecting impairments on the VFT by cannabis users. More recently, a contrary finding has been reported which is that cannabis users actually performed significantly better than controls on the COWAT (Becker et al., 2014). Although number of correct words produced was up, so was the number of words produced which were incorrect (i.e. set loss errors) and so this potentially could highlight a more impulsive speed-error trade off strategy. Due to the majority of all other studies finding conflicting results it is likely that this finding does not represent a cannabis induced cognitive improvement but rather a different strategy or a type I error. The finding would need replicating and a mechanism explaining this occurrence would have to be identified before concluding that cannabis may have a role in cognitive improvement.

1.4.5.2. Quantity/duration of cannabis use

Studies have found no cannabis related deficits between heavy users and light users (Pope & Yurgellun-Todd, 1996) and no dose-related effects on verbal fluency performance (Bolla et al., 2002). The study by Pope and Yurgellun-Todd (1996) did find verbal fluency deficits but only in the heavy cannabis users with low IQ scores. The authors suggest that those individuals with low IQ are more vulnerable to the attentional impairment of chronic cannabis use. Therefore a further possible explanation for McHale and Hunt's (2008) findings is that their participants had a lower than average IQ, however this was not measured in their study.

1.4.5.3. The age of onset of cannabis use

It is possible that previous studies examining cognition and cannabis use (without an age of onset analysis) could have detected greater impairments in performance if they had recruited earlier onset users. This is highlighted by one study finding no performance differences while analysing the whole cannabis group yet some differences emerged after dividing the group in early and late onset users. Gruber et al (2011) did not detect impairments between cannabis users and controls, however when they subsequently split the group they discovered that early cannabis users produced significantly fewer words than the late cannabis users. The cannabis users with a later age of onset appeared to be masking the deficits displayed by the earlier onset users when the cannabis groups were combined. Further ANCOVA analyses suggested these early onset deficits were not due to greater use of cannabis.

1.4.5.4. Neuroimaging data

There are no studies known to have used a neuroimaging device while employing a VFT in cannabis users (last search on 13/03/15). Given the wealth of neuroimaging data while using phonemic and semantic VFTs, it is unclear why this approach has not been examined with a sample of cannabis users (see Costafreda et al., 2006).

1.4.5.5. Summary

Although the majority of studies show that the verbal fluency remains unaffected by cannabis use, Gruber et al (2011) discovered decreased word production in early onset users (age of onset <17). However, a more recent study recruited a cannabis using group using the same age of onset criteria and found increased word production on the same VFT version, the COWAT (Becker et al., 2014). By observing the descriptive statistics across the two studies, these two samples of early onset cannabis users were comparable in terms of age and IQ, however the sample recruited by Gruber et al used cannabis over a year earlier on average despite the same criteria (<17) and used cannabis more frequently. This could explain why Gruber found deficits in performance yet is does not explain by Becker et al (2014) reported improvements.

1.4.6. Decision Making

1.4.6.1. Cannabis users vs. controls

A number of studies have examined decision making in cannabis users, the most commonly used tool being the Iowa Gambling Test (IGT). Bolla, Eldreth, Matochik and Cadet (2005) administered the IGT to cannabis users and controls and found that the users showed significant impairments in performance and that there was a significant relationship between weekly spliffs smoked and overall performance. Bolla et al (2005) administered the IGT twice and on trial two, only the controls and the moderate-use subset of the cannabis users showed significant improvement while the heavy-use subset failed to show improvements over the two trials of the task. These findings initially suggest that cannabis users do not utilise the necessary information to aid their decision making processes as time goes on. Whitlow et al (2004) found similar results with cannabis users selecting more cards from disadvantageous decks than controls. While both groups started by choosing disadvantageous cards the controls showed an improvement over time while the cannabis users did not appear to improve as the task went on. These findings have been replicated more recently with the performance differences only becoming apparent over the last 40 cards (out of 100; Becker et al., 2014). Despite these results, Becker et al (2014) found that overall performance on the IGT only displayed a trend for cannabis users to choose disadvantageous cards.

In order to identify the cognitive mechanisms which explain cannabis users' performance on the IGT, Fridberg et al (2010) administered the IGT to cannabis users and controls and ran two computational models of performance to assess the factors which contribute towards performance: the Expectancy-Valence Learning model (EVL) and the Prospect-Valence Learning model (PVL). The PVL is an updated version of the EVL and both assess motivation, memory and response processes in the participants during the task. The results from the experiment firstly supported previous findings in that the cannabis users displayed impaired performance on the task compared to controls through blocks 2-5 (21-100). Secondly, the findings suggest that the PVL model predicted group membership in 96.9% of participants which was higher than using IQ and IGT performance to predict group membership (84.4%). Thirdly, the authors suggest that psychological processes crucial for decision-making could be disrupted in chronic cannabis users. The disruptions are due to a relative insensitivity to losses and more sensitivity to gains in chronic cannabis users. Users also displayed a

recency effect, with decisions being weighted more on recent outcomes when compared to controls. Cannabis users also displayed less consistency, with selections being less consistent with their expectances of the outcomes from each deck. The authors suggest this finding is explained by impulsivity and a propensity for risk-seeking. These results highlight the cognitive mechanisms which may explain poor decision making abilities by chronic cannabis users on the IGT. These interpretations are backed up by non-cannabis using samples in which individual differences in impulsivity and risk taking are related to disadvantageous IGT performance (Upton, Bishara, Ahn & Stout, 2011; Burdick, Roy & Raver, 2013).

The Information Sampling Test (IST) is a measure of reflective impulsivity and therefore measures the ability to collect information necessary for a decision but before the decision has actually been made (Solowij et al., 2012). Solowij et al., (2012) study administered the IST to cannabis users, alcohol users and controls and found clear impairments on the task which were most likely associated with cannabis use, rather than alcohol use, other drug use or other confounding variables. These results support the data from studies using the IGT, by suggesting that cannabis use is associated with increased levels of impulsivity.

1.4.6.2. Quantity/duration of cannabis use

One study found that although cannabis users did not present with overall impairments compared to controls, there was also a dose-related response, with number of 'spliffs smoked' being negatively correlated with advantageous card selections on the IGT (Verdejo-Garcia et al., 2007). The authors also reported that controls and a cocaine using group showed improved performance over the five blocks while the cannabis users maintained a constant level throughout. These findings suggest that cannabis users have impairments in decision making and also a diminished capacity to learn from mistakes. This inability to learn could be due to the recency effect discussed earlier in which cannabis users have a tendency to make decisions based on more recent card selection than performance as a whole (Fridberg et al., 2010). Alternatively the lack of improvement over the whole test could be due to an attentional bias towards immediate gains; Fridberg et al (2010) noted that cannabis users display a hypersensitity to gains and a relative insensitivity to losses. As the disadvantageous cards are those which pay out greater amounts in the short term, this could explain why cannabis users persevered rather switching strategies. Alternatively, the cannabis users may be learning about the

consequences of their actions from repeated trial and error on the IGT, they just may not be acting advantageously on this information in a pattern previously discovered in those with VMPFC damage or sociopathology (Sobhani & Bechara, 2012).

1.4.6.3. The age of onset of cannabis

One study used a delay discounting paradigm and found that the age of onset of cannabis use was highly related to the probability of choosing initial short term gains over more beneficial long term gains (Kollins, 2003). Furthermore, multiple measures of performance on the IST have been found to be correlated with the age of onset of cannabis use (Solowij et al., 2012), suggesting that impaired assessments of information prior to decision making also gains severity with a decreasing age of onset. This analysis was correlational rather than quasi-experimental and thus there could be multiple salient confounding variables explaining this association.

1.4.6.4. Neuroimaging data

In addition to the behavioural abnormalities of decision making there has been some examination into the neurological underpinnings of these effects. During the IGT there is evidence of reduced activation specific to the right lateral OFC and DLPFC in cannabis users relative to controls, and increased activation in the left cerebellum (Bolla et al., 2005). When the same study divided the cannabis group into heavy and moderate users, the heavy users showed reductions in activation in the left medial OFC and DLPFC and increases in activity in the left cerebellum and parietal lobe when compared to the moderate group. The authors suggested that this abnormal pattern of activation within frontal reward networks highlights that long term drug use is associated with neuroplastic changes in brain function. The heavy users also showed diminished behavioural performance on the IGT during this study.

1.4.6.5. Summary

These studies provide evidence that chronic cannabis use results in altered functional activity within the prefrontal cortex and cerebellum during decision making processes and in addition to these functional changes, these impairments are detectable at the behavioural level, leading to impaired decision making on the IGT. Furthermore it is proposed that these faulty decision making processes are explained by a hypersensitivity to gains, a hyposensitivity to losses and the recency effect. There is limited research on

the age of onset of cannabis use and decision making, and none with regards to the IGT. Further research should explore this area.

As with the discussion on impulsivity leading to cannabis use found in section 1.4.1.3., it could be that there is a dynamic, transactional interplay between cannabis use and decision making. As suggested with delay discounting, the use of the IGT in an longitudinal study would address whether the consistently found impairments on this task are a product of the pharmacological effects of cannabis on the brain, or rather a factor involved in the initiation of cannabis itself.

1.4.7. Abstract and Conceptual Reasoning

Commonly used measures of abstract and conceptual reasoning include sorting tests such as the D-KEFS sorting test (Delis et al., 2001) and the Goldstein-Scheerer task (Goldstein & Scheerer, 1941), however the most prevalent is the WCST. Although the perseverative errors measured from the WCST has already been discussed as a measure of cognitive flexibility this section will focus on the measure 'total categories sorted' as an indicator of abstract and conceptual reasoning.

1.4.7.1. Cannabis users vs. controls

All of the studies examining this outcome measure of the WCST did not find any differences between cannabis users and controls (Gruber et al., 2011; Pope et al., 2001; Solowij et al., 2002). This suggests that abstract and conceptual reasoning is not affected by long term cannabis use.

1.4.7.2. Quantity/duration of cannabis use

An inspection of the effects of the quantity of cannabis use on this outcome measure showed initially that light users completed more categories than heavy users on the WCST (Pope & Yurgellun-Todd, 1996), however the authors explain this finding to increased errors on the task, so it is unclear if the deficits could be attributed to cognitive flexibility, abstract reasoning or another contributory cognitive process. Bolla et al (2002) found an inverse relationship between weekly spliffs smoked and number of categories completed, providing evidence that greater cannabis use leads to impaired performance on the WCST. Despite these two studies in support of a dose related effect, a comparison of short-term and long term users by Solowij et al (2002) only found evidence of long term use impairment on one outcome measure of the WCST, failure to

maintain the set, which as previously discussed is more likely to reflect attentional failings rather than a conceptual deficit.

1.4.7.3. The age of onset of cannabis use

The strongest evidence for the impact of cannabis on this measure of the WCST comes from studies looking into the effect of the age of onset. Gruber et al (2011) that early onset users displayed many deficits on the WCST compared to controls while the late onset users only displayed mild deficits. Similar findings were reported by Fontes et al (2011b) who found early cannabis users completed fewer categories than controls, while late users did not significantly differ from either group. In contrast to Gruber et al (2011), Fontes et al (2011b) did not control for lifetime use when examining the effect of the age of onset. Therefore the greater deficits could be due to the longer use and greater history of spliffs consumed by the early onset users.

1.4.7.4. Neuroimaging data

No known studies have administered a measure of abstract reasoning on cannabis users during a functional assessment of brain activity (last searched on 13/03/15). This could be accomplished by the use of a computerised version of the WCST, as done by Riehemann et al (2001).

1.4.7.5. Summary

While there appears to be no differences in abstract and conceptual reasoning between cannabis users and controls, there is tentative evidence suggesting that the quantity of cannabis use affects these processes in cannabis users and there is stronger evidence that the age of onset affects these processes in cannabis users. The majority of these studies employ the WCST however it is unknown if a study has used another measure of abstract or conceptual reasoning with cannabis users. Using a measure such as the D-KEFS sorting test, a measure which is more process pure than the WCST, would be a beneficial way of determining if deficits previously found are detectable by other measures of abstract and conceptual reasoning.

1.4.8. The Importance of Abstinence

This section will address whether the impairments found in previous studies are 1) due to the 'hangover' effects of cannabis, 2) due to the withdrawal effects or 3) are

symptomatic of cannabis induced neuropathology. It is unlikely that the findings discussed throughout section 1.4. are due to the acute intoxication of cannabis as the studies typically ensure a minimum abstinence period of 12 hours in which the acute effects are likely to be over. Some studies were deliberately not discussed as they included a mix of individuals who were abstinent and intoxicated (e.g. Ehrenriech et al., 1999) which therefore leads to interpretation problems.

The importance of abstinence is clear when considering the central tenet of the current thesis: the age of onset. Early onset cannabis use conferring greater vulnerability to the severity and prevalence of executive function deficits is one possible interpretation. Alternatively, it is possible that early onset users are more prone to physical dependence on cannabis and therefore are more likely to experience withdrawal effects than late onset users (Hall, 2014).

1.4.8.1. The Stages of Abstinence

Similar to alcohol, the use of cannabis leads to a hangover period, yet the nature of the 'hangover' is vastly different between the two substances. In a review by Crean, Crane and Mason (2012) the 'residual' period was described as occurring between seven hours and 20 days of abstinence. This is a problematic definition as it fails to discriminate between the 'hangover' period and the withdrawal effects of abstinence among those dependent on cannabis. Cognitive deficits have been observed in non-users of the drug following administration in the period 12-24 hours after receiving a dose of cannabis, suggestive of a "hangover" like experience (Pope, Gruber & Yurgellun-Todd, 1995). The withdrawal effects of cannabis are well documented, with approximately 42% of cannabis users having experienced withdrawal symptoms (Levin et al., 2010) and such symptoms becoming apparent after one day and lasting for around 20 days (Budney, Moore, Vandrey & Hughes, 2003). These withdrawal effects typically consisted of subjective, affective and behavioural states. Cognitive performance in this study was not measured however it is possible that these withdrawal effects are mediating the impairments found in cannabis users who have been abstinent for 1-20 days.

The ambiguities inherent in the term 'residual' reflect the relative difficulties surrounding the attribution of cognitive deficits to the stages of abstinence. The commonly used abstinence criteria for inclusion is 12 hours (e.g., Solowij et al., 2002; Pope et al., 2003; Gruber et al., 2011) and this means that attributing any discovered cognitive deficits to withdrawal effects, hangover effects or cannabis induced

neuropathology is not simple. In order to minimise the likelihood of such cognitive impairments being the result of withdrawal or hangover effects, studies which enforced a longer abstinence period will be discussed. For the purposes of this discussion, the definition of 'long term effects' by Crean et al (2012) is suitable (three weeks or more of abstinence) as this passes the withdrawal phase proposed by Budney et al (2003).

1.4.8.2. The Long Term Effects of Cannabis

While section 1.4 on executive function deficits in cannabis users included a number of studies examining cognitive deficits in cannabis users this section focusses on those which used a three week abstinence criteria. Thus, several studies will be re-examined, and others that were not included but which include cognitive measures not under the bracket of executive function will be included.

Perhaps the strongest piece of evidence within this debate was the meta-analysis conducted by Schreiner and Dunn (2012) which separated studies into two categories. Firstly, a meta-analysis of the effects of cannabis on cognition in which only acutely intoxicated cannabis users were excluded and a second meta-analysis on a subset of those studies which used a minimum 25 day abstinence criteria. The first meta-analysis which the authors conducted found cannabis-related impairments across many cognitive domains. The second meta-analysis found no effects of cannabis on cognition. This study provided convincing evidence that any of the deficits in cognitive performance discovered in cannabis users represents a temporary impairment which recovers over a period of weeks. Despite the conclusions drawn from this research there are three main limitations which suggest that cannabis may still be having a lasting effect on cognition. Firstly, the authors had to group test performance into domains (i.e. attention; motor; executive; etc.) due to the lack of neuropsychological test conformity across studies. This means that if performance on one test consistently detected cognitive impairments in cannabis users (i.e. the IGT) and it is combined with a test which does not (i.e. Digit Span) then the combined score may misleadingly suggest there is no impairment in the underlying cognitive construct (i.e. attention). Secondly, the follow up meta-analysis included 13 studies and thus a large number of participants, however when divided up into cognitive domains several of the analyses were lacking data. To illustrate this point the motor construct analysis only consisted of data from two studies. Thirdly, the meta-analysis did not consider variables such as the age of onset. As discovered by Gruber et al (2011) - a study not included in the meta-analysis - when considering cannabis users

as a whole group impairments in cognition may not be detected, however after splitting the users into early and late onset groups, impairments appear in the early onset group. Furthermore, the meta-analysis which consisted of long term cannabis use (>25 day abstinence criteria) found that the attention construct, which consisted of the Digit Span test, the TMT-A, the Continuous Performance Task and the IGT showed a trend towards group differences (p=.06). While the findings of this study should be considered as evidence that cannabis does not cause long lasting cognitive damage, the results should not be considered conclusive but rather an important milestone highlighting the need for more research.

A number of the individual studies discussed here were included in Schreiner and Dunn's (2012) meta-analysis. Those which were not included will be highlighted as such.

Pope et al (2001; 2002; 2003) conducted several pieces of research in which performance was tested at 0, 1, 7 and 28 days since last cannabis use. The use of daily or every other day urine tests ensured abstinence from cannabis during this time. Collectively these three studies found that deficits were present on multiple tasks throughout all stages before controlling for verbal IQ however these effects disappeared after controlling for verbal IQ. The problems with this methodology are discussed above (section 1.4.2.3) however the concluding remarks by the authors suggest that long term cannabis use is not associated with impaired cognition.

Hanson et al (2010) tested cannabis users' performance at three days, two weeks and three weeks following their last use of cannabis. Abstinence was measured by urine and breath tests every three to four days. This study was not included in the meta-analysis discussed above. While many cognitive measures highlighted impaired performance at three days, cannabis users were only impaired relative to controls on one test at three weeks. This was the Ruff 2 & 7 test of sustained visual attention using serial and parallel search components (Ruff & Allen, 1996).

After 23 days of abstinence another study discovered group status (cannabis vs. controls) was related to cognitive performance across multiple domains including set switching, complex attention, psychomotor speed and verbal store memory using composite scores from multiple assessments (Medina et al., 2007). Abstinence was measured by urine and breath tests every three to four days. Such widespread deficits were also discovered by Bolla et al (2002) after 28 days of abstinence, however this

study was looking specifically at the frequency of cannabis use. Frequency of cannabis use was inversely related to performance on the Grooved Pegboard, the WCST, and the Stroop test, in addition to several non-executive tests of cognition. Abstinence was measured by random drug tests and by admitting participants for 30 days into their research facility. This study by Bolla et al (2002) was not included in the meta-analysis.

While many of the previous studies discussed in section 1.4 found executive function impairments in cannabis users (e.g. Gruber et al., 2011; Fontes et al., 2011b) it is not clear if these are attributable to cannabis related withdrawal, hangover effects or neuropathology. However the studies discussed in this section clearly show that some deficits are still detectable after three weeks or more of abstinence providing evidence for longer lasting damage caused by chronic cannabis use.

1.5. Putatively Confounding Variables

The majority of studies addressing cognitive performance in cannabis users have used measures to control for the effects of confounding variables. This is necessary as the quasi-experimental design dictates that other factors could be mediating the between-group effects. These confounding variables which could potentially have an influence on this association are intelligence quotients (e.g. Mahone et al., 2002), education (e.g. Grimley & Banner, 2008), sex (e.g. Duff & Hampson, 2001), depression (e.g. Watkins & Brown, 2002), anxiety (e.g. Eysenck, Santos, Derakshan and Calvo, 2007), obsessive compulsive disorder (e.g. Gu et al., 2008), motivation (e.g. Macher & Earlywine, 2012), tobacco use (e.g. Jacobsen et al., 2005), brain trauma/disease (e.g. Alvarez & Emory, 2006), learning disorders (e.g. White, Burgess & Hill, 2009), chronic alcohol use (e.g. Yonker, Nilsson, Hernitz & Anthenelli, 2005), recent alcohol use (e.g. Howlan et al., 2010), other recreational drug use (e.g. Morgan & Curran, 2006), and recent drug use (e.g. Curran & Travill, 1997). The confounding variables are not mutually exclusive and potentially all could contribute to the associations discovered between cannabis use and impaired cognition. This is not an exhaustive list as practical considerations dictate that not every potential confounding variable can be assessed. These variables were selected based on reviews of previous research on cannabis and cognition (e.g. Gruber et al., 2012).

In order for a confounding variable to be considered it firstly must be related to the dependent variable (i.e., executive function; Dancey & Reidy, 2004). If a specific variable does not impact executive function in a beneficial or detrimental way then it

could not be an explanatory factor for the cognitive decline associated with cannabis use. Secondly, of the numerous factors which do impact cognition, those which are highly associated with cannabis use will be the most salient.

Many variables could be explaining the previously detected cognitive impairments detected in cannabis users as opposed to a causal explanation (e.g. neurotoxicity). Therefore relevant exclusion criteria, group matching, or statistical covariates need to be enacted where appropriate to deal with the effects of these potentially confounding variables.

1.6. Literature Review Summary

1.6.1. Synopsis

The chapter has demonstrated a clear link between chronic cannabis use and impaired executive functioning. The explanation for these deficits could be causal, a cannabis related neural toxicity which alters the developmental trajectory of cognition and its associated neural networks. There are many alternatives to the causal hypothesis and these other factors (e.g. education) may explain some of the group differences which have previously been discovered in cognitive performance (e.g. Pope et al., 2003), however based on the evidence reviewed it is likely that chronic cannabis use does have an impact on cognition.

1.6.2. Gap in the Literature

The associations between chronic cannabis use and executive function are quite strong in some cognitive domains, yet mixed in others. One series of explanations for these mixed findings are the patterns of behaviours relating to cannabis consumption. The earliest cannabis use behaviour to be explored in great detail was the quantity of cannabis use. Several studies (e.g. Pope & Yurgellun-Todd, 1996; Bolla et al., 2002) addressed the nature of quantity of use and their conclusions have been incorporated into a large number of subsequent studies. It is now common practice to include clear information regarding the quantity of cannabis used by each study's cannabis group or to include specific analyses addressing the impact of this variable.

A newer cannabis behavioural variable to be examined is the issue of the age of onset of cannabis use. Only a few studies have explicitly looked at early and late onset groups and the performance on cognitive tasks (Pope et al., 2003; Fontes et al., 2011b; Gruber

et al., 2011). The first study to explore this included individuals who were acutely intoxicated and therefore this was not considered (Ehrenreich et al., 1999). These three studies have addressed several of the components of executive function, yet not all (e.g. decision making, non-verbal fluency/initiation, and verbal set switching). Furthermore, there appears to be mixed findings among these three studies regarding which cognitive processes are affected by the age of onset of cannabis use.

1.6.3. Research Aims

The current research programme aims to build upon several studies (Pope et al., 2003; Fontes et al., 2011b; Gruber et al., 2011) by exploring if early onset cannabis use is associated with greater cognitive impairments than later onset users, with the following aims: 1) determine if early onset cannabis use is associated with more numerous and more severe deficits than late onset cannabis use; 2) if an association exists, to attempt to explore whether the relationship is causal; 3) to identify if specific cognitive domains are more vulnerable to cannabis than others; 4) to develop a new instrument for assessing cannabis use history among participants.

Chapter Two. Methodology

This chapter outlines the methodology used over the course of this research programme, covering two quasi-experimental studies and one survey study. The aim of the thesis is to study executive function abilities in cannabis users relative to control groups with a focus on the age of onset of cannabis use. This chapter will firstly discuss the research designs and statistical methods used in the research programme, and then will highlight the various methods for assessing executive function, drug use and relevant covariates.

Table 2.1.

A table describing the three studies of this thesis, the designs, and the primary outcome measures

Study	Method	Outcome Measures
Neuropsychological Study (Chapter Three)	Quasi-experimental, neuropsychological tasks, questionnaires	Cognition (e.g. executive function) IQ Mental health Lifestyles & drug use
Eye Tracking Study (Chapter Four)	Quasi-experimental, eye-tracker, computerised tasks, questionnaires	Cognition (e.g. executive function) IQ Mental health Lifestyles & drug use
Survey Study (Chapter Five)	Correlational, questionnaire	Lifestyles & drug use

Note. IQ=Intelligence Quotient.

2.1. Research Designs and Data Collection

This section will evaluate the methods in their capacity of addressing the research of cannabis use and cognition.

2.1.1. Quasi-Experiments

2.1.1.1. Overview

The quasi-experimental method involves the allocation of individuals to groups based on pre-existing criteria which cannot be randomised (e.g. cannabis use; Fife-Schaw, 2006). As the experimenter must allocate participants to groups based on pre-existing criteria, the cannabis using participants are automatically allocated to the cannabis group and the non-cannabis using participants are allocated to the control group.

As participants cannot be randomly allocated to the different levels of the independent variable - i.e. cannabis use (or equivalent) - studies using this method cannot infer causation without additional methods. Several criteria have been proposed for establishing causation (Hill, 1965) and although they individually differ in terms of relevance and validity across studies they are still used regularly to determine causal effects (Höfler, 2005). These criteria are: (1) strength of the association; (2) consistently finding an association; (3) associated a specific cause (e.g. cannabis use) with a specific effect (e.g. memory deficits); (4) temporality; (5) biological gradient/dose-response effect; (6) a plausible biological mechanism which explains a causal effect; (7) coherence with research in related fields; (8) the association is tested by experiment in randomised controlled trails; and (9) an analogous cause (e.g. another drug) has a similar effect (e.g. impaired cognition).

Some of these criteria provide less support than others and just because all criteria are met it does not necessarily prove a causal relationship, and in contrast, if a criterion is violated this does not necessarily preclude a causal relationship (Höfler, 2005). Single studies do not attempt to meet all of these criteria simultaneously however converging multidisciplinary research can help determine if the relationship between cannabis use and cognition is causal.

2.1.1.2. Limitations

Due to ethical and practical reasons a true experimental study cannot be utilised to investigate the harmful effects of chronic cannabis use and so a quasi-experimental approach is adopted within this thesis. This approach means that criterion eight of Hill's criteria (Hill, 1965), the use of experiments, cannot be used thus making it more difficult to infer a causal relationship. Therefore even if groups of "cannabis users" and

"controls" are compared it is not clear that the differences in cognition are due to the effect of cannabis or a confounding variable (Fife-Schaw 2006; Hill 1965; Höfler, 2005). The conclusions from the quasi-experimental studies in the current thesis must take this limitation into consideration, such that no causal link between cannabis and cognition can be made. In order to infer causation however, a link between cannabis and cognition in the current quasi-experimental studies would be a necessary, albeit insufficient criterion, namely Hill's criterion two.

Some have taken this critique further and suggested that in the presence of error, in this case referring to confounding variables, a conclusion cannot be supported (Mayo, 1996). Specifically, if an alternative explanation explains the pattern of data equally well then the experimental hypotheses cannot be supported by the experiment. Chalmers (1999) elaborates on this point by highlighting that even pure experimental tests are fallible when considering that any advance in technology or understanding can easily make an experimental result void. Thus, experimental, and to a greater extent, quasi-experimental research, is only reliable if the knowledge guiding the research is accurate.

2.1.1.3. Strengths

The true experimental approach has many strengths however there is one area in which quasi-experiments are considered superior. This is the area of external validity (Fife-Schaw, 2006). Recruiting cannabis users who have been using the drug for many years allows the findings of quasi-experiments to be representative of typical cannabis users. The patterns of cannabis use, methods of administration and strains of cannabis will more similar to those used by recreational users. Therefore, if an experimental approach was undertaken, causation would be easier to infer, yet less able to generalise to other cannabis users.

A strength of both categories of experiment is that of falsification (Popper, 2002). While Mayo (1996) argues that a true conclusion cannot be made from an experiment in situations where other explanations are also valid, an experimental approach can rule out other conclusions. The ability to falsify a proposition is essential to furthering understanding (Chalmers, 1999; Popper, 2002). While this means that if an association between cannabis use and cognition exists it cannot be proved; it also implies that if

such an association does not exist, then subjecting the proposition to experiment could falsify the claim. Furthermore, if such an association does exist between cannabis use and cognition then (quasi-) experiments can help rule out confounding variables (e.g. age), by ensuring that groups are matched for this variable.

2.1.2. Surveys, Questionnaires and Interviews

2.1.2.1. Overview

The Cannabis Use and Lifestyles Form (CannaForm; see section 2.3; Appendix A.2.1) was used in the current research programme to determine exclusion and inclusion criteria for several quasi-experimental studies (see Chapters Three and Four) in addition to collecting data to determine factors which may mediate the relationship between the age of onset of cannabis use and executive function (see Chapter Five). This questionnaire was developed within the research programme.

The CannaForm was developed to meet multiple needs and therefore could be described as a structured survey, a questionnaire, or a structured interview. The distinction made here between these three formats is that of: (1) the method of administration and (2) the intended use of the data, yet all the information gathered was in response to the same questions from the CannaForm. There were a number of participants who were interviewed and some who filled in the questionnaire themselves. For the interviews the experimenter read out the questions within the questionnaire; this was the favoured method as it maximised the possibility that every question was answered to a desired level of detail. With regards to purpose; some of the data was used for exclusion criteria, inclusion criteria, and descriptive demographic and lifestyle information for use within the quasi-experiments. However, the questionnaire data was also analysed to make statistical sample to population inferences about certain behaviours surrounding drug use, characteristic of a survey.

2.1.2.2. Survey Limitations

In order for sample to population inferences to be made there are several criteria which must be met, these are random sampling, sampling distributions and sample size (Sturgis, 2006). In order for a sample to represent the population it must be a random selection from the population, it must be representative of the various statistics taken

from other samples within the population (e.g. age) and it must be of sufficient size to generalise. If these criteria are not met then interferences made from the findings carry clear limitations. The participants used in Chapter Five were recruited using opportunity methods and thus the sample is biased towards certain sub-populations (e.g. students and females). This means that the results from the survey study cannot be considered representative of the general population.

2.1.2.3. Survey Strengths

The use of surveys is so prevalent among the social sciences for pragmatic reasons. They are cheap, easy and fast to both create and fill in (Sturgis, 2006). This allows a relatively easy way of gathering large amounts of data on a myriad of topics. With regards to the research discussed in the current thesis, the structured questions allows the examination of certain lifestyle and drug use behaviours across the sample, while several open questions allow the participants to list any additional behaviours or go into more detail, see example below:

15. How have you smoked cannabis in the past?

☐ Joints ☐ Bongs ☐ Pipe ☐ Other (please specify).....

The three examples listed above are the most commonly reported methods, however specialist cannabis paraphernalia websites and shops host a variety of novel and technologically advanced methods of consuming cannabis (e.g. vaporisers) which the participant can include in the 'Other' section if they so choose.

2.1.2.4. Questionnaire and Interview Limitations

Obtaining information for exclusion criteria, inclusion criteria and descriptive demographic and lifestyle information for use within the quasi-experiments was done either *via* self-report questionnaire, or structured interview, with the experimenter reading out the questions from the questionnaire.

Using this method for assessing lifestyle factors has several limitations which are not unique to this section, but which can also be applied to the survey discussion in the previous section. Firstly, the use of a questionnaire assumes the participant has perfect memory about behaviour and events in an individual's lifetime which is not the reality (Fife-Schaw, 2006). For example, the CannaForm includes a question about an individual's GCSE grades, this could be misremembered by the participant. A more accurate, yet time consuming, method would be accessing the grades by contacting the appropriate school or asking to see certificates. This was not done as it would not be possible under the current anonymity procedure. Secondly, sensitive information may be misreported or not reported at all. For example, the CannaForm asks the participant to list the illegal drugs they have tried at least once and to give information about their last use and amount of use. The participant may be motivated to not reveal their previous drug use and a more accurate way of assessing this could be through the biological analysis of hair, urine, blood or saliva samples. Despite concerns of the reliability of self-report drug questionnaires, a review of studies suggests that reliability is high for test-retest and inter-rater reliability (80+%; Darke, 1998). This could mean that the drug users are just very consistent with their lies however, repeatedly reporting the same misinformation. When validity is examined, in particular comparing self-reported drug use to urine or hair tests, there is also high levels of concordance (80+%; Darke, 1998). This suggests that while there may be individual fluctuations in levels of accuracy about drug use, on average participants are good – albeit not excellent – at reporting their drug use histories.

2.1.2.5. Questionnaire and Interview Strengths

As with the survey section, the strengths for assessing drug use behaviours and lifestyles are primarily for pragmatic reasons regarding cost, ease and speed. Costly and labour intensive methods may provide more accurate results for certain questions asked yet are unpractical for gaining large amounts of information from a large amount of participants.

2.1.3. Recruitment Methods

This section will discuss the various recruitment methods which were employed over the survey and quasi-experimental stages of the research programme.

2.1.3.1. Survey Recruitment

The first stage of the research involved administering the CannaForm to a large number of individuals. The first recruitment strategy employed was opportunity sampling in which individuals were approached on several locations of an English university's grounds, at student accommodations, and during psychology seminars. Psychology seminars were specifically targeted due to the need for psychology first years to obtain credits for taking part in psychology research projects. This method yielded the largest percentage of the total participants recruited. Participants from all groups (controls, tobacco users and cannabis users) were recruited using this method.

The second strategy was purposive sampling in which cannabis users were specifically targeted for recruitment via a local cannabis society. This online based group are involved in the dissemination of news stories and research about cannabis use. After receiving permission from the administrators of the group, information on the current research was put online with a contact e-mail address. The information instructed people who were either cannabis users, or non-smoking individuals (for the control group) to contact the primary researcher without declaring any sensitive or incriminating information. Upon contact, the full electronic version of the information sheet (see Appendix A.3.1) was sent to the potential participants with the instructions to read it and reply if they are still interested in taking part. If the individual agreed to take part then the CannaForm would be administered over the phone.

The final strategy was the snow-ball technique, in which recruited participants would inform suitable friends or acquaintances to contact the primary researcher and express an interest in taking part. This last strategy was primarily used for the further recruitment of cannabis users.

The primary purpose of typical quantitative studies is to generalise findings to the general population. In order to do this, random sampling methods need to be used (Sturgis, 2006). The present study did not use random sampling methods and therefore certain limitations need to be considered. Firstly, the opportunity sampling methods resulted in a narrow sample; predominately students, predominately adolescents and young adults, and predominately those currently residing in the north of England (see Chapter Three for more information). These demographic characteristics are not representative of the general English population. Secondly, purposive sampling methods

resulted in the recruitment of cannabis users who visited the cannabis society's web page. Finally, the snow-ball technique methods resulted in the recruitment of people who were friends or acquaintances of those who had already taken part. These two subsets of cannabis users may not be typical of the general cannabis using population and thus may lead to a biased sample.

2.1.3.2. Quasi-Experimental Recruitment

The recruitment procedure for the quasi-experiments directly followed from the survey recruitment. Of the individuals whom were both suitable and willing to take part in the quasi-experiments, the participants were contacted via e-mail to arrange a convenient time. The suitability for the study was assessed by determining if the responses in the CannaForm met or violated the many inclusion and exclusion criteria (see the Methods sections of Chapter Three and Four). The willingness was assessed on the consent form preceding the CannaForm, in which the participants could state whether or not they wished to be contacted for later stages of the research.

2.1.4. Ethical Considerations

Due to the sensitive nature of the information collected, the present research programme had greater than minimal risk of psychological harm or stress to the participants (British Psychological Society research ethics, 2010). The British Psychological Society (BPS) suggests a number of criteria which, if met, could lead to an increased risk of the harms mentioned above. The first criterion which was met by the current research programme was related to the information collected on the participants' illegal drug use, health and education. Secondly, this research also involves the collection of biological samples. The sample collected was hair strands and thus are exempt from human tissue laws.

Ethical approval for all phases and elements of the research were jointly provided by Sheffield Hallam University's Biosciences Ethics Review Group and the Faculty of Development and Society's ethics committee. The Biosciences Ethics Review Group was primarily contacted due to the collection of hair samples from the participants.

2.1.4.1. Sensitive Information

The first BPS criterion for risk which was met consisted of the collection of personal and sensitive information relating to illegal drug use. In order to minimise the risk of

psychological harm or stress associated with revealing such information several methods were employed. The first method involved providing information about the sort of questions to be asked and the rights of the participant. The information sheet provided a clear account of the sort of questions which were to be asked so the individual could make an informed choice about whether or not to take part, and also included a statement which clearly stated that the participant did not have to answer any questions which they did not want to.

The second method ensured the participant that any information they provided would be anonymous and therefore such sensitive information could not be linked with their name. This was accomplished by coding every piece of data collected (The CannaForm, cognitive tests, questionnaires, hair samples) with a unique code instead of their name. The participant's name was only recorded on the consent form and therefore it is on record that an individual took part in the study, yet no sensitive information or data can be linked with any name.

2.1.4.2. Biological Samples

The collection of any biological data carries the potential to distress the individual depending on the specific sample selected (hair, blood, saliva, etc.) The selected sample - hair - was thought to be one of the least distressing, perhaps comparable with saliva. Urine and blood samples have the potential for the participant to feel embarrassed, stressed or experience actual physical pain, and were avoided for these reasons (see section 2.5). In order to minimise the potential stress caused by taking a hair sample, the participants were informed that individual hairs would be cut with scissors one at a time from separate location on the head to alleviate the worry of a patch of hair going missing. Furthermore, the participants were given the opportunity to opt out of the procedure on two separate occasions, on the consent form and also during the experiment when the experimenter asked the participant if they were still happy to provide a hair sample.

2.1.4.3. Informed Consent

All participants read the information sheet and consent form which included the option to (1) complete the questionnaire, (2) participate in the cognitive testing phase, (3) provide a hair sample, or all of the above (see Appendix A.3.2). The participant was

only contacted for the cognitive phase of the study if they consented to do so, if they provided an appropriate means of contact, and if they were suitable based on the inclusion and exclusion criteria.

2.2. Data and Statistical Methods

This section will outline the type of data collected and the statistical methods and analyses used over the three quasi-experiments (Chapters Three and Four) and the survey and questionnaire based study (Chapter Five).

2.2.1. Data

2.2.1.1. Cognitive Tasks

The cognitive testing involved the administration of a number of paper, computer, and orally based tasks over multiple studies and was recorded in terms of reaction times, completion times, total correct responses, errors, and percentage of advantageous responses. All of these data which were collected and analysed were continuous and ratio in nature.

The administration of the three Delis Kaplan Executive Function System (D-KEFS) tests (see Section 2.5) were divided into two categories. The Trail Making Test was scored on the length of time taken to complete each component while the Verbal Fluency Test and the Design Fluency Test were scored on the amount of correct responses within a given time limit. For all of these three tests the raw performance scores were converted into age scaled scores. Age is one of the biggest predictors of variance in task performance (Delis et al., 2001) and the use of age-scaled scores minimised the influence of age on test performance. In addition to the D-KEFS tasks, only the IQ subtests were provided with age scaled conversion scores and therefore only the Symbol Search Task from the WAIS-iii (see Section 2.9.1) and the numerous components of the Wechsler Abbreviated Scale of Intelligence (see Section 2.10) were converted into age-scaled scores. For the remaining cognitive tasks: the Grooved Pegboard and the Iowa Gambling Task; raw scores were used.

The majority of data collected from these cognitive tasks were parametric, however in order to meet the assumptions for parametric analyses several of these scores were transformed or trimmed in order to increase statistical power (Ratcliff, 1993). The

precise details regarding the transformation selected and the specific outcome variable which needed transforming are discussed in the methods sections of the chapters describing the relevant studies (Chapters Three, Four, and Five).

2.2.1.2. Mental Health Questionnaires

The three mental health questionnaires used throughout the research programme all required the response to statements on a Likert, or Likert-style, response format and therefore are ordinal in nature. These three questionnaires on depressions and anxiety (see Section 2.11), obsessions and compulsions (see Section 2.12), and motivation (see Section 2.13) were included along with the IQ tests and various other variables to act as potential covariates. For each of the five dimensions from these three questionnaires, the sum of the responses was used to estimate each mental health or emotional state.

These confounding variables also needed to be checked for parametric assumptions and therefore appropriate transformations and data trimming were employed. The precise details regarding the methods selected and the specific outcome variable which needed transforming are discussed in the methods sections of the chapters describing the relevant studies (Chapters Three and Four).

2.2.1.3. Reaction Times

The Tobii Visual Search Task and the Tobii Set Switching Task (Section 2.17) are both computer based tasks which yield behavioural reaction times and gaze data. Such data are normally not parametric (Whelan, 2008) and require specific transformation methods.

In order to meet the assumptions for parametric analyses several of these scores were transformed or trimmed in order to increase statistical power (Ratcliff, 1993). The precise details regarding the transformation selected and the specific outcome variable which needed transforming are discussed in the method section of the chapter describing the relevant study (Chapter Four).

2.2.1.4. CannaForm Data

The CannaForm contains numerous questions on demographics, education, health, alcohol use, tobacco use and illegal drug use. The variety of questions yields nominal data such as:

What is your primary method of smoking cannabis?

☐ Joints ☐ Bongs ☐ Pipes ☐ Other (please specify).....

The CannaForm also yields ratio data such as:

On how many days would you drink alcohol in a typical week?

.....

The presence of nominal data and of numerous outliers dictated that the majority of data was non-parametric. The use of these data was not always for inferential analyses, but rather for descriptive statistics, inclusion criteria and exclusions criteria into subsequent stages of the studies. Therefore transformations were not always necessary.

For the occasions when transformations or data trimming was required, the details regarding these transformations and the specific outcome variable which needed transforming are discussed in the methods sections of the chapters describing the relevant studies (Chapters Three, Four, and Five).

2.2.2. Statistical Analyses

A variety of statistical tests were used within the current thesis including AN(C)OVAs, post hoc testing, correlations, logistic regression, and non-parametric equivalents of these tests. The selected tests were chosen based on guidelines put forth by various manuals (e.g. Hosmer & Lemeshow, 2000; Meyers et al, 2013, Tabanick & Fidell, 2010). Relevant parametric and test specific assumptions of the data were checked prior to implementing such analyses based on guidelines by these manuals and supplemented with statistical articles (e.g. Owen & Froman, 1998; Ratcliff, 1993). For further information see the method sections of Chapters Three, Four, and Five.

2.3. The Cannabis Use and Lifestyles Form (CannaForm)

The CannaForm was designed during this research programme to fulfil three purposes. Firstly, the CannaForm acted as a screening tool; collecting information about the participant which could influence performance on the neuropsychological battery of tasks, leading to the subsequent exclusion or inclusion into the experimental studies. Secondly, after the participant had been deemed acceptable to take part in the

experiments (if they were), the information provided in the CannaForm determined the group to which they were allocated (i.e. cannabis, early onset cannabis, late onset cannabis, tobacco or control). Finally, the CannaForm was also completed by a large number of participants who did not take part in the experimental studies, with the aim of determining if any lifestyle variables could be mediating the relationship between the age of onset of cannabis use and executive function. This was done by looking at variables previously found to be linked with executive function (e.g. educational achievement; Grimley & Banner, 2008) and investigating if these variables are related to the age of onset of cannabis use.

2.3.1. The Creation of the CannaForm

Previous measures of assessing drug use and lifestyles typically within the cannabis-cognition field have involved screening questions in the form of an interview conducted in person or via telephone (e.g. Pope et al., 2001; Medina et al., 2007; Fontes et al., 2011). As no widely available screening questionnaire with a cannabis focus has been developed, the first goal was to create such a device to be used throughout the current research programme. One exception to this is a drug use questionnaire developed by Solowij (1998) however this lacked the depth of questions which was desired for the current experiments. The first version of the CannaForm, version 1.0 (v1.0), was used and adapted throughout the research programme, leading to v2.0. Figure 2.1 describes the basic stages of the CannaForm's development however more information can be found in Chapter Five.

2.3.2. Exclusion Criteria

One of the primary purposes of the CannaForm was collect information on demographics, lifestyles and drug use to determine whether or not an individual needed to be excluded from subsequent cognitive testing. Based on suggestions from Gonzalez et al., (2002), previous comparable studies (e.g. Pope et al., 2001; 2003; Medina et al., 2007; Gruber et al., 2011) and further research from the primary researcher, a list of seven categories of exclusion criteria was created: 1) brain trauma, 2) learning disorders, 3) non-native English speakers, 4) chronic alcohol use, 5) recent alcohol use, 6) other drug use, 7) mental health problems and 8) recent drug use. The rationale for selecting these criteria was that each variable covaried with cannabis use and cognition (see Section 1.5. for a full discussion).

2.3.3. Inclusion Criteria

The criteria necessary to allocate individuals to groups will now be discussed. The current thesis included several quasi-experiments with a number of different groups. These groups included a cannabis using group, an early onset cannabis using group, a late onset cannabis using group, a tobacco using group and a control group, each with specific criteria for inclusion.

2.3.3.1. The Cannabis Group

The cannabis group criteria needed to ensure that the primary substance of use was cannabis (Gonzalez et al., 2002) in addition to the general exclusion criteria discussed above. Previous studies have taken different approaches relating to cannabis inclusion criteria, ranging from recruiting those diagnosed with cannabis dependence to those who use recreationally. The focus of the current thesis was decided to be focussed on the more recreational user, a non-treatment seeking individual who uses primarily for recreational purposes. The next aim was to differentiate from those who have 'tried' cannabis to those who have used for a prolonged period of time. As there are no set criteria on this, the current thesis used the criteria: 1) the individual must have been using cannabis regularly for a period of at least six months OR 2) the individual must have accumulated at least 50 separate lifetime uses of cannabis.

2.3.3.2. The Early and Late Onset Cannabis Groups

There were two criteria for the age at which the group was split was based. Before the divide could occur it needed to be identified what was considered an 'early' onset group. Examining previous similar studies shows a small range of different definitions with some studies splitting at the age of onset of ≤15 years (Fontes et al., 2011), ≤16 years (Gruber et al., 2011) and ≤17 years old (Wilson et al., 2000; Pope et al., 2003).

The aim was to define an early group as a period in which maturational processes for executive function had not reached adult levels, and thus are susceptible to interference from cannabis. By observing neurological data and cognitive data (Section 1.3), this could be anywhere between ages 15-30. Due to this vague guideline, it was decided that the divide would be data-led and that a median split would be used. This was done to ensure that similar numbers of cannabis users were allocated to each of the two

groups. For all studies, the divide was chosen as ≤15 years for early onset users and ≥16 years for late onset users.

2.3.3.3. The Tobacco Group

The use of a tobacco 'control' group in addition to a 'non-smoking' control group for comparison with cannabis groups is relatively novel, with only one known study previously employing this method (McHale & Hunt, 2008). It was aimed to have a group of tobacco users who matched the cannabis group for tobacco use as a method of dissociating any effects of tobacco on cognition from the effects of cannabis on cognition. The inclusion criterion into the tobacco group was regular use for a period of no less than six months.

2.3.3.4. The Control Group

A non-smoking control group is commonly used in comparable studies unlike the previous tobacco smoking control group described above. The only additional criterion to be included in the non-smoking control group, the individual must have used other drugs (including cannabis and tobacco) less than 15 times in total.

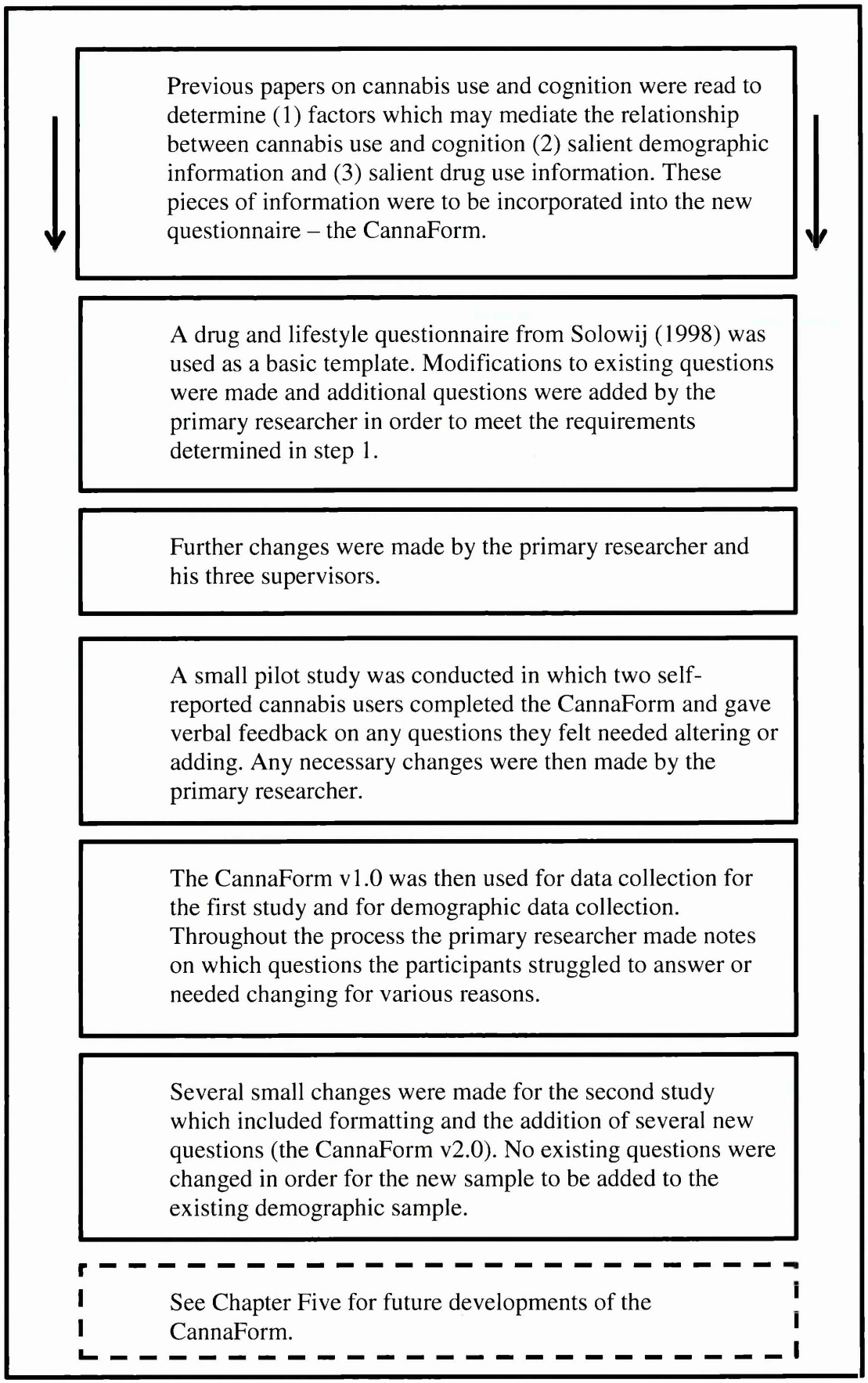


Figure 2.1. The steps taken to create the CannaForm in its current form along with a proposed next step to be taken after the completion of the research programme.

2.4. The Recent Use Questionnaire

The method of recruiting participants into the two quasi-experimental studies began with the completion of the CannaForm; the subsequent procedure however was split into two options. Some participants were immediately accepted based on a review of the CannaForm and the neuropsychological testing phase began immediately. The majority of participants were contacted at a later date and a time was agreed via e-mail or phone correspondence to arrange the testing phase. The criterion for these two separate methods was based on the participant's availability. For those who were contacted later, an additional questionnaire was created which solely included questions on the participant's recent drug and alcohol use taken from the CannaForm (see Appendix A.2.1.4). Before the cognitive testing, all participants were informed at least once that they must abstain from alcohol use for 24 hours (although exceptions to this rule can be found in Section 2.3.2.5.), from cannabis use for 24 hours and other recreational drug use for seven days.

2.5. Biological Analysis of Hair Samples

Due the limited reliability of self-report drug use (Tourangeau & Yan, 2007) a second method was considered to measure drug use. Urine testing is the most frequent choice for drug testing within comparable cognition-cannabis use studies (Pope & Yurgelun-Todd, 1996; Pope et al, 2001). In addition some studies have tested hair for cannabinoids (Hermann et al., 2009), while others have tested saliva and blood samples (Kauert, Ramaekers, Schneider, Moeller, & Toennes, 2007). While saliva, urine, and blood are good for testing recent drug use, the reliability of these methods is still relatively poor (Musshof & Madea, 2006). For example a positive urine test may indicate that an individual has used cannabis within 24 hours or seven days, the former would violate an exclusion criterion of the current studies while the latter would not and it would not be possible to determine which. This reliability it partially influenced by the tool used to analyse the samples (e.g. gas chromatography; Musshof & Madea, 2006).

The decision of which medium to collect was based upon the desired type of information collected, the discomfort caused to the participant, practical issues relating to funding, storage and ethics. It is for these reasons that hair was chosen to be tested. The negative corollary of this decision is that recent use information cannot be

ascertained. Advantages include that it is the most sensitive method, a method which causes minimal discomfort to the participant and is the cheapest method in terms of storage costs as it does not need to be refrigerated or frozen (Musshof & Madea, 2006).

2.6. The Delis-Kaplan Executive Function System™ Battery (D-KEFS)

The D-KEFS consists of nine separate tasks designed to measure different components of executive function (Delis et al., 2001). Within the present research program, three of these tasks were selected as part of a neuropsychological battery for measuring executive function. These tasks are the Trail Making Test, the Verbal Fluency Test and the Design Fluency Test. In addition to the materials for the individual tasks, several supporting materials were used. The **Manual** provided the information necessary for administering each of the tasks correctly, the **Standard Record Form** was used to score and keep a record of the participant's performances and the **Stimulus Booklet** was used in conjunction with each of the individual task materials, providing visual reminder of the rules and instructions for each task, in addition to containing all the information to convert the raw scores into age-scaled scores.

The D-KEFS was chosen as a primary source of neuropsychological tests as it is widely used in clinical and healthy populations (e.g. Delis et al., 2001; Huey et al., 2009; Mahurin et al., 2006), it has extensive normative data (Delis et al., 2001), it has been extensively tested for reliability and validity (Delis et al, 2001), and it has been shown to be sensitive to prefrontal cortex damage (e.g. Yochin, Baldo, Nelson, & Delis, 2007; Yochin, Baldo, Kane, & Delis, 2009). The D-KEFS also provides the option to create age-scaled scores for the majority of the outcome measures and utilises multiple methods of contrasting different scores which aids in maximising process purity.

Table 2.2

A list of the selected D-KEFS tests and the primary processes measured as reported by the authors.

	Primary Processes Measured
Trial Making test	Visual scanning, numerical sequencing, alphabetical sequencing, cognitive flexibility, working memory, motor speed
Verbal Fluency test	Initiation, strategic retrieval of lexical items, attention, verbal knowledge, working memory, cognitive flexibility
Design Fluency test	Visual attention, non-verbal creativity, motor speed, initiation, cognitive flexibility, working memory

Note. There are six more D-KEFS tests which were not used in the current research programme.

2.6.1. The Trail Making test

The Trail Making Test (TMT) was incorporated into the Halstead-Reitan battery in its original form of 'Trails A' and 'Trails B' (Reitan & Wolfson, 1985). The total D-KEFS version (Delis et al., 2001) contains five components: Visual Scanning, Number Sequencing (i.e. Trials A), Letter Sequencing, Number-Letter Switching (i.e. Trails B), and Motor Speed.

All subtests within the TMT include an array of numbers and letters, each enclosed by a circle, which are spread sparsely over sheet of A3 paper. Each subtest requires the participant accomplish a different goal with each array of alphanumerical stimuli. For all subtests the rules were verbally administered to the participant, the un-timed practice section is completed and the experimenter corrects any mistakes made. Once the practice is over the participant is instructed that they can begin the main section and that they will be timed.

2.6.1.1. Rationale

The rationale for choosing the TMT for the first study was that previous experiments have identified that this task recruits executive processes (Arthbunutt & Frank, 2000; Sanchez-Cubillo et al., 2006) including set switching, working memory, and inhibition. While TMT variants have been used before to identify cognitive impairments in cannabis users (Medina et al., 2007) and to examine the age of onset of cannabis use hypothesis (Gruber et al., 2011), the results are still inconclusive as discussed in section 1.4.2. This test was included to help elucidate the relationship between cannabis use variables and the cognitive processes which contribute towards performance on the TMT.

2.6.1.2. Visual Scanning

The goal of the Visual Scanning is to draw a line through each circle which contains the number '3'. This component primarily measures visual scanning and selective attention (Delis et al, 2001). It also measures several more fundamental processes such as recognition of numbers and thus acts as a control condition, in order to detect any fundamental deficits which could masquerade as executive dysfunction in the switching component (section 2.7.1.5). The indicator of performance used in the first study is the age-scaled score of the total time taken to complete this task.

2.6.1.3. Number Sequencing

This subtest requires that the participant connects the numbers, while ignoring the letters, by drawing a line in ascending order from '1' to '16' across a new array of numbers and letters. This component primarily tests fundamental numerical processing, visual scanning, selective attention, and motor speed (Delis et al, 2001). It is primarily used as a control condition for the switching component and the indicator of performance for this subtest used in the first study is the age-scaled score of the total time taken to complete this task.

2.6.1.4. Letter Sequencing

This subtest requires that the participant connect the letters, while ignoring the numbers, in order from 'a' to 'p'. This also acts as a control condition for the switching component, testing verbal skills, visual scanning, selective attention, and motor speed

(Delis et al, 2001). The indicator of performance for this subtest used in the first study is the age scaled score of the total time taken to complete this task.

By combining the scaled score from this, and the previous subtest, a combined Number Sequencing and Letter Sequencing score can be produced, referred to as the composite scaled score. The use of this composite score is discussed below in section 2.7.1.5.

2.6.1.5. Number-Letter Switching

The fourth component, also known as 'trails B', is the primary measure of executive function within the TMT. The participant is required to draw a line, in ascending order, while switching between numbers and letters, so that they must draw a line from '1' to 'a' to '2' and continuing in such a pattern until the task culminates at the letter 'p'. The primary function tested in this subtest is set switching in the form of a prespecified task sequence paradigm (Delis et al, 2001). The task also recruits the processes measured in previous components: visual scanning, selective attention, motor speed, numerical/alphabetical processing.

There were three indicators of performance derived from this task and reported in first study. These were the (1) age-scale score of the total time taken to complete the task, (2) the number of errors made during this task, and (3) the contrast score. This contrast score involves subtracting the age scaled composite score discussed in the previous section from "(1)", reported in this section. This score is then converted into a secondary age-scaled score. This contrast process aims to minimise the other contributory processes involved in the task (e.g. visual scanning) and be a purer measure of executive function. Construct validity testing suggests this process yields a better estimate of executive function than the basic time taken to complete the task (Sanchez-Cubillo et al., 2009).

2.6.1.6. Motor Speed

This subtest involves connecting the circles by drawing a line along a designated path in the quickest possible time. The task was introduced to ascertain whether any pre-existing fundamental motor related deficit existed which could impair performance on the Number-Letter Switching subtest. The participant is required to connect the dots which are marked with a dotted line, requiring only basic motor skills to complete the task (Delis et al, 2001). As with the other control conditions, one indicator of

performance is used here, the age-scaled score of the total time taken to complete this test.

2.7.2. The Verbal Fluency Test

Numerous versions of verbal fluency tests exist including one by Bechtoldt, Benton and Fogel (1962) featuring the letters F, A, and S. While many letters can be used for this test, FAS are the most common, leading to many calling the task the "FAS task". Delis et al., (2001) incorporated the original FAS test into a larger verbal fluency measure, including three subtests: letter fluency, category fluency, and category switching. Each one of these three tasks involves verbally explaining the rules to the participant followed by their attempts. Responses are written down by the experimenter and coded for errors.

2.7.2.1. Rationale

The rationale for selecting the verbal fluency test was that a set of experiments has shown that retrieval ability on this test was influenced by constraints and individual differences in working memory capacity and focussed attention (Rosen & Engle, 1997). These findings suggest that this test measures some key processes associated with executive function. This test has also been shown to be sensitive to detecting deficits in individuals with frontal lobe trauma compared to healthy controls and non-frontal trauma patients (Ferstyl, Guthke & von Cramon, 2002). The majority of research on the fluency tests has suggested that cannabis use is not related to performance (see Section 1.4.5) however there is evidence that early onset users are vulnerable to performance on the letter fluency test but not the category fluency test (Gruber et al., 2011) while Pope et al (2003) found the opposite, with evidence of early onset related impairments on the category fluency test but not the letter fluency test. The inclusion of both of these tests will help resolve these contradictory findings.

The D-KEFS version of the verbal fluency test also includes the set switching condition which has never been administered to cannabis users before and therefore provides an opportunity to further extend the cannabis-cognition literature.

2.7.2.2. Letter Fluency

Within the Letter Fluency task the participant is given one minute to name as many words as they can think of whilst adhering to certain rules. The participant may not provide any variation of a word they have already provided (e.g. *hard* and *harder*) and may not provide the names of places, people, or numbers. The task was repeated three times, with three different letters, F, A, and S. This component measures initiation, working memory, strategy formation, attention, and speed of verbal processing (Delis et al, 2001). The number of correct responses over the three conditions are summed and then converted into an age-scaled score to indicate the level of performance on this task.

2.7.2.3. Category Fluency

For Category Fluency the participant is given one minute to name as many words that they can think of which belong to a certain semantic category. This component contains two trials with different categorical specifications (i.e. names of animals and boys names). This task involves mostly the same processes as letter fluency, however this component tends to be less sensitive to damage, as lexical items are more readily organised semantically and thus easier to retrieve (Delis et al, 2001). The total correct responses across these two categories are summed and converted into an age-scaled score to indicate the level of performance on this task.

2.7.2.4. Category Switching

Category Switching, similar to the previous component, requires the naming of items which belong to a given category, however the participant must alternate between naming items from two sets of categories (i.e. items of fruit and items of furniture). This component involves the same processes as the category fluency task, however there is also a set switching factor built into this component, furthermore the demands placed on working memory are greater, as the participant must maintain and update two lists of semantic lexical items as opposed to one (Delis et al., 2001). This task contains two indicators of performance: the age-scaled score of the total number of correct responses on this task and the age-scaled contrast score. The contrast score, like the TMT, involves controlling for more fundamental processes by subtracting the score from the Category Fluency subtest from the Category Switching subtest. The score is then age-scaled again to provide the Switching Contrast score. This is to increase the process

purity of the set switching involvement however, unlike the TMT, validity testing by an unaffiliated research group is yet to confirm this suggestion.

Furthermore, two error scores were derived from this test. The total number of repetition errors and set loss errors (rule violations) were calculated and then converted into a percentage of the total responses.

2.7.3. The Design Fluency Test

In the 1980's the five-point test was designed in order to be a nonverbal counterpart to the verbal fluency tests (Regard, Strauss & Knapp, 1982). A design fluency task did already exist in which participants must draw novel and nonsense images, but a lack of standardised scoring data and inter-experimenter scoring variances resulted in a lack of usage by the academic community. The new five-point test involved the creation of as many novel designs as the participant could create based on the premise of drawing straight lines between a series of proximate dots on a piece of paper. This task provided the standardised scoring system and data which the previous design fluency task lacked.

The D-KEFS version of this task (Delis et al., 2001) contains three components: filled dots, empty dots, and filled-empty switching. For each task the participant is verbally given instructions, and then allowed a short practice attempt, before being required to create as many designs as they can within the time limit whilst adhering to the rules.

2.7.3.1. Rationale

This measure is a D-KEFS standardised task with age scaled scores and shown to be sensitive in detecting impairments among certain populations including frontal lobe lesions and epileptic patients (Baldo, Shimanmura, Delis, Kramer & Kaplan, 2001; McDonald, Delis, Norman, Tecoma & Iragui, 2005). While the verbal fluency test is particularly sensitive to left frontal lobe lesions (Paulesu et al., 1997; Phelps, Hyder, Blamire & Shulman, 1997) the design fluency test is particular sensitive to lesions in the right frontal lobe (Ruff et al., 1994; Lee et al., 1997).

The selection of this test was partly influenced by the fact that it has not been previously used to test for impairments associated with chronic cannabis use. This test therefore provided a unique and novel approach to assessing cognitive integrity in cannabis users.

2.7.3.2. Filled Dots

The first component of the Design Fluency Task consists of a page containing 80 identical boxes, each containing five filled black circles, or 'filled dots'. The test involves the creation of a unique design within each box by connecting the filled dots with four straight lines and to complete as many of these designs as possible within one minute. This subtest is a measure of visual attention, non-verbal creativity, and motor planning (Delis et al., 2001; Suchy et al., 2010). The total number of correct and unique designs is converted into an age scaled score and used as the main indicator of performance for this subtest.

2.7.3.3. Empty Dots

This component differs from the first in that each one of the identical boxes now contains a number of filled black circles and hollow black circles, or 'empty dots'. The task involves the creation of a unique design within each box by connecting the empty dots with four straight lines. This subtest is a measure of visual attention, inhibition, non-verbal creativity and motor planning (Delis et al., 2001; Suchy et al., 2010). The total number of correct and unique designs is converted into an age scaled score and used as the main indicator of performance for this subtest.

The two scores from the filled and empty dot tests are combined into a composite score which is then used to control for non-switching related processes after completion of the third subtest.

2.7.3.4. Switching

This subtest contains a series of boxes containing both filled and empty dots, yet here the participant is required to alternate between connecting the two varieties of dot. Such that if a line begins at a filled dot it must terminate at an empty dot. This subtest measures all the same processes described in the earlier subtests however it also measures set switching (Delis et al., 2001). In contrast, Suchy et al (2010) found that this measure was related to visual search and attentional resources yet surprisingly was unrelated to cognitive flexibility. The total number of correct and unique designs is converted into an age scaled score and used as the main indicator of performance for this subtest.

By contrasting the age scaled score for this subtest with the composite score from the first two subtests, a new score is created which aims to be a purer measure of set switching (Delis et al., 2001). Unlike the TMT, validity testing by an unaffiliated research group is yet to confirm this suggestion.

Furthermore, two error scores were derived from this test. The total number of repetition errors and set loss errors (rule violations) were calculated and then converted into a percentage of the total responses.

2.7. The Grooved Pegboard

The Grooved Pegboard Test (GPT) has been found to be a sensitive measure of motor performance used in a number of test batteries (Mathews & Klove, 1964). There are 25 pegs which are used in the task which resemble two long metal cylinders of different diameters which have been fused together. Traditionally the task involves the placing of these identical pegs into holes, however the pegs must be rotated a certain amount in order to fit the peg in. This is first completed by the dominant hand and subsequently by the non-dominant hand. The participant's performance on this task is measured by the time taken to complete it with each hand.

2.7.1. Rationale

This test was chosen as it has been found to be sensitive to nigrostriatal damage (Bohnen et al., 2007) in addition to providing a more complex assessment of manual dexterity beyond the basic level of motor speed measured by completing the motor speed subtest of the TMT. The relationship between GPT and cannabis use is not clear however one study exploring the relationship found a dose-response effect with more frequent cannabis users displaying slower completion times on the task (Bolla et al., 2002). The effect of the age of onset of cannabis use on the GPT has not been explored and therefore this represents an opportunity to extend the literature on how chronic cannabis use affects manual dexterity.

2.7.2. The Place Task

The primary use of the grooved pegboard is the placing of the 25 pegs from the tray into the holes contained within the board, completed first with the dominant hand and then the non-dominant hand. This component has been suggested to measure visuomotor

control, complex motor speed (Bryden & Roy, 2005) and motor planning (Baser & Ruff, 1987) while recent validity research suggests that the role of basic motor speed is smaller than a cognitive role in GPT completion (Bezdicek et al., 2014; Strenge, Niederberger & Seelhorst, 2002). These studies suggest that attention, visual speed, and a continuous monitoring of performance are involved in task completion. The main performance indicator is the total time taken to *place* all 25 pegs into the holes and this is assessed with both hands yielding two scores.

2.7.3. The Remove Task

This requires the participant to remove the pegs from the holes and place them back into the tray from which they came. This has been suggested to be a purer measure of motor speed as it reduces the use of such processes as motor planning and attention (Bryden & Roy, 2005). Up until this time there had been no validity testing to confirm this hypothesis and therefore the current thesis included an analysis for confirmation. The results are discussed in Chapter Three, and they support Bryden & Roy's (2005) hypothesis for a larger role of motor speed in this subtest. The main performance indicator is the total time taken to *remove* all 25 pegs out of the holes and this is assessed with both hands yielding two scores.

2.7.4. The Contrast Measure

The current research programme introduces a new method of analysing performance on the grooved pegboard task. This is analysed by contrasting the two previous measures (place task time taken - remove task time taken) for both the dominant and non-dominant hand. This contrast aimed to minimise the effects of motor speed and results in a purer measure of the cognitive abilities, such as attention, motor planning, and visuo-motor coordination. Validity testing is also conducted on this measure and reported in Chapter Three. While the tests could not identify what is influencing performance on this measure, they do highlight that the motor speed is not involved in this measure as opposed to the place task or the remove task.

2.8. The Iowa Gambling Task

This computer based task was originally developed to detect damage to the ventromedial prefrontal cortex within a gambling paradigm (Bechara et al, 1994). It involves four decks of cards which can either result in the participant gaining or loosing

virtual money. Decks 'A' and 'B' are set to provide large short term gains of £1000 per 10 cards, but long term losses of £1250 per 10 cards, generating a net loss of £250. Cards 'C' and 'D' are set to provide smaller short term gains of £500 per 10 cards and long-term losses of £250 per 10 cards which generates a net profit of £250 (see Figure 2.9). The task is completed when the participant has selected 100 cards. Performance on this task is measured by the number of advantageous cards chosen, with the presumption that those who identify the long term gains sooner will switch to choosing the advantageous cards.

The authors of the task suggest that intuitive or emotional guided decision making processes are the primary cognitive resources recorded by the task (e.g. Bechara et al., 1994) and validity studies seem to confirm this suggestion (Buelow & Suhr, 2009). It appears that "hot" decision making processes i.e. emotional more than cognitive, are explaining performance which explains mixed findings when correlating performance with measures of executive function. There also seems to be a link between IGT performance and risk taking behaviour as assessed by real-world risk taking behaviours such as drug use and gambling (Buelow & Suhr, 2009).

Bechara et al., (1994; 1999; 2005) have suggested that non-conscious emotions influence decision making, to an extent, before conscious realisation of the correct decision becomes apparent. According to the authors, these 'hunches' are manifested physically in the form of an autonomic response, such as increased skin conductance which is mediated by activation of the ventromedial prefrontal cortex and amygdala. Physiological testing showed that the healthy controls had this physiological response after a certain amount of cards had been chosen, the stage the authors named 'pre-hunch'. The test subjects, those with ventromedial prefrontal lesions, did not display this skin conductance response (SCR) whilst pondering the selection of a disadvantageous card. Further research has recruited those with amygdala lesions, in addition to VMPFC and controls, to take part in the IGT while measuring SCRs (Bechara et al., 1999). Both lesions groups not only performed worse on the task, but both showed significantly diminished SCRs whilst pondering the disadvantageous cards. This research now suggests that the autonomic responses, which are influenced by the VMPFC and the amygdala, influence the ability to make good decisions on this task.

Figure 2.8. A screenshot of the IGT, displaying the four decks, the total amount won, the total amount borrowed and the amount won on the previous selection of deck A.

2.8.1. Rationale

As discussed this task has shown to be sensitive in detecting impairments by those afflicted with VMPFC and amygdala trauma. While this task has been largely successful in detecting impairments in chronic cannabis users (Whitlow et al., 2004; Bolla et al., 2005; Fridberg et al., 2006; Verdejo-Garcia et al., 2007) there is no data on whether the age of onset mediates deficits on this task. Therefore the current research programme will make an original contribution to this area by determining how the age of onset of cannabis use influences decision making.

Furthermore, this task is a relatively ecologically valid measure of decision making (Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006). Whereas some tasks isolate deficits within an experimental paradigm which then must be extrapolated to real life behaviours, this task creates a situation which is more applicable to behaviours that occur outside of the laboratory.

2.9. The Affectiva™ Qsensor

Within the current research program the Qsensor was used in conjunction with the Iowa gambling task and measures SCR, a form of autonomic nervous system arousal. The Qsensor is a portable, wrist worn device, containing two electrodes which measure SCR (Poh, Swenson & Picard, 2010).

SCR changes occur to situations which have subjective salience, including winning and losing, potential threats, emotions, anticipation of a salient outcome and cognitively demanding tasks (Critchley, 2000). SCR is influenced by the sympathetic

subcomponent of the autonomic nervous system. There is evidence that such activity is mediated by the hypothalamus and the brainstem, with additional regions including the VMPFC, DLPFC, amygdala, anterior cingulate, insula, and parietal lobe. The region of influence is dependent on the situation, with the VMPFC and amygdala being associated with motivational behaviour, while the anterior cingulate cortex influences SCR during risk assessment (Frederikson et al., 1998; Critchley et al., 2001) and the right parietal lobule influences SCR during visual attention (Critchley et al., 2000).

The Qsensor was chosen to be administered in tandem with the IGT to determine if decision making processes in cannabis users were influenced by anticipatory SCRs comparable with VMPFC/amygdala trauma patients (Bechara et al., 2004). Although data collection was conducted with this device the analysis was not completed as the company supplying the hardware and analytical software discontinued the product during the data collection process.

2.10. The Wechsler Adult Intelligence Scale® Third Edition (WAIS-iii)

The WAIS-iii (Wechsler, 1997) contains a 14 individual sub components which measure various intellectual properties, however in the current research programme only the symbol search task was used. Additionally the **record form** was used to record the scores of the participants and the **administration and scoring manual** was used for the conversion of raw scores into age-scaled scores.

2.10.1. The Symbol Search Task

This task requires the participant to determine whether one of two target symbols appear in a row of a further five random symbols (see Figure 2.11). The participant makes their choice by marking either the 'yes' or 'no' boxes. After the allotted two minutes has expired, or the participant has completed the 60 trials, the task is stopped and the score calculated. The total correct responses score is converted into an age-scaled score using the administration and scoring manual. This task measures visual processing speed and motor speed (Wechsler, 1997).

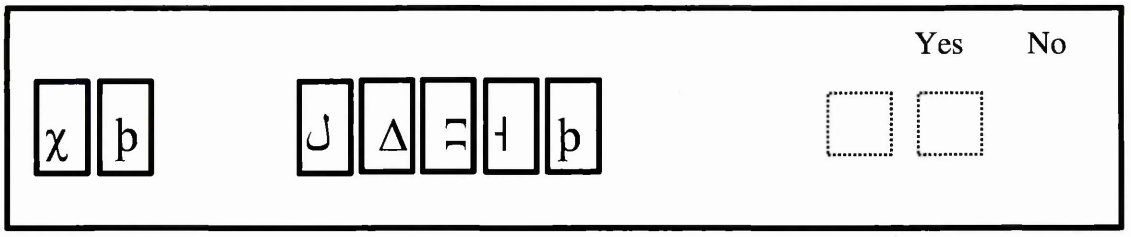


Figure 2.11. An example of one item of the Symbol Search Task in which one of the targets is present in the stimuli.

2.10.1.1. Rationale

This task was chosen as a measure an additional measure of visual processing (Wechsler, 1997). Although not considered an executive function, a number of other visual tasks were included which recruit visual processing speed as a contributory process (e.g. TMT; DFT) and therefore the inclusion of a more process pure assessment of this cognitive construct would allow an in-depth analysis of which processes are affected (if any) by chronic cannabis use.

2.11. The Wechsler Abbreviated Scale of Intelligence (WASI)

To create this IQ score the WASI was employed which includes four tasks: vocabulary and similarities, block design, and matrix reasoning (Wechsler, 1999). All four components create a full scale IQ score, which was the statistic used as a covariate in the first and second studies (see Chapters Three and Four). All responses from each subcomponent are recorded within the **record form**, while scoring and administration was aided by the **manual**. During the administration of certain sections of the test the **stimulus booklet** was used to provide the participant with necessary visual information.

2.11.1. Rationale

The present study included the WASI estimated full scale IQ (FSIQ) scores as a predictor of premorbid intelligence. Lezak et al., (2004) advised against using a single measure for premorbid estimates and suggested that as much information as possible should be utilised where possible. This is partly due to the fact that individuals can vary largely in their abilities across different cognitive domains (Taylor & Heaton, 2001) and the use of a single task thought to be resistant to the effects of insult may be inaccurate. It is for these reasons that the FSIQ, comprised of two verbal and two performance IQ subtests, was used to estimate premorbid intelligence.

The rationale for choosing the WASI as opposed to the full WAIS-IV was partly for practical reasons, being that including the full scale version would increase the testing time of a cognitive battery which already includes a large number of questionnaires and neuropsychological tests and this would therefore increase potential fatigue effects. Furthermore, WASI scores have been shown to be strongly correlated with WAIS-iii scores in a normal sample (.84 to .92) although slightly less in a mixed clinical sample (.71 to .82; Axelrod, 2002).

All four subtests of the WASI are administered to the participant and the raw scores are then converted into age-scaled *t*-scores which are then converted into verbal, performance, and FSIQ scores. See Table 2.8 below for the authors' account of which areas of intelligence are tested.

Table 2.3

An account of the four WASI subtests and the primary areas of intelligence measured.

WASI Subtest	Primary cognitive processes measured
Vocabulary	memory, crystallized intelligence
Block design	spatial visualisation, general intelligence
Similarities	abstract verbal reasoning, general intelligence
Matrix reasoning	non-verbal fluid reasoning, general intelligence

2.12. The Hospital Anxiety and Depressions Scale (HADS)

The HADS was developed by Zigmond and Snaith (1983) with the aim of a quick and reliable measure of depression and anxiety. The questionnaire combines seven depression orientated statements and seven statements aimed to measure anxiety with a four point Likert-style response section ranging from 0-3.

The participant's results can suggest that they fall within the normal range (0-7), borderline abnormal (8-10) or abnormal range (11+) for depression or anxiety (Zigmond & Snaith, 1994). A typical statement is presented in the following format:

1) I feel tense or wound up:
   3. Most of the time
   2. A lot of the time
   1. From time to time/occasionally
   0. Not at all

2.12.1. Rationale

The rationale for choosing a measure of anxiety and depression is that these two conditions are both prevalent among cannabis users and can have a negative impact on cognition (see Section 1.5.5). The inclusion of such a measure would help determine whether cannabis-related impairments in executive function are mediated through anxiety and depression, or whether such deficits are independent of these mental health problems.

The rationale for choosing the HADS was based on the desire for a quick and simple method of assessing mental health symptoms in those who have not received a psychiatric diagnosis. A review of a large number of studies examining the reliability and validity of the HADS was conducted by Bjelland, Dahl, Haug & Neckelmann (2002). The findings highlight a satisfactory to excellent internal reliability (Cronbach's α=.68-.93) and this remains fairly consistent across males, females, a wide range of ages and many clinical samples. The HADS anxiety sub-score also shows satisfactory to good concurrent reliability with the State -Trait Anxiety Inventory (.64 - .81) and the depression sub-score shows good concurrent reliability with the Beck Depression Inventory (.61 - .83). The main critique of the HADS is that nearly half (9 out of 20) of the reviewed papers conducting factor analysis found greater than a two factor model, suggesting the measure does not just measure anxiety and depression, but also a third latent variable (occasionally called restlessness). Despite this critique, the authors (Bjelland et al., 2002) suggest that the data still best fits a two-factor model with a certain degree of overlap to be expected due to the co-morbidity of anxiety and depression.

2.13. The Clark-Beck Obsessive-Compulsive Inventory (CBOCI)

The CBOCI was produced to detect the severity of obsessive and compulsive symptoms (Clark, Beck, Antony, Swinson & Steer, 2005). The CBOCI can provide information regarding obsessions, assessed over fourteen items; compulsions, assessed over eleven items and a combination of the two subcomponents, assessed using the full twenty-five items, all using a four-point graded-response format. A typical section followed the following format:

0. I **never** or **rarely** have obsessional intrusive thoughts, images, or impulses of dirt or contamination
1. I **occasionally** (less than weekly) have obsessional intrusions of dirt or contamination
2. I **frequently** (several times a week) have obsessional intrusions of dirt or contamination
3. I **very frequently** (daily) have obsessional intrusions of dirt or contamination

The participant was instructed to read the passage on the front sheet of the CBOCI which explains the process of completing the questionnaire. The participant must respond by circling the number of the statement which best describes their thoughts, feelings or behaviours during the day of testing and the previous two weeks.

2.13.1. Rationale

The rationale for choosing a measure of OCD within the current research programme is based on the effects that obsessions and compulsions can have on executive function and the prevalence of OCD symptoms present in drug users (see Section 1.5). The inclusion of this measure may help determine whether cannabis-related impairments in executive function are mediated through obsessions and compulsions, or whether such deficits are independent of these mental health issues.

The CBOCI was chosen to provide an easy assessment of obsessive and compulsive symptoms without the need of a trained clinician. The measure boasts good internal reliability for healthy, OCD and mixed clinical samples across the two sub-scores and the combined total (Cronbach's α=.79-.95; Clark et al., 2005). Additionally the model shows good concurrent validity as determined by high correlations (.74) with an established 'gold standard' of OCD measures, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), which is administered by trained clinicians (Steketee, 1994). Factorial validity was also high, with a principal component analysis supporting a two-factor

model with only a single item from the CBOCI not loading on its theorised factor (Clark et al., 2005).

2.14. The Apathy Evaluation Scale (AES)

The AES was developed to measure diminished motivational states which are not attributable to cognitive impairment, emotional distress, or diminished consciousness (Marin, Biedrzycki & Firinciogullari, 1991). The self-report version was used in the current research programme which required the participant to respond to statements on a four-point Likert style response section. A typical section followed the following format:

2. I get things done during the day

Not at all Slightly Somewhat A Lot

The participant is required to circle the answer that best describes their thoughts, feelings and activities during the past four weeks.

2.14.1. Rationale

As with the two other mental health questionnaires, the AES is an easy to use and fast measure of a particular state - in this case - apathy/motivation. This was included due to reports of diminished motivation in cannabis users and due to motivation's role in executive function (see Section 1.5).

The AES was chosen as the measure of motivation for several reasons. The primary reason was that this specific measure has uncovered differences before between cannabis users and alcohol using controls (Solowij et al., 2011), suggesting that it is a sensitive measure for detecting diminished motivation in cannabis users, if any is present. Furthermore, the measure has shown good internal reliability (Cronbach's α=.86), yet predicative validity was weaker in the self-report measure than the clinician or informant measure (Marin et al., 1991). The study found that three of five behavioural measures of motivation were significantly associated with AES self report scores compared to five out of five for the clinician and informant version of the AES.

Whether or not these behavioural measures actually predict motivation themselves however is questionable, as performance on the computer game PACman was used as one of the measures. While several of the measures including 'PACman latency' (how long it took for the participant to decide to play another game) may indicate motivational levels, performance itself may be reflective of previous computer game experience or other factors unrelated to motivation.

2.15. Mental Health Summary

The original plan was to use the questionnaires (HADS and OBOCI) for exclusion criteria purposes however the criteria for an abnormal score in HADS ranged vastly across different studies (from 3-11 out of a possible 21; Bjelland et al., 2002) and therefore it was decided instead to use the data as a potential covariate and to match the two groups for scores across the four sub components (anxiety, depression, obsessions, and compulsions). The AES was also adopted for this purpose in the eye-tracking study (Chapter Four).

2.16. Tobii Visual Search Test

2.16.1. Rationale

The neuropsychological study reported in this thesis (Chapter Three) suggested a combination of set switching and visual attention deficits in the cannabis users. In order to deconstruct the processes relating to these two areas of cognition, a computerised analogue of the Visual Scanning subtest from the D-KEFS TMT was created. The use of a computerised version of this task with the Tobii eye tracker allowed a number of different outcomes measures to be derived from both behavioural data and eye tracking data. These different outcome measures aimed to isolate the area/s which is impaired, in a similar fashion to that conducted by Huestegge, Radach, Kunert and Heller (2002).

2.16.2. The Tobii Eye Tracker

The device used to monitor gaze was a Tobii T120 with the eye tracking cameras built into a 17" monitor which presented the stimuli used in the task described in Section 2.16.3.

2.16.3. Task Structure

The computerised adaptation of the visual search test from the TMT, hereinafter called Tobii VST, was designed using Tobii Studio. The computerised adaptation of the Number-Letter Switching task from the TMT, hereinafter called the Tobii SST was also designed using Tobii studio. The task which was designed for use with the Tobii eye tracker was aimed to replicate the task demands of the visual scanning and set switching subtests from the D-KEFS TMT.

The process of creating the new tasks required the consideration of the following aspects: number of trials, target to non-target ratio, the stimulus size, the display size, the set size per trial, the target symbol, the non-target symbols, the spatial density, and the stimulus arrangement. The criteria for creating each aspect of the new task were based on at least one of the four following sources. Firstly, where possible the new task would replicate the D-KEFS version of the visual search subtest. Secondly, the new task would aim to replicate previous comparable studies (Ehrenreich et al., 1999; Huestegge et al., 2002). Thirdly, theoretical considerations would be applied to the construction of a given aspect and finally, where necessary, practical considerations would take priority. Further information on this process can be found in Appendix A.2.2.

The Tobii VST involved a participant identifying whether or not a target symbol was presented amongst an array of distractor stimuli. The Tobii SST, maintained the same premise, however the target symbol would switch every trial from a target letter to a target number and then back again. An example of a trial can be seen below (Figure 2.17).

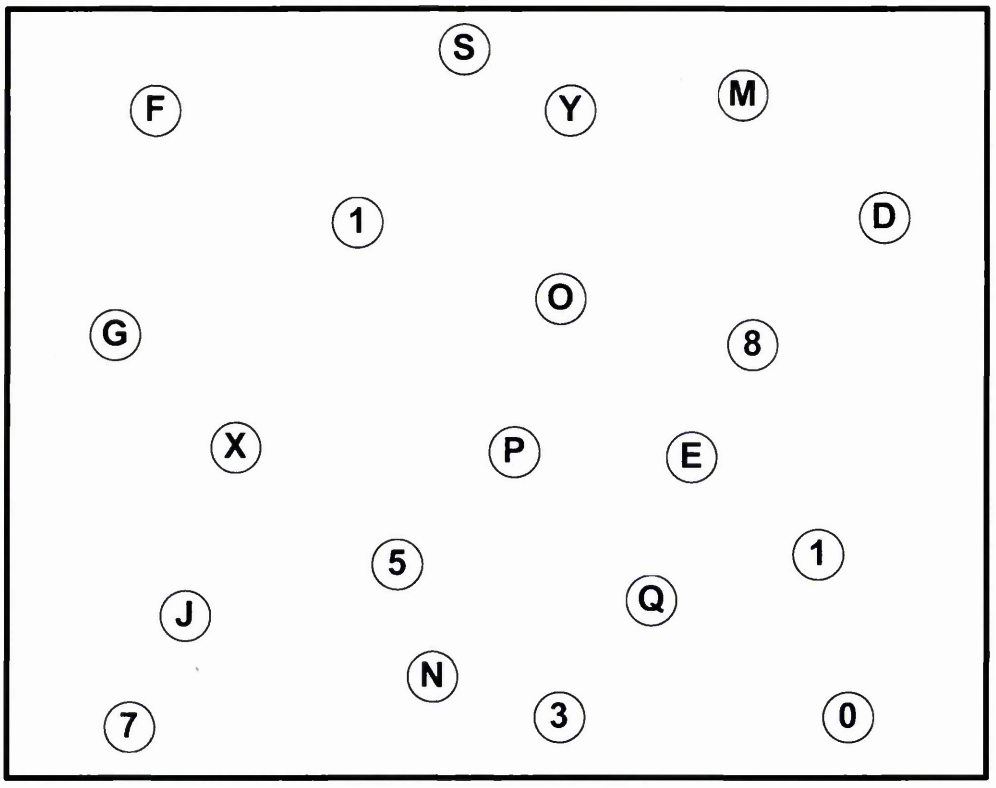


Figure 2.17. A sample target trial taken from the Tobii VST

2.16.4. Behavioural Outcome Measures

2.16.4.1. Areas of Interest

Before eye-tracking analyses could be conducted the areas of interest (AOIs) needed to be determined. A stage in the analysis using the Tobii eye tracker, studio and analysis package, is to code various areas on the test with AOIs. This allows the software to determine whether or not a fixation landed within a given area. Although there are no official guidelines on AOI dimensions, Goldberg & Helfman (2010) suggest that practical concerns along with empirically led information about foveal focal dimensions (Raynor, 1998) should guide AOI sizes. It is for these reasons that all 20 stimuli per trial were categorised as AOIs with a 1.2cm "padding" extending beyond the edges of each stimulus.

2.16.4.2. Reaction times

The mean reaction time for the target trials was assessed for both the Tobii VST and the SST. The reaction time for the target trials encapsulates the majority of processes involved in the task: time taken to employ a search strategy, time taken to shift foveal

focus across the array, time taken to process the stimulus and determine if it is a target or not, time taken to coordinate the appropriate motor response (button pressing) once the target has been located and time taken for the motor response to be initiated and completed. This unfiltered measure is likely to be the one which most replicates performance on the TMT subtests. Furthermore, this measure can be broken down from a total reaction time score into a 'correct' reaction time score, the mean time taken to identify a target across all trials in which the participant correctly identified the target.

The mean reaction time for the non-target trials includes additional processing. Once the target is found in target trials the search no longer needs to proceed, however for the non-target trials the individual must proceed until the participant reaches a threshold level of confidence that the target is not present. This is supported by the larger reaction times for non-target trials found by Huestegge et al (2002).

2.16.4.3. Errors

Omission errors (not identifying a target) and commissions errors (identifying a target which does not exist) were included for the analysis. This was considered alongside the reaction time data to determine the nature of the performance on the task. It is worth noting that increased errors could also be descriptive of more severe abnormalities such as an inability to process and identify symbols, however this has never been identified before in tasks which require cannabis users to identify abstract symbols (see Chapter Three) or read sentences (Huestegge, Kunert & Radach, 2010).

2.16.5. Eye-Tracking Outcome Measures

2.16.5.1. Unique Fixation Count

One of the primary measures investigated by Huestegge et al (2002) was the total fixation count which is the mean number of fixations per trial. The total number of revisits was also included by these authors however a different approach was chosen in this thesis. As revisits will increase the total number of fixations, the current study aimed to just look at the total number of unique fixations which increases the process purity of this measure. The number of unique fixations per trial describes search efficiency: the number of steps taken before the target is located, and therefore could be an indicator of strategic search efficiency (Najemnik & Geisler, 2005). When searching

a visual scene, attention does not dart around randomly, but rather it follows a systematic pattern even when it appears to be random. Najemnik and Geisler (2005) describe several characteristics of the theoretical 'ideal' search strategy which include searching regions of 'high gravity', in which focus is drawn to clusters of high information (or stimuli).

2.16.5.2. Fixation Duration

This is the mean amount of time spent gazing at a particular location before a saccade is made. This period of fixation is the primary point at which information can be processed as the velocity of saccades leads to a marked reduction in the sensitivity to acquire new information, a term dubbed *saccadic suppression* (Matin, 1974). This fixation duration time is dependent on several factors: the extraction and visual processing of the stimulus within the foveal focus, the amplitude/distance of the previous saccade, peripheral scanning of stimuli outside the foveal focus and the planning and initiation of a subsequent occulomotor action (Salthouse & Ellis, 1980; Hooge & Erkenlens, 1998; Radach & Heller, 2000). Longer fixation latencies could be indicative of needing longer to process the content of the visually available information. This has been shown by varying the discriminability of the stimuli across trials (Hooge & Erkenlens, 1998) and by varying the stimulus exposure time (Salthouse & Ellis, 1990). The role of peripheral processing in fixation durations has been identified by the discovery that longer fixations tend to follow large saccades. Following a short saccade there would have been a certain degree of extra-foveal or peripheral processing and therefore subsequent durations would be reduced. The destination after a longer saccade would have received minimal prior processing and therefore after this eye movement there have been shown to be longer fixation durations (Radach & Heller, 2000; Rayner, 2009).

2.16.5.3. Fixation revisits

Frequent revisiting to a previously fixated region of the array was a measure used by Huestegge et al (2002) which uncovered impairments in their cannabis using sample. There have been suggestions that memory is not involved in visual search, most notably by Horowtiz & Wolfe (1998) who found that performance did not differ between a static search grid (target 'T' among distractor 'L's) and a changing search grid in which

the letters shifted position every 111ms. This study suggested that the use of memory regarding previous searched areas in every array did not aid performance in this specific task. Further support comes in the form of a dual-task format in which Woodman, Vogel and Luck (2001) found that manipulating the load placed in visual working memory, in the form of the colour of objects, did not impair visual search processes. However, subsequent research from the same group (Woodman & Luck, 2004) found that by changing the visual working memory task with a spatial working memory task, visual search became impaired during a comparable dual-task format. In addition to these findings, it has been shown that the number of revisits in a search array is lower than would be expected by chance, which suggests a role of a memory system in visual search, albeit an imperfect memory system as revisits still occurred (Gilchrist & Harvey, 2000). Therefore, greater numbers of fixation revisits in the current task could be interpreted as spatial working memory impairments. Although this should be interpreted with caution as fewer revisits may be due to an organised 'reading-like' search strategy, rather than an accurate memory of previously visited areas.

2.17. The Visual Object and Space Perception Battery

2.17.1. Exclusion Criteria

In order for the individual to take part in the Tobii tasks it was essential to ensure that any performance variance was not due to impaired vision. To avoid this possibility, every individual completed four subtests of the VOSP: Object Detection, Incomplete Letters, Position Discrimination, and Number Location (Warrington & James, 1991). These tests were chosen as each one recruited a fundamental visual process required to complete the Tobii tasks. The pass/fail guidelines suggested by the authors were divided into two age categories, those under the age of 50 and those who were 50 and above. Table 2.4 displays the information about each of the four subtests of the VOSP which were used in the experiment discussed in Chapter Six.

Table 2.4.

The four subtests of the VOSP with the pass/fail scores and the aspects of perception measured.

Subtest	Possible Scores	Fail Score (age <50)	Fail Score (age ≥50)	Processes measured
Object Detection	0-20	15 or less	15 or less	VOP
Incomplete Letters	0-20	17 or less	16 or less	VOP; alphabetical recognition
Position Discrimination	0-20	18 or less	18 or less	VSP
Number Location	0-10	7 or less	7 or less	VSP; numerical recognition

Note. VOP = visual object perception; VSP = visual spatial perception.

Chapter Three. Visuo-motor and Set Switching Deficits in Early Onset, Abstinent Cannabis Users

3.1. Introduction

Previous studies have identified widespread cognitive deficits in chronic cannabis users yet there still remains some controversy as to why these results are not always replicated (Pope et al., 2001; Pope et al., 2002; Medina et al., 2007; McHale & Hunt, 2008). Explanations for these inconsistent results tend to relate to either 1) methodological factors such as the tasks which were administered, 2) factors associated with cannabis use which act as confounding variables or 3) non-cannabis related confounding variables such as sex and IQ. The cannabis use variables include the length of abstinence from cannabis (for review see: Crean et al., 2010), the lifetime quantity or duration of cannabis use (Bolla et al., 2002; Solowij et al., 2002), the frequency of cannabis use (Gruber et al., 2011; Pope & Yurgellun-Todd, 1996) and the age of onset of cannabis use (Pope et al., 2003; Fontes et al., 2011; Gruber et al., 2011).

3.1.1. Executive Function and the Age of Onset Hypothesis

The age of onset hypothesis was first suggested after observations of the protracted functional and structural development of the brain, particularly the frontal cortex, which continues to develop beyond adolescence (Reiss et al., 1996; Giedd et al., 1999; Gogtay et al., 2004). The dorsolateral (DLPFC), ventrolateral (VLPFC), and orbitofrontal (OFC) have a protracted development and mediate executive functions to varying degrees (Alvarez & Emory, 2006). These morphological developments are accompanied by changes in executive function which continue to mature into the third decade of life (Romine & Reynolds, 2005). Due to the possibility that exposure to Δ^9-THC confers greater adverse consequences due to the interruption of normal development through CB_1 receptor activation, a number of studies have tested the hypothesis that early onset cannabis use leads to greater and more widespread cognitive deficits than later use (Ehrenreich et al., 1999; Pope et al., 2003; Fontes et al., 2011b; Gruber et al., 2011). The earliest study to investigate the age of onset hypothesis in cannabis users found that the early onset users presented with deficits in visual scanning and divided attention

(Ehreneich et al., 1999). However, this study included users whose abstinence periods ranged from two hours to one week suggesting that a proportion of the effects discovered could be attributed to acute intoxication or 'hangover' effects rather than the long lasting damage from chronic cannabis use.

Pope et al (2003) administered a battery of cognitive tasks to early onset cannabis (EoC) users (≤16 years), late onset cannabis (LoC) users (≥17 years), and controls and found greater performance deficits in EoC users than LoC users when compared to each other and a control group. These deficits were on a verbal fluency task and the Wisconsin card sorting task (WCST), however these group differences were removed when verbal IQ was used a covariate. The authors used verbal IQ as an estimate of premorbid intelligence however they only used one test to estimate this score, the vocabulary subtest from the WAIS-III. The problem with using this IQ variable as a covariate is that it was found to be significantly reduced in cannabis users. If it was cannabis use which caused both the deficits on the executive function tasks and the deficits on the IQ test then this analysis would remove some of the variance in the dependent variable associated with the independent variable (early onset cannabis use vs. late onset cannabis use vs. controls) which leads to a reduction in power (Owen & Froman, 1998). This method by Pope et al (2003) could be improved by collecting IQ estimates from a range of tests and using a full scale IQ score which could reduce the possibility of it being fragile to the effects long term cannabis use. Although Pope et al's study does not show a clear association between the age of onset and executive function, it suggests that EoC use could be related to impaired performance on the verbal fluency task and the WCST. Pope et al (2003) also included measures of sustained attention (Conners' Continuous Performance test) and inhibition (the Stroop test) however no between group differences were discovered on these measures before or after controlling for VIQ. In comparison with Ehrenreich et al's (1999) abstinence criteria, Pope et al (2003) used a 28 day 'monitored' abstinence period. This excludes the possibility that the cannabis groups' performance is due to acute intoxication, 'hangover' effects (Pope et al., 1995) or withdrawal effects (Budney et al., 2003) as all these phases are likely to have passed.

Another study detected impairments across a number of different executive function measures in cannabis users compared to controls (Gruber et al., 2011). In the second

half of the analysis Gruber et al (2011) divided the cannabis group into an EoC group (≤15 years) and a LoC group (≥16 years old). It became apparent that the early onset group were accounting for most of these previous impairments in the whole cannabis group. Gruber et al partially replicated the findings from Pope et al (2003) by detecting early onset related deficits on the WCST. However, while Pope et al (2003) did not discover any deficits on the Stroop task, Gruber et al's (2011) findings did identify such deficits in the early onset group. Gruber et al's abstinence period was set at 12 hours, this makes acute intoxication unlikely, however leads to issues attributing the effects to 'hangovers' (Pope et al., 1995), withdrawal (Budney et al., 2003) or long lasting damage. While Gruber et al (2011) did use covariate methods to control for the effects of cannabis use variables (e.g. frequency of use) they did not apply the same approach used by Pope et al (2003) and control for the effects of IQ. Gruber et al (2011) did include strict exclusion criteria and matched groups for age and IQ to ensure these variables were not explaining group differences in cognition.

A study was conducted by Fontes et al (2011a; 2011b) who administered the Frontal Assessment Battery (FAB) to a group of chronic cannabis users and controls. This battery measures conceptualisation, verbal fluency, motor programming, inhibition and environmental autonomy, all related to frontal circuitry (Guedj et al., 2008). When observing the cannabis group there were clear deficits in performance on the overall FAB score and the motor programming subtest (Fontes et al., 2011a). As with Gruber et al (2011), the cannabis group was subsequently divided into early (≤14 years) and late (≥15 years) onset cannabis groups (Fontes et al., 2011b). The EoC group presented with deficits on the total FAB score compared to both controls and a LoC group while no deficits were apparent between the LoC group and controls on any measures (Fontes et al., 2011b). In addition, Fontes et al (2011b) examined performance on the WCST and the Stroop test which both highlighted impairments in the EoC group yet not the LoC group. These studies provide strong evidence that EoC use confers greater cognitive consequences related to cognitive flexibility and interference control (Pope et al., 2003; Gruber et al., 2011; Fontes et al., 2011b), furthermore Fontes et al (2011b) found impairments on the combined score of the FAB, perhaps suggesting more general frontal abnormalities in functioning. These studies have found preliminary evidence for a period of cognitive vulnerability, susceptible to the effects of chronic cannabis use.

One study tested the age of onset hypothesis on verbal working memory during fMRI (Becker, Wagner, Gouzoulis-Mayfrank, Spuentrup & Daumann, 2010). No performance differences were found on a verbal working memory task between EoC users (≤15 years) and LoC users (≥16 years), however fMRI data suggested greater and more widespread cortical activity in the early users suggestive of inefficient processing. This increased activity only correlated with age of onset and did not correlate with the period of abstinence, total lifetime use or frequency of use. These correlations were with activity localised to primarily prefrontal and parietal regions, consistent with previous uses of the n-back test (Owen et al., 2005). Similar findings were shown by a comparable study investigating inhibitory processes in cannabis users during fMRI (Gruber, Dahlgren, Sagar, Gönenc & Killgore, 2012). Although this study also showed no differences in behavioural performance, the early (≤15 years) and late (≥16 years) onset groups differed in the levels of activation within an area often implicated in inhibitory processing, the anterior cingulate cortex (Bush & Shin, 2006). It appears that when no behavioural abnormalities are evident, there are distinct differences in functional brain activity between early and late onset cannabis users.

These studies described above (Becker et al., 2010; Fontes et al., 2011b; Gruber et al., 2011; Gruber et al., 2012; Pope et al., 2003) have all used a methodology which compares an EoC group with a LoC group, however earlier initiation of cannabis use could potentially have the corollary of increased lifetime cannabis use which could therefore be explaining these deficits. As already discussed, Gruber et al (2012) used correlations between appropriate confounding variables and regional functional brain activity to determine this and found a significant correlation with the age of onset but not total cannabis use. Two of these studies included estimated total lifetime cannabis use as a covariate and re-ran the analysis which had little effect on the results, suggesting that this variable did not explain the differences between groups (Pope et al., 2003; Gruber et al., 2011). Fontes et al (2011b) did not control for the effects of lifetime cannabis use, however the two groups (EoC users and LoC users) had similar lifetime cannabis use, with no significant differences (6790 and 5160 lifetime spliffs, respectively). It is therefore unlikely that lifetime cannabis used mediated the performance deficits shown by early onset cannabis users. Becker et al (2010) found a similar pattern of cannabis use, that there were no difference in lifetime use between their early and late onset groups, however they did discover that the EoC group used

cannabis more frequently (uses per month) and therefore used this as a covariate. The results remained unchanged after this analysis. With this combination of methods used over five studies, it seems unlikely that the age of onset effects discovered were due to lifetime cannabis use. Gruber et al (2011) also found that cannabis frequency (smokes/week) and magnitude (grams/week) was also related to poorer performance on several tasks however after controlling for these two variables in the main analysis there was still an age of onset effect. When combined with other studies showing a similar effect (Pope & Yurgelun-Todd, 1996; Bolla et al., 2002), this suggests that several cannabis use variables (e.g. age of onset; frequency of use) have contributory, adverse effects on cognitive performance.

3.1.2. Confounding Variables

Cannabis is typically smoked with a tobacco product to increase the ease at which it can burn. A recent study surveying drug users found that 94.6% of people who have smoked cannabis, always or occasionally smoke it with tobacco (See Chapter Five). Despite this, only one known study has accounted for tobacco use by the inclusion of as tobacco using control group (McHale & Hunt, 2008). When considering there is a potential dual-causality with altered cognition being both a product of tobacco use (Rezvani & Levin, 2001; Jacobsen et al., 2005), in addition to being a risk factor for it (Dinn, Aycicegi & Harris, 2004; Perry & Carrol, 2008), it becomes even more important to account for the effects of tobacco use when studying the cognitive alterations associated with chronic cannabis use. While tobacco is rarely considered as a confounding variable, alcohol and other drug abuse are frequently incorporated into exclusion criteria while weekly alcohol use is often statistically controlled (e.g. Pope et al., 2001; Solowij et al., 2002; Gruber et al., 2011). This is necessary as alcohol and drug use have also been associated with impaired cognition during acute intoxication, hangover symptoms and in terms of the residual effects of the respective drugs (Morgan & Curran, 2006; Stephens et al., 2008; Verdejo-Garcia et al., 2007).

In addition to the effects of tobacco, estimated IQ scores have shown moderate correlations with tests of executive function (Ardila, Pineda & Rosselli, 2000). It is necessary to examine any possible group differences in intelligence to ensure that if any deficits in executive function are found, they are not a product of lower intelligence. Furthermore, certain mental health problems have a high prevalence rate among

cannabis users (Patton et al., 2002) and such conditions, e.g. anxiety and depression, can impact on executive functioning (Eysenck, Santos, Derakshan & Calvo, 2007; McDermott & Ebmeier, 2009). Based on the previous use of exclusion criteria and statistical covariates from previous cannabis-cognition research, in addition to further empirical data on diminished executive function, this study utilises a broad range of measures to account for confounding variables.

The present study aims to follow on from previous research examining executive function abilities in cannabis users when compared to a tobacco using group and a non-smoking control group. This study will include: 1) measures which have been used before in the literature which have detected deficits in order to replicate findings; 2) updated and improved measures of older tasks to replicate previous findings with better tools; and 3) several measures which have not been tested on a cannabis sample in order to add to the literature by exploring new areas of cognition in long term cannabis users. This battery of tasks will test previous findings, provide more rigorous and sensitive testing procedures and allow the discovery of new and up-to-date information on chronic cannabis use across a broad range of executive function components and modalities. The inclusion of a tobacco group will test whether previously detected cognitive deficits associated with cannabis use will be found when compared to tobacco users. It is predicted that the cannabis users will show impairments on each of the tasks when compared to controls and tobacco smokers.

3.1.3. Summary

The present study aimed to extend previous age of onset research, examining whether EoC use leads to worse executive functioning than LoC users, controls and tobacco users. It was also predicted that LoC users will present with deficits relative to the controls and tobacco users, albeit less than the EoC group. In a manner similar to Gruber et al (2011) and Fontes et al (2011a; 2011b), the cannabis users were first analysed as a whole group and then as separate EoC and LoC groups. The present study assessed decision making, non-verbal fluency, verbal set switching, motor coordination and visual processing speed, all areas previously unexplored with regards to the age of onset hypothesis. In addition to these domains, visual scanning, non-verbal set switching, verbal fluency and motor speed were assessed similar to previous age onset research (Ehrenreich et al., 1999; Pope et al., 2003; Fontes et al., 2011; Gruber et al.,

2011) in an attempt to replicate previous findings with a more robust measure (the D-KEFS; Delis et al., 2001).

3.2. Method

3.2.1. Participants

The cannabis users in the current study were non-treatment seeking recreational users recruited primarily from the student population. Participants were contacted during undergraduate seminars, through student accommodation, and using the 'snowball' technique. Following completion of the CannaForm participants were excluded from the experiment if they met any of the following criteria: serious head injuries, any neurological conditions, any learning, developmental or genetic disorders, English not being their first language, other drug use (>15 lifetime uses), excessive alcohol use (>37 units/week) and recent drug (past week) and alcohol use (more than 7.2 [males] or 4.9 [females] units in past 24 hours; See Section 2.3.2). From the original sample of 378 participants who completed the CannaForm, and after inclusion criteria inspections and subsequent participant contact, a total of 84 individuals participated in the study. Participants were firstly assigned to one of three separate groups: a non-smoking control group (n=27), a tobacco smoking control group (n=25), and a cannabis using group (n=32). The criterion for entry into the cannabis and tobacco groups was a history of regular use of the respective drug. Regular use was determined by >1 uses per month, for a period of no less than 6 months or total lifetime use exceeding 50 uses. See Table 3.2 for further demographic information and Table 3.4 for further drug use information.

For the secondary analysis, the cannabis group was divided into early onset cannabis users (EoC; age of onset $\leq$ 15 years; n=16), late onset cannabis users (LoC; age of onset $\geq$16 years; n=16). See Table 3.3 for further demographic information and Table 3.5 for further drug use information.

3.2.2. Ethical Considerations

In order to protect the anonymity of the participants a careful procedure was enacted. The first two pages of the CannaForm contained an information sheet and a consent form (see Appendix A.3.1). The information sheet stated that there were two primary data collection phases; the completion of the CannaForm and the administration of a

battery of neuropsychological tasks. A detailed account of the purpose and nature of these two phases, along with the participant's rights were explained in information sheet. The consent form provided the opportunity to state if the participant would like to take part in the CannaForm phase or both of the phases.

Once the participants had completed the CannaForm the responses were examined to determine whether a) they elected to take part in phase two and b) they met the criteria to take part in phase two. If both of these conditions were met then the contact details were recorded in a separate document which indicated they were suitable for phase two. Irrespective of whether these conditions were met or not, the consent form was separated from the CannaForm resulting in an anonymous questionnaire identifiable only by a unique code which the participant created.

Participants who were suitable for the cognitive testing phase were contacted via the means they provided and a testing date was arranged. Upon arrival the participant was asked to reproduce their unique code so that all cognitive tasks would be labelled with the code which was reported on their completed CannaForm. At the end of the cognitive testing the participant was asked to provide a hair sample. The reason for this procedure and the consent for providing a sample were contained within the information sheet and consent form, however this information was given to the participant again and they were given the option to opt out.

Upon completion of both of the CannaForm phase and the cognitive testing phase, the participant was provided with a debrief sheet. This was to inform the participant of the nature of the study, their rights and the contact information of the experimenter.

3.2.3. Drug Use

The drug use data for the cannabis use analysis can be seen in Table 3.4 and the drug use data for the age of onset of cannabis use analysis can be found in Table 3.5. For further information on how these values were estimated see Appendix A.2.1.5.

In addition to the self-reported questionnaire responses on drug use approximately 50-100mg of hair taken from the scalp but not containing the hair root was cut and collected by the experimenter. Due to a prolonged endeavour to create a sensitive and accurate method for detecting cannabinoids and other drug derivatives in the hair

samples using Matrix-Assisted Laser Desorption/Ionisation (MALDI), the method is not finalised at time of writing. Despite not being able to validate the self-report data using the hair samples, Gruber et al (2011) report that the act of collecting urine samples and informing participants that they were to be tested for drug use improved the honesty of drug use reports. The current study used a similar method with the hair samples and in support of this claim one participant requested to change their drug use information after learning the purpose of collecting the hair sample.

3.2.4. Neuropsychological measures

A battery of neuropsychological tasks was used to measure a comprehensive range of cognitive functions. Task order was counterbalanced and testing lasted approximately two hours for each participant.

Table 3.1.

Table of the neuropsychological tests used and the cognitive processes they measure.

Neuropsychological Task	Outcome Measures	Primary cognitive processes measured
D-KEFS - TMT	Visual Scanning	Visual scanning, visual attention
	Number Sequencing	Numerical sequencing, motor speed
	Letter Sequencing	Alphabetical sequencing, motor speed
	Set switching	Set switching, motor speed, visual scanning
	Switching contrast	Set switching
	Errors	Set switching, maintaining the set
D-KEFS - VFT	Letter Fluency	Initiation, inhibition, strategy formation, working memory
	Category Fluency	Initiation, inhibition, strategy formation, working memory
	Category switching	Set switching, inhibition, strategy formation, working memory
	Switching contrast	Set switching
	% of set loss errors	Verbal learning problems
	% of repetition errors	Perseveration, working memory
D-KEFS - DFT	Design fluency	Non-verbal creativity, initiation, strategy formation
	Design switching	Non-verbal creativity, initiation, strategy formation, set switching
	Switching Contrast	Set switching
	Set Loss Errors	Working memory, set switching
	Repetition Errors	Perseveration, working memory
IGT	% of advantageous decks	Decision making
SST	Scaled Score	Visual processing speed
	Errors	Visual processing
Grooved Pegboard	Place task	Motor programming, motor speed, visuo-motor coordination
	Remove task	Motor speed
	Place/remove contrast	Motor programming, visuo-motor coordination

Note. D-KEFS = Delis Kaplan Executive Function System; TMT = Trail Making Test; VFT = Verbal Fluency Test; DFT = Design Fluency Test; IGT = Iowa Gambling Task; SST = Symbol Search Task.

3.2.5. Questionnaires and Physiological Measures

The CannaForm was used to screen any unsuitable participants and allocated suitable participants into the appropriate group. Two standardised mental health/emotional questionnaires were also included in the present study: the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) and the Clark-Beck Obsessive-Compulsive Inventory (CBOCI; Clark & Beck, 2002). During the Iowa Gambling Task an Affectiva Q™ Sensor (Poh, Swenson & Picard, 2010) was attached to the non-dominant wrist of the participant to record anticipatory skin conductance responses (SCRs). As the company which produced the hardware and the software for the Q™ Sensor discontinued the product during data collection the analysis the SCR data could not be completed.

3.2.6. Design

The present study employed a quasi-experimental approach, with the participant's smoking habits determining which condition they were allocated to. The first independent variable was cannabis use, with three levels including: cannabis users, tobacco smokers and a non-smoking control group. The dependant variables were the 28 cognitive task outcome measures. To ensure the groups were matched for IQ, clinical and demographic variables, the CannaForm was administered alongside the HADS, the CBOCI, and the WASI.

The second independent variable was the age of onset of cannabis use, with four levels including: EoC users, LoC users, tobacco users, and a non-smoking control group. The dependant variables were unchanged from the first stage.

3.2.7. Procedure

Participants were recruited primarily on University campuses, student accommodations and using the snowball technique. Each individual received the CannaForm which was either administered by the experimenter or self-completed. The questionnaire was then checked to determine if the participant met the inclusion criteria.

Once participants had been accepted and allocated into a group they were either tested immediately or subsequently contacted to arrange a time for testing. Immediate or delayed testing was solely dependent on participant availability. The testing session

lasted approximately two hours per individual and the order of the tasks was randomised. In addition to demographic data, further information was collected including the temperature of the room and the dominant hand (right, left or ambidextrous) of the participant. For physiological recordings the Q-sensor was placed on the non-dominant wrist of the participant and activated before the IGT was administered. The participant wore the Q-sensor for approximately five minutes before the IGT was initiated to allow the device to acclimatise to the individual and for a baseline measure to be taken.

At the end of the experiment the participant was asked to provide a hair sample of approximately 50mg, this was collected using scissors and cut as near to the scalp as possible, without removing the root of the hair. The participant was then debriefed.

3.2.8. Statistical Analysis

3.2.8.1. ANOVA and Kruskal-Wallis

The main analysis process consisted of six steps. The assumptions tested for the ANOVA included the presence of outliers, normality and homogeneity of variance. 1) Univariate outliers were checked by converting raw scores to *z*-scores and observing whether any cases were ±3 *z*-scores from the group mean (e.g. Whelan, 2008). In order to keep the data which were considered outliers the Winsorising method was used by converting all outliers to the nearest non-outlier score (Field, 2013). 2) Razali and Wah (2011) recommend that the most effective way to assess normality is through a combination of graphical inspection, formal tests and observation of skewness/kurtosis statistics and these three methods are hereinafter referred to as the normality protocol. This normality protocol was implemented in the current study with the chosen graphical method being histograms, the chosen formal test being Shapiro-Wilk's due to its suitability for group sizes between three and 50 (Shapiro & Wilk, 1965). Finally, skewness and kurtosis statistics were inspected based on Leech, Barrett and Morgan's (2005) guidelines, any value ±1 or greater was considered non-normal. This process was only aimed to rule out severely non-normal distributions as ANOVAs have been found to be robust to non-normal distributions (Schmider, Ziegler, Danay, Beyer & Bühner, 2010). Meyers, Gamst and Guerino (2009) set out guidelines to deal with severe non-normal distributions which involved five different transformation methods. Each of

these methods was applied to each non-normal distribution to determine if normal distributions could be achieved. These methods were the square root of X ($\sqrt{x}$), base 10 logarithm of X ($log10(x)$), inverse of X (x^{-1}), square of X (x^2) and cube of X (x^3). Following successful attempts to transform the non-normal distributions, ANOVAs were run on the data and following the unsuccessful attempts, a Kruskal-Wallis test was used in place of the ANOVA. For these Kruskal-Wallis tests the original data was used instead of the Winsorised data. 3) For the remaining variables which were to be analysed using the ANOVA method homogeneity of variance was tested. The standard Levene's test is overly sensitive to slight variations in variances (Howell, 2011) and thus any dependent variable which yielded a significant (α = .01; Meyers et al., 2012) effect from a Levene's test or Brown-Forsythe test (Brown & Forsythe, 1974) was subject to further examination of standard deviations and variances. If standard deviations between groups differed by a magnitude of four or variances differed by a magnitude of 10 then these were considered heterogeneous variances (Tabachnick & Fidell, 2010). Any dependent variable which violated the assumption of homogeneity of variance was assigned to the Kruskal-Wallis method. 4) The ANOVA and Kruskal-Wallis tests were then run. 5) Tukey's HSD (for approximately equal sample sizes) and Hochberg's GT2 (for uneven sample sizes) were run to follow up any significant ANOVA test 6) Bonferroni corrected Dunn's tests were run to follow up any significant Kruskal-Wallis test.

In post hoc situations where prior research informed the directional hypothesis then one-tailed hypotheses tests were conducted, however in situations were no such directional hypothesis was made then two-tailed hypothesis were used. Each post hoc test is labelled appropriately. When one-tailed tests were used the *p*-value was adjusted by dividing the value by two.

3.2.8.2. Categorical analyses

For categorical data 2x3 chi square tests were run. This analysis process consisted of three steps. 1) Contingency tables were examined to test the expected frequencies assumption. If any expected counts were 0, 1, or more than 20% were greater than 5 then this assumption was violated. 2) If the assumption was violated the Fisher's exact test was used which accounts for this violation (Field, 2013). If the assumption was not

violated then the likelihood ratio was chosen over the Pearson chi-square test as it is more suitable for small sample sizes, such as the sample in the current study.

3.2.8.3. ANCOVA

In order to control for the effects of salient covariates an ANCOVA method was implemented which consisted of five steps. 1) Any potential analysis using the ANCOVA method must meet the assumptions necessary for an ANOVA and therefore any previous transformations applied to dependent variables were maintained for the ANCOVA. Furthermore, analyses which were assigned to the Kruskal-Wallis method were unsuitable for ANCOVA. 2) Independence of the treatment and covariate effect was tested. This assumption states that the potential covariate must be un-related to the independent variable in the analysis. If this is not the case then including a covariate will lose some of the variance associated with the grouping variable and thus lead to an underpowered analysis and misleading results (Owen & Froman, 1998; Field, 2013). 3) Associations between the covariate and the dependent variable need to be present in order for ANCOVA to be justified (Dancey & Reidy, 2011). Furthermore, this association needs to be large enough to account for the reduction in power associated with running an ANCOVA (Owen & Froman, 1998). Pearson's (for parametric data) and Spearman's (for non-parametric data) correlations were run to test this assumption. Any significant association ($\alpha = .05$) was considered as a covariate. 4) The next assumption is linearity of regression which assumes that the covariate is linearly associated with the dependent variable (Meyers et al., 2012). Visual inspections of scatter graphs checked this assumption. The transformation protocol (see Section 3.2.8.1.) was applied following the violations of this assumption and scatter graphs were re-examined to check if the violation had been corrected. 5) The final assumption is homogeneity of regression (Meyers et al., 2012) which assumes that different levels of the independent variable will have similar regression slopes with the dependent variable. This was tested by observing the independent variable X covariate interaction effect in the ANCOVA output (Meyers et al., 2012).

Table 3.2.

Between subject effects and descriptive statistics for the three-group demographic data.

Demographic Variable	**Control** ***n*=27**	**Tobacco users** ***n*=25**	**Cannabis users** ***n*=32**	***p*-value**
Sex $^{\chi^2}$	7m	7m	16m	.114
Age ^{KW}	18.00 (1.00) [18-26]	19.00 (2.00) [18-24]	19.50 (3.00) [18-31]	**.032**
Nationality $^{\chi^2}$	26 BR; 1 JA	24 BR; 1 AB	31BR; 1 SW	.559
First Language	27 ENG	25 ENG	32 ENG	-
Handedness $^{\chi^2}$	25 R; 2 L	23 R; 2 L	29 R; 3 L	1.00
Years of education ^{KW}	14.00 (1.00) [13-21]	14.00 (1.00) [11-16]	14.50 (2.00) [11-19]	.307
Educ. Achievement (GCSE a-c) ^{AN}	10.41 ± 1.42 [8-13]	9.68 ± 2.50 [4-13]	9.13 ± 2.22 [2-13]	.087

Note. *n*= number of participants; m= male; BR= British; JA=Jamaican; AB= African/British; SW= Swedish; ENG= English; R= right handed; L= left handed; GCSE a-c= general certificate of secondary education grades a-c. χ^2 = chi-square; KW= Kruskal-Wallis; AN= ANOVA. For continuous data the descriptive statistics are presented as mean ± standard deviation [range] when parametric, and median (interquartile range) [range] when non-parametric.

3.3. Results

3.3.1. Demographic Data

Data from the CannaForm pertaining to demographic characteristics were collected and analysed to determine whether relevant factors differed between the three groups.

There were three variables which could be analysed through the ANOVA method and therefore assumptions were tested. These three variables were checked for outliers and one case was at ±3 z-scores from the group mean which was subsequently Winsorised. The normality protocol of assessing histograms, the Shapiro-Wilk's test, skewness statistics and kurtosis statistics suggested that there were deviations from normality for the educational achievement variable. The six transformation methods described in section 3.2.8 were implemented and the normality protocol suggested that the square method was the most effective for the educational achievement variable. The age and years of education variables for both analyses proved to be non-normal and the transformation protocol followed by a repeated normality protocol suggested that the distribution could not be corrected. Therefore years of education and age were analysed using the Kruskal-Wallis method.

3.3.1.1. Cannabis Use Analyses

A one-way ANOVA was run to test whether the groups (Controls vs. Tobacco users vs. Cannabis users) were matched for educational achievement (see Table 3.2). There was no main effect between groups for the educational achievement variable [$F_{(2,80)}$=2.51, p=.087, partial η^2=.059].

Two Kruskal-Wallis tests were run to test whether the groups (Controls vs. Tobacco users vs. Cannabis users) were matched for two demographic variables. There was no main effect between groups for the years of education variable [$\chi^2_{(2)}$=2.36, p=.307] however there was a significant main effect of age [$\chi^2_{(2)}$=6.91, p=.032]. Follow-up Dunn's tests were run on the age variable. This showed that the cannabis group were significantly older than the controls [$t_{(57)}$=15.97, p=.026, 2-tailed] while there was no difference between the cannabis users and tobacco users [$t_{(55)}$=7.85, p=.618, 2-tailed] and no difference between the controls and tobacco users [$t_{(50)}$=8.12, p=.625, 2-tailed].

In order to analyse the categorical data three separate 2x3 chi-square tests were run to test the hypothesis that sex, nationality, and handedness were matched across groups (controls vs. tobacco users vs. cannabis users). Two of the variables, nationality and handedness, violated the assumption of expected frequencies and thus were analysed using Fisher's exact test. Sex did not violate this assumption and therefore was analysed with the Likelihood ratio method. There was no significant main effect of cannabis use on sex [$\chi^2_{(2)}$=4.58 p=.114 (likelihood ratio)], nationality [χ^2=5.53, p=.559 (Fisher's)], or handedness [χ^2=0.24, p=1.00 (Fisher's)].

3.3.1.2. Age of Onset Analyses

A one-way ANOVA was run to test whether the groups (Controls vs. Tobacco users vs. EoC vs. LoC) were matched for educational achievement (see Table 3.3). There was no main effect between groups on for the educational achievement variable [$F_{(3,79)}$=1.84, p=.147, partial η^2=.065].

Two Kruskal-Wallis tests were run to test whether the groups (Controls vs. Tobacco users vs. EoC vs. LoC) were matched for two demographic variables. There was no main effect between groups for the years of education variable [$\chi^2_{(3)}$=2.63, p=.452] or the age variable [$\chi^2_{(3)}$=7.02, p=.071].

In order to analyse the categorical data three separate 2x4 chi-square tests were run to test if sex, nationality and handedness were matched across the groups (controls vs. tobacco users vs. EoC users vs. LoC users). Two of the variables, nationality and handedness, violated the assumption of expected frequencies and thus were analysed using Fisher's exact test. Sex did not violate this assumption and therefore was analysed with the Likelihood ratio method. There was no significant main effect of cannabis use on sex [$\chi^2_{(3)}$=5.08, p=.166 (likelihood ratio)], nationality [χ^2=8.50, p=.650 (Fisher's exact test)],or handedness [χ^2=0.79, p=.905 (Fisher's exact test)].

Table 3.3.

Between subject effects and descriptive statistics for the four-group demographic data.

Demographic Variable	**Control** ***n*=27**	**Tobacco users** ***n*=25**	**EoC (≤15 years)** ***n*=16**	**LoC (≥16 years)** ***n*=16**	***p*-value**
Sex $^{\chi^2}$	7m	7m	7m	9m	.166
Age ^{KW}	18.00 (1.00) [18-26]	19.00 (2.00) [18-24]	19.00 (2.00) [18-25]	20.00 (3.75) [18-31]	.071
Nationality $^{\chi^2}$	26 BR; 1 JA	24 BR; 1 AB	16 BR	15 BR; 1 SW	.650
First Language	27 ENG	25 ENG	16 ENG	16 ENG	-
Handedness $^{\chi^2}$	25 R; 2 L	23 R; 2 L	15 R; 1 L	14 R; 2 L	.905
Years of education ^{KW}	14.00 (1.00) [13-21]	14.00 (1.00) [11-16]	14.50 (1.80) [12-19]	14.50 (3.80) [11-19]	.452
Educ. Attainment (GCSE a-c) ^{s}	10.41 ± 1.42 [8-13]	9.68 ± 2.50 [4-13]	9.25 ± 2.60 [2-13]	9.00 ± 1.81 [5-11]	.147

Note. See Table 3.2 for notes.

Table 3.4.

Between subject effects and descriptive statistics for the three-group drug use data.

Drug Use Variable	Control *n*=27		Tobacco users *n*=25		Cannabis users *n*=32		*p*-value
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	
Alcohol Units (p/w)[r]	12.60 ± 9.60	[0.00-36.90]	17.97 ± 9.94c	[5.00-45.90]	17.76 ± 10.10[a]	[6.00-46.80]	**.036**
Tobacco (LT)[kw]	0.00 (0.00)[ac]	[0-26]	3,650.00 (5,213.50)[c]	[208-27,365]	883.00 (7,300.00)[a]	[0-43,800]	**<.001**
Cannabis (LT) [kw]	0.00 (0.00)[ac]	[0-5]	0.50 (4.75)	[0-24]	940.80 (1434.00)[ab]	[48-5,820]	**<.001**
Cannabis (YoU) [kw]	0.00 (0.00)[a]	[0-1]	0.00 (1.00)	[0-3]	4.00 (3.00)[ab]	[1-8]	**<.001**
Cannabis (AoO)[r]	-	-	16.15 ± 1.52	[13-19]	15.47 ± 1.74	[12-21]	.395
Cannabis (Intox)	-	-	5.29 ± 2.81	[2-10]	6.22 ± 2.14	[1-10]	.567
Amphetamines (LT) [kw]	0.00 (0.00)	[0]	0.00 (0.00)	[0-1]	0.00 (0.00)	[0-8]	.051
Cocaine (LT) [kw]	0.00 (0.00)[a]	[0]	0.00 (0.00)	[0-2]	0.00 (0.00)[a]	[0-6]	**.025**
Mushrooms (LT) [kw]	0.00 (0.00)[a]	[0]	0.00 (0.00)[c]	[0]	0.00 (0.00)[ab]	[0-30]	**.034**
Ecstasy (LT) [kw]	0.00 (0.00)[a]	[0]	0.00 (0.00)[c]	[0-4]	0.00 (1.00)[ab]	[0-5]	**.002**
Other Drug Use* (LT) [kw]	0.00 (0.00)[a]	[0]	0.00 (0.00)[c]	[0-4]	0.50 (4.00)[ab]	[0-30]	**<.001**

Note. p/w= per week; LT= lifetime use; AoO= age of onset; YoU=Years of Use; Intox=desired level of intoxication reached on a scale from 0 (sober) to 10 (wasted). Significant omnibus effects (p<.05) are noted in bold. [a] [b] & [c] indicate significant (*p*<.05) one-tailed differences between the groups. Lifetime cannabis was not compared between groups as it violated the assumption of equality of variances. Omnibus tests were analysed using an ANOVA unless labelled with [kw] which indicates a Kruskal-Wallis test. For the non-parametric data the median (interquartile range) are presented instead of the mean ± standard deviation. [r] indicates a root transformation preceding an ANOVA however untransformed descriptive statistics are presented. * other drug use indicates all recreational drug use excluding cannabis, tobacco and alcohol.

3.3.2. Drug Use Data

When a testing date and time was arranged the participants were asked to abstain from alcohol use and cannabis use for twenty-four hours and other recreational drug use for one week prior to the testing time. All participants reported their last alcohol and drug use which showed drug use within the accepted timeframe for all participants. The aim was to recruit participants with less than 15 uses of cannabis use for the control and tobacco users however and although this was met for the controls, five participants from the tobacco group violated this criterion [range=0-24 spliffs; $\bar{x}$=3.42; *SD*=5.63]. It was aimed to have less than 15 users of tobacco for controls, this criterion was violated for one participant [range=0-26 cigarettes; $\bar{x}$=1.11; *SD*=4.99]. It was also aimed to have less than 15 episodes of other drug use (total episodes of drug use; not including cannabis, alcohol or tobacco) across all three groups. This criterion was met for the control group and the tobacco group however was violated for three of the participants from the cannabis group (see Table 3.3). As these violations were only small, these participants were kept in the study.

The normality protocol of assessing histograms, the Shapiro-Wilk's test, skewness statistics and kurtosis statistics suggested that there were deviations from normality for the all of the drug use variables seen in Table 3.3, with the exception of the desired cannabis intoxication level. The five transformation methods described in section 3.2.8 were implemented on the non-normally distributed variables and a repeated normality protocol suggested that the root method was the most effective for weekly alcohol use and age of onset of cannabis use. The remaining variables could not be transformed therefore these variables were to be analysed using the Kruskal-Wallis test.

3.3.2.1. Cannabis use analyses

Three one-way ANOVAs were run to test if the groups (Controls vs. Tobacco users vs. Cannabis users) were matched for weekly alcohol use, the age of onset of cannabis use and the desired intoxication level when using cannabis (see Table 3.4). There was a significant main effect between groups for the weekly alcohol use variable [$F_{(2,74)}$=3.49, p=.036, partial η^2=.086]. In contrast, there were no significant main effects between groups for the age of onset of cannabis use [$F_{(2,45)}$=0.95, p=.395, partial η^2=.040] or the desired level of intoxication during cannabis use [$F_{(2,37)}$=0.58, p=.567, partial η^2=.031].

Seven Kruskal-Wallis tests were run to test if the groups (Controls vs. Tobacco users vs. Cannabis users) were matched on seven drug use variables (see Table 3.3). There was no main effect between groups for the number of amphetamine uses [$\chi^2_{(2)}$=5.97, p=.051, η^2=.072] however there was a significant main effect of lifetime cannabis use [$\chi^2_{(2)}$=65.19, p<.001, η^2=.804], length of cannabis use in years [$\chi^2_{(2)}$=59.22, p<.001, η^2=.790], lifetime tobacco use [$\chi^2_{(2)}$=41.62, p<.001, η^2=.501], lifetime ecstasy use [$\chi^2_{(2)}$=12.70, p=.002, η^2=.153], lifetime cocaine use [$\chi^2_{(2)}$=7.37, p=.025, η^2=.089], lifetime magic mushroom use [$\chi^2_{(2)}$=6.74, p=.034, η^2=.081] and lifetime other drug use [$\chi^2_{(2)}$=19.63, p<.001, η^2=.237].

3.3.2.1.1. Controls vs tobacco users (Hochberg's GT2 and Dunn's test)

The post hoc tests suggested that tobacco users consumed significantly more alcohol per week than controls [$t_{(50)}$=2.33, p=.033, d=0.81, 1-Tailed GT2] and significantly more tobacco than controls [$t_{(50)}$=40.61, p<.001, r=0.86, 1-Tailed Dunn's].

In contrast, there were no differences between controls and tobacco users in lifetime cannabis use [$t_{(50)}$=10.63, p=.145, r=0.23, 1-Tailed Dunn's], years of cannabis use [$t_{(50)}$=9.44, p=.197, r=0.21, 1-Tailed Dunn's], lifetime ecstasy use [$t_{(50)}$=5.06, p=.374, r=0.16, 1-Tailed Dunn's], lifetime cocaine use [$t_{(50)}$=1.74, p=.500, r=0.07, 1-Tailed Dunn's], lifetime mushroom use [$t_{(50)}$=0.00, p=.500, r=0.00, 1-Tailed Dunn's] and lifetime total drug use [$t_{(50)}$=9.36, p=.190, r=0.25, 1-Tailed Dunn's].

3.3.2.1.2. Controls vs cannabis users (Hochberg's GT2 and Dunn's test)

The post hoc tests suggested that cannabis users consumed significantly more alcohol per week than controls [$t_{(57)}$=2.26, p=.039, d=0.60, 1-Tailed GT2], significantly more tobacco than controls [$t_{(57)}$=29.52, p<.001, r=0.62, 1-Tailed Dunn's], significantly more cannabis than controls [$t_{(57)}$=46.00, p<.001, r=1.00, 1-Tailed Dunn's], significantly longer use of cannabis than controls [$t_{(57)}$=40.89, p<.001, r=0.95, 1-Tailed Dunn's], significantly more ecstasy than controls [$t_{(57)}$=14.42, p<.001, r=0.45, 1-Tailed Dunn's], significantly more cocaine than controls [$t_{(57)}$=7.83, p=.016, r=0.33, 1-Tailed Dunn's], significantly more magic mushrooms than controls [$t_{(57)}$=5.25, p=.039, r=0.29, 1-Tailed Dunn's] and significantly more other drugs than controls [$t_{(57)}$=21.56, p<.001, r=0.57, 1-Tailed Dunn's].

It is necessary to clarify at this point that the statistically significant differences between controls and cannabis users for ecstasy, cocaine, magic mushrooms and other drug use does not represent a substantively significant difference (see Table 3.4). However, the difference between these two groups weekly alcohol use, lifetime tobacco use, lifetime cannabis use and duration of cannabis use does represent a substantively significant difference.

3.3.2.1.3. Tobacco Users vs Cannabis Users (Hochberg's GT2 and Dunn's test)

The post hoc tests suggested than cannabis users have consumed significantly more cannabis than tobacco users [$t_{(55)}$=35.38, p<.001, r=0.76, 1-Tailed Dunn's], significantly longer use of cannabis than tobacco users [$t_{(55)}$=31.45, p<.001, r=0.70, 1-Tailed Dunn's], significantly more ecstasy than tobacco users [$t_{(55)}$=9.36, p=.040, r=0.29, 1-Tailed Dunn's], significantly more magic mushrooms than tobacco users [$t_{(55)}$=5.25, p=.044, r=0.29, 1-Tailed Dunn's] and significantly more other drugs than tobacco users [$t_{(55)}$=12.20, p=.022, r=0.34, 1-Tailed Dunn's]. It is necessary to clarify at this point that the statistically significant differences between tobacco users and cannabis users for ecstasy, magic mushrooms and other drug use does not represent a substantively significant difference (see Table 3.3). However, the difference between these two groups in lifetime cannabis use and duration of cannabis use does represent a substantively significant difference.

There were no significant differences between cannabis users and tobacco users for units of alcohol consumed per week [$t_{(55)}$=0.16, p=.500, d=0.07, 1-Tailed GT2], lifetime tobacco use [$t_{(55)}$=11.09, p=.120, r=0.24, 1-Tailed Dunn's], and cocaine use [$t_{(55)}$=6.09, p=.077, r=0.27, 1-Tailed Dunn's].

3.3.2.2. Age of onset analyses

Three one-way ANOVAs were run to test whether the groups (Controls vs. Tobacco users vs. EoC vs. LoC) were matched for estimates of drug use as measured by weekly alcohol use, the age of onset of cannabis use and the desired intoxication level when using cannabis (see Table 3.2). There was a significant main effect between groups for the age of onset of cannabis use [$F_{(3,44)}$=11.68, p<.001, partial η^2=.443]. In contrast, there were no significant main effects discovered between groups for the weekly alcohol use variable [$F_{(3,73)}$=2.43, p=.072, partial η^2=.091] or the desired level of intoxication

during cannabis use [$F_{(3,36)}$=0.54, p=.657, partial η^2=.043]. Only significant omnibus tests are followed up with post hoc tests. Controls were not included in the follow up analysis for age of onset as only three participants reported an age of onset of cannabis.

Seven Kruskal-Wallis tests were run to test whether the groups (Controls vs. Tobacco users vs. EoC vs. LoC) were matched for estimates of drug use as measured by seven variables (see Table 3.5). There was a significant main effect between groups for the all tests including lifetime tobacco use [$\chi^2_{(3)}$=43.65, p<.001, η^2=.526], lifetime cannabis use [$\chi^2_{(3)}$=65.21, p<.001, η^2=.805], years of cannabis use [$\chi^2_{(3)}$=60.58, p<.001, η^2=.808], number of amphetamine uses [$\chi^2_{(3)}$=10.45, p=.015, η^2=.126], lifetime cocaine use [$\chi^2_{(3)}$=9.17, p=.027, η^2=.110], lifetime magic mushroom use [$\chi^2_{(3)}$=9.53, p=.023, η^2=.115], lifetime ecstasy use [$\chi^2_{(3)}$=12.86, p=.005, η^2=.155] and lifetime other drug use [$\chi^2_{(3)}$=21.77, p<.001, η^2=.262].

3.3.2.2.1. Controls vs EoC users (Hochberg's GT2 and Dunn's test)

The post hoc tests suggested that EoC users consumed significantly more tobacco than controls [$t_{(42)}$=35.49, p<.001, r=0.72, 1-Tailed Dunn's], significantly more cannabis than controls [$t_{(42)}$=45.40, p<.001, r=0.94, 1-Tailed Dunn's], significantly longer use of cannabis than controls [$t_{(42)}$=45.39, p<.001, r=0.84, 1-Tailed Dunn's], significantly more amphetamine use than controls [$t_{(42)}$=10.69, p=.006, r=0.47, 1-Tailed Dunn's], significantly more cocaine than controls [$t_{(42)}$=10.59, p=.012, r=0.44, 1-Tailed Dunn's], significantly more mushroom use than controls [$t_{(42)}$=7.91, p=.016, r=0.42, 1-Tailed Dunn's], significantly more ecstasy use than controls [$t_{(42)}$=13.28, p=.024, r=0.41, 1-Tailed Dunn's], and significantly more other drug use than controls [$t_{(42)}$=25.41, p<.001, r=0.66, 1-Tailed Dunn's].

It is necessary to clarify at this point that the statistically significant differences between controls and EoC users for amphetamines, ecstasy, cocaine, magic mushrooms and other drug use does not represent a substantively significant difference (see Table 3.5). However, the difference between these two groups for lifetime tobacco use, lifetime cannabis use and duration of cannabis use does represent a substantively significant difference.

3.3.2.2.2. Controls vs LoC users (Hochberg's GT2 and Dunn's test)

The post hoc tests suggested that LoC users consumed significantly more tobacco than controls [$t_{(42)}$=23.55, p=.005, r=0.48, 1-Tailed Dunn's], significantly more cannabis than controls [$t_{(42)}$=46.56, p<.001, r=0.99, 1-Tailed Dunn's], significantly longer use of cannabis than controls [$t_{(42)}$=36.66, p<.001, r=0.84, 1-Tailed Dunn's], significantly more ecstasy use than controls [$t_{(42)}$=15.56, p=.006, r=0.48, 1-Tailed Dunn's], and significantly more other drug use than controls [$t_{(42)}$=17.44, p=.009, r=0.45, 1-Tailed Dunn's].

In contrast, there were no differences between LoC users and controls for amphetamine use [$t_{(42)}$=2.53, p=.500, r=0.11, 1-Tailed Dunn's], cocaine use [$t_{(42)}$=5.06, p=.500, r=0.21, 1-Tailed Dunn's], or mushroom use [$t_{(42)}$=2.59, p=.500, r=0.14, 1-Tailed Dunn's].

It is necessary to clarify at this point that the statistically significant differences between controls and LoC users for ecstasy and other drug use does not represent a substantively significant difference (see Table 3.5). However, the difference between these two groups lifetime tobacco use, lifetime cannabis use, and duration of cannabis use does represent a substantively significant difference.

3.3.2.2.3. Tobacco users vs EoC users (Hochberg's GT2 and Dunn's test)

The post hoc tests suggested than EoC users has a significantly higher lifetime cannabis use than tobacco users [$t_{(40)}$=34.78, p<.001, r=0.72, 1-Tailed Dunn's], significantly longer use of cannabis than tobacco users [$t_{(40)}$=35.96, p<.001, r=0.79, 1-Tailed Dunn's], started using cannabis significantly earlier than tobacco users [$t_{(28)}$=4.18, p<.001, d=1.45, 1-Tailed Hochberg's], had significantly more amphetamine use than tobacco users [$t_{(40)}$=9.07, p=.028, r=0.41, 1-Tailed Dunn's], had significantly more magic mushroom use [$t_{(40)}$=7.91, p=.018, r=0.43, 1-Tailed Dunn's], and significantly more other drug use than tobacco users [$t_{(40)}$=17.55, p=.010, r=0.46, 1-Tailed Dunn's].

There were no significant differences between EoC users and tobacco users for lifetime tobacco use [$t_{(40)}$=5.12, p=.500, r=0.11, 1-Tailed Dunn's], ecstasy use [$t_{(40)}$=8.22, p=.314, r=0.25, 1-Tailed Dunn's], and cocaine use [$t_{(40)}$=8.85, p=.054, r=0.37, 1-Tailed Dunn's].

It is necessary to clarify at this point that the statistically significant differences between tobacco users and EoC users for amphetamines, magic mushrooms and other drug use does not represent a substantively significant difference (see Table 3.5). However, the difference between these two groups in lifetime cannabis use, age of onset of cannabis use and duration of cannabis use does represent a substantively significant difference.

3.3.2.2.4. Tobacco users vs LoC users (Hochberg's GT2 and Dunn's test)

The post hoc tests suggested that LoC users have a significantly higher lifetime cannabis use than tobacco users [$t_{(40)}$=35.94, p<.001, r=0.76, 1-Tailed Dunn's] and significantly longer use of cannabis than tobacco users [$t_{(40)}$=27.23, p<.001, r=0.61, 1-Tailed Dunn's].

There were no significant differences between LoC users and tobacco users for lifetime tobacco use [$t_{(40)}$= 17.06, p=.074, r=0.35, 1-Tailed Dunn's], age of onset of cannabis use [$t_{(28)}$=1.16, p=.812, d=0.38, 1-Tailed Hochberg's], amphetamine use [$t_{(40)}$=0.91, p=.500, r=0.04, 1-Tailed Dunn's], magic mushroom use [$t_{(40)}$=2.59, p=.500, r=0.14, 1-Tailed Dunn's], ecstasy use [$t_{(40)}$=10.50, p=.115, r=0.32, 1-Tailed Dunn's], cocaine use [$t_{(40)}$=3.32, p=.500, r=0.14, 1-Tailed Dunn's], and other drug use [$t_{(40)}$=9.58, p=.320, r=0.25, 1-Tailed Dunn's].

Unlike previous two-group comparisons in this section, both statistically significant results between tobacco users and LoC users do highlight substantively significant differences (see Table 3.5).

3.3.2.2.5. EoC Users vs LoC Users (Tukey's HSD and Dunn's test)

The post hoc tests suggested than EoC users started using cannabis significantly earlier than LoC users [$t_{(31)}$=5.64, p<.001, d=2.10, 1-Tailed Tukey's].

There were no significant differences between LoC users and EoC users for lifetime cannabis use [$t_{(31)}$=1.16, p=.500, r=0.02, 1-Tailed Dunn's], years of cannabis use [$t_{(31)}$=8.73, p=.500, r=0.18, 1-Tailed Dunn's], lifetime tobacco use [$t_{(31)}$=11.94, p=.463, r=0.22, 1-Tailed Dunn's], amphetamine use [$t_{(31)}$=8.16, p=.103, r=0.33, 1-Tailed Dunn's], magic mushroom use [$t_{(31)}$=5.31, p=.285, r=0.26, 1-Tailed Dunn's], ecstasy use [$t_{(31)}$=2.28, p=.500, r=0.06, 1-Tailed Dunn's], cocaine use [$t_{(31)}$=5.53, p=.500, r=0.21, 1-Tailed Dunn's], and other drug use [$t_{(31)}$=7.97, p=.500, r=0.19, 1-Tailed Dunn's].

The only statistically significant result here, in the age of onset of cannabis use, is a substantively significant result.

Table 3.5.

Between subject effects and descriptive statistics for the four-group drug use data.

Drug Use Variable	Control *n*=27		Tobacco users *n*=25		EoC (≤15 years) *n*=16		LoC (≥16 years) *n*=16		*p*-value
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	
Alcohol (p/w)[r]	12.60 ± 9.60	[0.00-36.90]	17.97 ± 9.94	[5.00-45.90]	16.38 ± 9.25	[6.00-34.40]	18.50 ± 10.08	[9.00-46.80]	.072
Tobacco (LT)[kw]	0.00 (0.00)[abc]	[0-26]	3,650.00 (5,213.50)[a]	[208-27,365]	2,860.00 (19,833.00)[b]	[0-43,800]	390.50 (5,018.75)[c]	[0-18,250]	**<.001**
Cannabis (LT) [kw]	0.00 (0.00)[bc]	[0-5]	0.50 (4.75)[de]	[0-24]	940.80 (1,338.0)[bd]	[48-2,556]	1,014.00 (2,181.00)[ce]	[60-5,820]	**<.001**
Cannabis (YoU) [kw]	0.00 (0.00)[bc]	[0-1]	0.00 (1.00)[de]	[0-3]	5.00 (2.00)[bd]	[1-8]	3.00 (2.75)[ce]	[1-6]	**<.001**
Cannabis (AoO)[r]	-	-	16.15 ± 1.52[d]	[13-19]	14.25 ± 1.00[df]	[12-21]	16.69 ± 1.30[f]	[16-21]	**<.001**
Cannabis (Intox)	-	-	5.29 ± 2.81	[2-10]	6.50 ± 1.67	[2-9]	5.94 ± 2.54	[1-10]	.657
Amphetamines (LT) [kw]	0.00 (0.00)[b]	[0]	0.00 (0.00)[d]	[0-1]	0.00 (0.75)[bd]	[0-8]	0.00 (0.00)	[0-1]	**.015**
Cocaine (LT) [kw]	0.00 (0.00)[b]	[0]	0.00 (0.00)	[0-2]	0.00 (0.75)[b]	[0-6]	0.00 (0.00)	[0-1]	**.027**
Mushrooms (LT) [kw]	0.00 (0.00)[b]	[0]	0.00 (0.00)[d]	[0]	0.00 (0.00)[bd]	[0-30]	0.00 (0.00)	[0-1]	**.023**
Ecstasy (LT) [kw]	0.00 (0.00)[bc]	[0]	0.00 (0.00)	[0-4]	0.00 (1.00)[b]	[0-5]	0.00 (1.00)[c]	[0-5]	**.005**
Other Drug Use* (LT) [kw]	0.00 (0.00)[bc]	[0]	0.00 (0.00)[d]	[0-4]	1.00 (7.00)[bd]	[0-30]	0.00 (1.00)[c]	[0-5]	**<.001**

Note. See Table 3.4 for notes.

Table 3.6.

Between subject effects and descriptive statistics for the three-group mental health data.

Mental Health Variable	**Control** ***n*=27**		**Tobacco users** ***n*=25**		**Cannabis users** ***n*=32**		***p*-value**
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
HADS							
Anxiety	6.74 ± 3.18	[5.48-8.00]	7.16 ± 3.91	[5.55-8.77]	7.00 ± 3.69	[5.67-8.33]	.914
Depression[r]	2.15 ± 2.01	[1.35-2.94]	3.56 ± 3.10	[2.28-4.83]	2.97 ± 2.29	[2.14-3.80]	.089
CB-OCi							
Obsessions	7.70 ± 3.94	[6.15-9.26]	9.24 ± 4.83	[7.25-11.23]	8.28 ± 3.88	[6.88-9.68]	.418
Compulsions[r]	5.48 ± 4.51	[3.69-7.27]	7.32 ± 5.79	[4.93-9.71]	5.94 ± 5.02	[4.13-7.75]	.456

Note. HADS= Hospital Anxiety and Depression Scale; CB-OCi= Clark-Beck Obsessive-Compulsive inventory. [r]= square root transformed for the ANOVA (the un-transformed descriptive statistics are presented). Higher means reflect higher levels of the given dimension for all of the variables.

3.3.3. Mental Health Data

Data from the HADS and the CBOCI was collected for each of the four outcome variables to determine whether the three groups differed on measures of depression, anxiety, obsessions and compulsions. The possible scores on the two HADS tests ranged from 0-21 with higher scores indicating higher levels of anxiety or depression. The possible scores on the CBOCI ranged from 0-42 for the obsessions scale and from 0-33 for the compulsions scale with higher scores indicating more severe symptoms of OCD.

The four variables were checked for outliers and three cases were at ±3 z-scores from the group mean which were subsequently Winsorised. The normality protocol of assessing histograms, the Shapiro-Wilk's test, skewness statistics and kurtosis statistics suggested that there were mild deviations from normality for the anxiety measure from the HADS and the obsessions measure from the CBOCI however due to the robustness of the ANOVA method these were not altered. The depression measure from the HADS and the compulsions measure from the CBOCI deviated more severely from normality and thus were transformed using the root transformation. The six transformation methods described in section 3.2.8 were implemented and the normality protocol suggested that the root method was the most effective.

Before the ANOVA procedure was completed, homogeneity of variance was checked using the Levene test and the Brown-Forsythe test and assumptions were met.

3.3.3.1. Cannabis Use Analyses

Four one-way ANOVAs were run to test if the groups (Controls vs. Tobacco users vs. Cannabis users) were matched for mental health symptoms, as measured by four variables (see Table 3.6). Between-subject effects showed no significant differences between groups on individual measures of mental health: anxiety [$F_{(2,81)}$=0.09, p=.914, partial η^2=.002], depression [$F_{(2,81)}$=2.49, p=.089, partial η^2=.058], obsessions [$F_{(2,81)}$=0.88, p=.418, partial η^2=.021] and compulsions [$F_{(2,81)}$=0.79, p=.456, partial η^2=.019]. As there were no significant main effects of cannabis use on mental health traits, post hoc comparisons were not run.

3.3.3.2. Age of Onset Analyses

Four one-way ANOVAs were run to test whether the groups (Controls vs. Tobacco users vs. EoC vs. LoC) were matched for estimated of mental health symptoms, as measured by four variables (see Table 3.7). Between-subject effects showed no significant differences between groups on individual measures of mental health: anxiety [$F_{(3,80)}$=0.26, p=.851, partial η^2=.010], depression [$F_{(3,80)}$=1.74, p=.167, partial η^2=.061], obsessions [$F_{(3,80)}$=0.60, p=.620, partial η^2=.022] and compulsions [$F_{(3,80)}$=0.90, p=.447, partial η^2=.033]. As there were no significant main effects of cannabis use on mental health traits, post hoc comparisons were not run.

Table 3.7.

Between subject effects and descriptive statistics for the four-group mental health data.

Mental Health Variable	**Control** *n*=27		**Tobacco users** *n*=25		**EoC (≤15 years)** *n*=16		**LoC (≥16 years)** *n*=16		***p*-value**
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
HADS									
Anxiety	6.74 ± 3.18	[5.48-8.00]	7.16 ± 3.91	[5.55-8.77]	7.50 ± 4.12	[5.31-9.69]	6.50 ± 3.27	[4.76-8.24]	.851
Depression[r]	2.15 ± 3.10	[1.35-2.94]	3.56 ± 3.10	[2.28-4.83]	3.13 ± 2.47	[1.81-4.44]	2.81 ± 2.17	[1.66-3.97]	.167
CB-OCi									
Obsessions	7.70 ± 3.94	[6.15-9.26]	9.24 ± 4.83	[7.25-11.23]	8.13 ± 3.42	[6.30-9.95]	8.44 ± 4.40	[6.09-10.78]	.620
Compulsions[r]	5.48 ± 4.51	[3.69-7.27]	7.32 ± 5.79	[4.93-9.71]	6.63 ± 5.02	[3.95-9.30]	5.25 ± 5.08	[2.54-7.96]	.447

Note. See Table 3.6 for notes.

Table 3.8.

Between subject effects and descriptive statistics for the three-group IQ data.

IQ Variable	Control *n*=27		Tobacco users *n*=25		Cannabis users *n*=32		*p*-value
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
FSIQ	103.22 ± 9.84	[99.33-107.11]	105.28 ± 7.74	[102.08-108.48]	108.38 ± 9.65	[104.89-111.86]	.101
Vocabulary	47.88 ± 9.05	[44.05-51.70]	49.79 ± 8.51	[46.20-53.39]	52.78 ± 7.12	[50.21-55.35]	.082
Block Design	57.46 ± 7.53	[54.28-60.64]	57.00 ± 5.21	[54.80-59.20]	57.47 ± 7.29	[54.84-60.10]	.962
Similarities	53.92 ± 5.65	[51.53-56.30]	52.71 ± 6.31	[50.04-55.37]	54.56 ± 5.83	[52.46-56.66]	.511
Matrix Reasoning	49.25 ± 8.09	[45.83-52.67]	52.50 ± 7.70	[49.25-55.75]	53.81 ± 6.11	[51.61-56.02]	.067

Note. FSIQ= full scale intelligence quotient; Higher scores on all of these variables indicate better performance. All omnibus tests were conducted by ANOVAs. There was missing data for three control participants and one tobacco user for all four subtest scores.

3.3.4. IQ Data

The estimates of IQ derived from the WASI were collected and analysed to determine whether the three groups differed on measures of FSIQ and each of the four subtests. A qualitative interpretation by the authors breaks up performance into extremely low (69 and below), borderline (70-79), low average (80-89), average (90-109), high average (110-119), superior (120-129) and very superior (130 and above) categories (Wechsler et al., 1999). The remaining possible scores (age-scaled) are 20-73 for the Vocabulary subtest, 24-73 for the Block Design subtest, 20-71 for the Similarities subtest, and 20-69 for the Matrix Reasoning subtest. Higher scores on all of the subtests indicate better performance.

The five variables were checked for outliers and seven cases were at ±3 z-scores from the group mean which were subsequently Winsorised. The normality protocol of assessing histograms, the Shapiro-Wilk's test, skewness statistics and kurtosis statistics suggested that there were mild deviations from normality for all of the variables but none so severe that they warranted transformations and were thus deemed appropriate for ANOVA testing. Before the ANOVA procedure was completed, homogeneity of variance was checked using the Levene test and the Brown-Forsythe test and there were no violations.

3.3.4.1. Cannabis Use Analyses

Five one-way ANOVAs were run to test if the groups (Controls vs. Tobacco users vs. Cannabis users) were matched for IQ estimates, as measured by five variables (see Table 3.8). There were no significant main effects of cannabis use on full-scale IQ [$F_{(2,81)}$=2.36, p=.101, partial η^2=.055], vocabulary subtest [$F_{(2,77)}$=2.58, p=.082, partial η^2=.063], block design subtest [$F_{(2,77)}$=0.04, p=.962, partial η^2=.001], similarities subtest [$F_{(2,77)}$=0.68, p=.511, partial η^2=.017] and the matrix reasoning subtest [$F_{(2,77)}$=2.80, p=.067, partial η^2=.068]. As there were no significant main effects of cannabis use on IQ post hoc comparisons were not run.

3.3.4.2. Age of Onset Analyses

Five one-way ANOVAs were run to test whether the groups (Controls vs. Tobacco users vs. EoC vs. LoC) were matched for estimated of IQ, as measured by five variables

(see table 4.4). There were no significant main effects of cannabis use on full-scale IQ [$F_{(3,80)}$=1.68, p=.177, partial η^2=.059], vocabulary subtest [$F_{(3,76)}$=1.70, p=.174, partial η^2=.063], block design subtest [$F_{(3,76)}$=0.08, p=.973, partial η^2=.003], similarities subtest [$F_{(3,76)}$=0.84, p=.478, partial η^2=.032] and the matrix reasoning subtest [$F_{(3,76)}$=1.85, p=.145, partial η^2=.068]. As there were no significant main effects of cannabis use on IQ post hoc comparisons were not run.

Table 3.9.

Between subject effects and descriptive statistics for the four-group IQ data.

IQ Variable	**Control** ***n*=27**		**Tobacco users** ***n*=25**		**EoC (≤15 years)** ***n*=16**		**LoC (≥16 years)** ***n*=16**		***p*-value**
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
FSIQ	103.22 ± 9.84	[99.69-106.76]	105.28 ± 7.74	[101.61-108.95]	109.38 ± 10.93	[104.78-113.97]	107.38 ± 8.43	[102.78-111.97]	.177
Vocabulary	47.88 ± 9.05	[44.54-51.21]	49.79 ± 8.51	[46.46-53.13]	52.94 ± 7.89	[48.85-57.02]	52.63 ± 6.52	[48.54-56.71]	.174
Block Design	57.46 ± 7.53	[54.67-60.24]	57.00 ± 5.21	[54.22-59.79]	57.94 ± 8.41	[54.53-61.35]	57.00 ± 6.73	[53.59-60.41]	.973
Similarities	53.92 ± 5.65	[51.51-56.32]	52.71 ± 6.31	[50.30-55.12]	55.69 ± 5.87	[52.74-58.64]	53.44 ± 5.75	[50.49-56.39]	.478
Matrix Reasoning	49.25 ± 8.09	[46.29-52.21]	52.50 ± 7.70	[49.54-55.46]	54.06 ± 6.57	[50.44-57.69]	53.56 ± 5.82	[49.94-57.19]	.145

Note. See Table 3.8 for notes.

Table 3.10.

Between subject effects and descriptive statistics for the three-group cognitive data

Neurocognitive Variable	**Control**		**Tobacco users**		**Cannabis users**		***p*-value**
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
Trail Making Task							
Visual Scanning	11.58 ± 1.96[a]	[10.86-12.29]	11.45 ± 2.43[b]	[10.71-12.19]	10.26 ± 1.87 [ab]	[9.60-10.91]	**.013***
Number Sequencing	10.14 ± 2.96	[9.20-11.07]	10.15 ± 2.35	[9.19-11.12]	10.45 ± 1.92	[9.61-11.30]	.850
Letter Sequencing	10.30 ± 3.18	[9.04-11.56]	10.28 ± 2.60	[9.20-11.36]	10.59 ± 1.79	[9.70-11.49]	.868
Motor Speed[3]	11.00 ± 2.13	[10.16-11.84]	11.08 ± 1.47	[10.47-11.69]	11.16 ± 1.35	[10.67-11.64]	.968
Switching	11.46 ± 1.81[b]	[10.88-12.04]	10.76 ± 1.62	[10.17-11.36]	10.11 ± 1.53[b]	[9.58-10.64]	**.005****
Switching Contrast	10.24 ± 2.14	[9.45-11.04]	9.98 ± 1.82	[9.16-10.79]	9.44 ± 2.05	[8.74-10.14]	.305
Errors[KW]	12.00 (2.00)	[10.00-12.00]	12.00 (2.50)	[10.00-12.00]	12.00 (0.00)	[12.00-12.00]	.194
Verbal Fluency Task							
Letter Fluency[2]	10.70 ± 3.12	[9.59-11.94]	11.00 ± 3.42	[9.59-12.41]	10.72 ± 2.41	[9.85-11.59]	.762
Category Fluency	12.59 ± 3.21	[11.44-13.74]	13.52 ± 3.62	[12.34-14.70]	12.53 ± 3.07	[11.47-13.59]	.401
Switching Fluency	12.22 ± 2.92	[11.06-13.38]	12.44 ± 3.16	[11.13-13.75]	11.25 ± 2.91	[10.20-12.30]	.273
Switching Contrast	10.07 ± 3.72	[8.60-11.55]	9.00 ± 3.50	[7.55-10.44]	8.53 ± 3.14	[7.40-9.66]	.227
Set Loss Errors[KW]	13.00 (1.00)	[13.00-13.00]	13.00 (2.50)	[11.00-13.00]	13.00 (2.00)	[11.00-13.00]	.263
Repetition Errors[KW]	11.00 (3.00)	[10.00-13.00]	13.00 (2.50)	[11.00-13.00]	12.50 (3.00)	[11.00-13.00]	.723
Design Fluency Task							
Filled Dots[r]	10.24 ± 3.15	[9.20-11.28]	10.37 ± 2.43	[9.30-11.28]	9.91 ± 2.77	[8.95-10.87]	.777
Empty Dots[r]	10.81 ± 2.99	[9.83-11.78]	10.38 ± 2.32	[9.37-11.38]	10.56 ± 2.71	[9.66-11.45]	.879
Switching	13.23 ± 3.00[a]	[12.23-14.23]	12.12 ± 2.86	[11.09-13.14]	10.44 ± 2.73[a]	[9.52-11.36]	**.001*****
Switching Contrast	12.30 ± 3.09[a]	[11.23-13.36]	11.36 ± 1.91[b]	[10.57-12.15]	10.16 ± 2.13[ab]	[9.39-10.92]	**.002****

Set Loss Errors^{KW}	13.00 (2.00)	[12.00-14.00]	13.00 (2.00)	[12.00-14.00]	12.00 (1.75)	[12.00-13.00]	.113
Repetition Errors^{KW}	13.00 (1.00)	[12.00-13.00]	12.00 (1.00)	[12.00-13.00]	13.00 (1.00)	[12.00-13.00]	.916
Grooved Pegboard							
DH Place Task*	63.87 ± 10.43	[60.78-66.96]	60.05 ± 6.15	[56.85-63.25]	65.28 ± 7.03	[62.41-68.15]	.054
DH Remove Task*	23.00 ± 3.29	[21.74-24.25]	23.56 ± 3.12	[22.25-24.86]	22.56 ± 3.54	[21.42-23.72]	.530
DH Contrast*	41.30 ± 9.98^{c}	[37.35-45.25]	36.34 ± 6.42^{cb}	[33.69-38.99]	42.39 ± 6.44^{b}	[40.07-44.72]	**.012***
NDH Place Task^{2}*	66.66 ± 8.88	[63.15-70.17]	65.91 ± 8.87	[62.25-69.57]	66.95 ± 5.98	[64.80-69.11]	.931
NDH Remove Task^{3}*	22.66 ± 3.75	[21.18-24.15]	22.96 ± 3.36	[21.58-24.35]	22.88 ± 3.34	[21.67-24.08]	.979
NDH Contrast*	43.11 ± 10.54	[38.94-47.28]	42.92 ± 8.07	[39.59-46.25]	44.08 ± 5.08	[42.24-45.91]	.840
Symbol Search Task							
Scaled Score^{r}	12.81 ± 2.72	[11.74-13.89]	12.60 ± 2.86	[11.42-13.78]	13.03 ± 2.88	[11.99-14.07]	.843
Errors^{KW} *	1.00 (2.00)	[0.00-1.00]	0.00 (1.50)	[0.00-1.00]	0.00 (1.00)	[0.00-1.00]	.527
Iowa Gambling Task							
% of beneficial decks	50.22 ± 12.89	[45.12-55.32]	47.28 ± 10.65	[42.88-51.68]	47.72 ± 9.97	[44.72-51.31]	.583

Note. The symbols ^{a}, ^{b} and ^{c} denote significant post hoc differences (p<.05) between the two groups coded with that symbol. The symbol * denotes that a higher mean score indicates worse performance. The Symbol ^{KW} indicates that a Kruskal-Wallis test was run on this variable instead of an ANOVA. ^{r} denotes a square root transformation. ^{2}denotes a square transformation. ^{3}denotes a cube transformation. *$p < .05$, ** $p < .01$, and *** $p < .001$, highlight which tests survived corrections for multiple comparisons.

3.3.5 Cognitive Data

Data from the battery of neuropsychological tests was collected and analysed to determine whether the three groups differed on measures of executive function and other domains of cognition. Variables from four of the tests (TMT; VFT; DFT; SST) contained normative data which enabled the raw data to be converted in age scaled scores. There was one exception to this; the number of errors on the SST remains a raw score. This resulted in 20 dependent variables which were transformed into age scaled scores. For the primary (i.e. not the errors) age-scaled scores the possible range of scores was 1-19 with a score of 10 representing an 'average' score. For the error scores on the TMT, VFT and DFT, the possible range of scores was typically 1-13, with a score of 10 still representing an 'average' score. From the remaining variables, the IGT data was converted into the percentage of beneficial selections with a possible range of 0-100%. The GPT Place and Remove scores are self-terminating, with lower scores indicating faster performance. The GPT Contrast Measure needs to be compared with the Place and Remove Tasks for interpretation, with higher or lower scores suggesting impaired motor coordination or speed, respectively.

The 28 variables were checked for outliers and fourteen cases were at ±3 *z*-scores from the group mean which were subsequently Winsorised. The normality protocol of assessing histograms, the Shapiro-Wilk's test, skewness statistics and kurtosis statistics suggested that there were mild deviations from normality the majority of the variables however these were within acceptable limits for the ANOVA. The six transformation methods described in section 3.2.8 were implemented and the normality protocol dictated which transformation method was selected (see Table 3.10 for which variables were transformed). All error scores from the TMT, VFT, DFT and SST were non-normally distributed and the transformation protocol proved ineffective and therefore these variables were subject to the Kruskal-Wallis test. ANCOVAs were run in situations where a confounding variable was identified and met the appropriate assumptions, whereas ANOVAs were run in the remaining situations.

3.3.5.1. Cannabis Use Analysis

22 one-way AN(C)OVAs were run to test the hypothesis that there would be mean differences between cannabis use (Controls vs. Tobacco users vs. Cannabis users) and

executive function, as measured by 22 variables (see Table 3.10). There was a significant main effect between groups on the TMT Visual Scanning test when controlling for anxiety, depression and obsessions [$F_{(2,79)}$=4.59, p=.013, partial η^2=.104], TMT Switching when controlling for FSIQ [$F_{(2,80)}$=5.66, p=.005, partial η^2=.124], DFT Switching when controlling for FSIQ [$F_{(2,80)}$=8.34, p=.001, partial η^2=.172], DFT Switching Contrast [$F_{(2,81)}$=6.62, p=.002, partial η^2=.141], and GPT (DH) Contrast Measure [$F_{(2,81)}$=4.65, p=.012, partial η^2=.103]. Based on Cohen's (1998) guidelines of a small ($\eta^2 \approx .01$), medium ($\eta^2 \approx .059$) and large ($\eta^2 \approx .138$) effect sizes, the significant ANCOVAs from the current analyses appear to range in effects sizes from medium to large. In this context the effect size represents the percentage of variance of the dependant variable accounted for by the independent variable. By example, the largest effect size produced in this analysis, the DFT Switching variable (partial η^2=.172), suggests that approximately 17% of the variance in DFT switching performance can be accounted for the smoking status of the individual.

The remaining measures did not show a significant main effect including TMT Letter Sequencing [$F_{(2,81)}$=0.14, p=.868, partial η^2=.004], TMT Number Sequencing when controlling for depression [$F_{(2,80)}$=0.94, p=.977, partial η^2=.001], TMT Motor Speed [$F_{(2,81)}$=0.03, p=.968, partial η^2=.001], TMT Switching Contrast when controlling for sex [$F_{(2,80)}$=1.21, p=.305, partial η^2=.029], VFT Letter Fluency [$F_{(2,81)}$=0.27, p=.762, partial η^2=.007], VFT Category Fluency when controlling for FSIQ [$F_{(2,80)}$=0.93, p=.401, partial η^2=.023], VFT Switching [$F_{(2,81)}$=1.32, p=.273, partial η^2=.032], VFT Switching Contrast [$F_{(2,81)}$=1.51, p=.227, partial η^2=.036], DFT Filled Dots when controlling for FSIQ [$F_{(2,80)}$=0.25, p=.777, partial η^2=.006], DFT Empty Dots when controlling for FSIQ [$F_{(2,80)}$=0.13, p=.879, partial η^2=.003], GPT (DH) Place Task when controlling for sex [$F_{(2,80)}$=2.16, p=.054, partial η^2=.070], GPT (DH) Remove Task when controlling for anxiety [$F_{(2,80)}$=0.64, p=.530, partial η^2=.016], GPT (NDH) Place Task [$F_{(2,81)}$=0.07, p=.931, partial η^2=.002], GPT (NDH) Remove Task [$F_{(2,81)}$=0.02, p=.979, partial η^2=.001], GPT (NDH) contrast [$F_{(2,81)}$=0.17, p=.840, partial η^2=.004], SST Scale Score while controlling for sex [$F_{(2,80)}$=0.53, p=.594, partial η^2=.013] and IGT advantageous decks [$F_{(2,81)}$=0.54, p=.583, partial η^2=.013].

Six Kruskal-Wallis tests were run on the data which could not be transformed and did not meet parametric assumptions. These tested the hypothesis that there would be mean

differences between cannabis use (Controls vs. Tobacco users vs. Cannabis users) and executive function, as measured by six error variables (see Table 3.10). There were no significant main effects between groups for the TMT error measure [$\chi^2_{(2)}$=3.276, p=.194], percentage of set loss error on the VFT [$\chi^2_{(2)}$=2.670, p=.263], percentage of repetition errors on the VFT [$\chi^2_{(2)}$=0.649, p=.723], set loss errors on the DFT [$\chi^2_{(2)}$=4.358, p=.113], repetition errors on the DFT [$\chi^2_{(2)}$=0.178, p=.915] and number of errors on the SST [$\chi^2_{(2)}$=1.280, p=.527]. As there were no significant main effects follow up post hoc tests were not run.

After correcting for multiple comparisons ($p < .01$) it can be seen that the TMT Visual Scanning and GPT DH Contrast measre tests no longer displayed a significant main effect of cannabis use, however TMT Switching, DFT Switching and Switching Contrast did remain significant. After using a more strict correction ($p < .001$) only DFT Switching remained significant.

For the cognitive variables which showed significant ANOVA main effects, post hoc one-tailed Hochberg's GT2s and Tukey's HSDs were conducted to further explore the effects. The GT2 test was selected to account for the uneven sample sizes between the control/tobacco groups and the cannabis group. As the samples sizes of the tobacco and control group were approximately equal, Tukey's HSD was deemed appropriate for this comparison. Cohen's d was also calculated to examine the size of the differences observed between groups. Effect size interpretations were derived from Cohen (1988; small $d\approx.3$, moderate $d\approx.5$, large $d\approx.8$).

3.3.5.2. Age of onset analysis

22 one-way AN(C)OVAs were run to test the hypothesis that there would be mean differences between the age of onset of cannabis use (Controls vs. Tobacco users vs. EoC users vs. LoC users) and executive function, as measured by 22 variables (see Table 3.11). There was a significant main effect between groups on the TMT Visual Scanning test while controlling for anxiety, depression and obsessions [$F_{(3,78)}$=3.11, p=.031, partial η^2=.107], TMT Switching while controlling for FSIQ [$F_{(3,79)}$=5.65, p=.001, partial η^2=.177], TMT Switching Contrast while controlling for sex [$F_{(3,79)}$=3.04, p=.034, partial η^2=.103], DFT Switching while controlling for FSIQ [$F_{(3,79)}$=5.48, p=.002, partial η^2=.172], DFT Switching Contrast [$F_{(3,80)}$=4.55, p=.005,

partial η^2=.146] and GPT (DH) Contrast Measure [$F_{(3,80)}$=4.11, p=.009, partial η^2=.134]. The largest effect size produced in this analysis, the TMT Switching variable (partial η^2=.177), suggests that approximately 18% of the variance in TMT switching performance can be accounted for the smoking status of the individual.

The remaining measures did not show a significant main effect including TMT Number Sequencing while controlling for depression and FSIQ [$F_{(3,78)}$=0.24, p=.872, partial η^2=.009], TMT Letter Sequencing [$F_{(3,80)}$=0.13, p=.940, partial η^2=.005], TMT Motor Speed while controlling for FSIQ [$F_{(3,79)}$=0.61, p=.613, partial η^2=.023], VFT Letter Fluency [$F_{(3,80)}$=0.23, p=.873, partial η^2=.009], VFT Category Fluency while controlling for FSIQ [$F_{(3,79)}$=0.81, p=.491, partial η^2=.030],VFT Switching [$F_{(3,80)}$=0.99, p=.403, partial η^2=.036], VFT Switching Contrast [$F_{(3,80)}$=1.40, p=.249, partial η^2=.050], DFT Filled Dots while controlling for FSIQ [$F_{(3,79)}$=0.88, p=.457, partial η^2=.032], DFT Empty Dots while controlling for FSIQ [$F_{(3,79)}$=0.09, p=.968, partial η^2=.003], GPT (DH) Place Task while controlling for sex [$F_{(3,79)}$=2.54, p=.062, partial η^2=.088], GPT (DH) Remove Task while controlling for anxiety [$F_{(3,79)}$=0.47, p=.708, partial η^2=.017], GPT (NDH) Place Task while controlling for educational achievement [$F_{(3,78)}$=0.15, p=.930, partial η^2=.006], GPT (NDH) Remove Task [$F_{(3,80)}$=0.02, p=.997, partial η^2=.001], GPT (NDH) Contrast Measure [$F_{(3,80)}$=0.36, p=.781, partial η^2=.013], SST Scaled Score while controlling for sex and educational achievement [$F_{(3,77)}$=0.07, p=.686, partial η^2=.019] and IGT advantageous decks [$F_{(3,80)}$=0.47, p=.702, partial η^2=.017].

Six Kruskal-Wallis tests were run to test the hypothesis that there would be mean differences between the age of onset of cannabis use (Controls vs. Tobacco users vs. EoC vs. LoC) and cognition as measured by eight variables (see Table 3.11). There was no significant effects for any of the error variables including TMT errors [$H_{(3)}$=6.16, p=.104], the percentage of set loss errors on the VFT [$H_{(3)}$=5.01, p=.171], the percentage of repetition errors on the VFT [$H_{(3)}$=0.66, p=.883], the number of set loss errors on the DFT [$H_{(3)}$=6.25, p=.100], the number of repetition errors on the DFT [$H_{(3)}$=1.11, p=.775], and total number of errors on the SST [$H_{(3)}$=1.45, p=.693]. As the Kruskal-Wallis tests were not significant follow-up Dunn's tests were not conducted.

After correcting for multiple comparisons ($p < .01$) it can be seen that the TMT Visual Scanning and Switching Contrast tests no longer displayed a significant main effect of

the age of onset of cannabis use, however TMT Switching, DFT Switching and Switching Contrast, and GPT DH Contrast measure did remain significant. After using a more strict correction ($p < .001$) only TMT Switching remained significant.

3.3.5.3. Controls vs. cannabis users.

Significant differences were observed between cannabis users and controls for four of the cognitive variables. Cannabis users presented with lower scores on the TMT Visual Scanning test [$t_{(57)}$=2.71, p=.012, d=0.69, 1-tailed Bonferroni] and the TMT Switching test [$t_{(57)}$=3.36, p=.002, d=0.81, 1-tailed Bonferroni] when compared to controls, yielding large effect sizes. The cannabis group also presented with lower scores compared to controls on the DFT Switching [$t_{(57)}$=4.03, p<.001, d=0.97, 1-tailed Bonferroni] and DFT Switching Contrast [$t_{(57)}$=3.62, p=.001, d=0.88, 1-tailed GT2], both showing large effect sizes. These lower scores by the cannabis group represent performance deficits relative to the controls.

There were no significant differences between cannabis users and controls for the GPT (DH) Place Task [$t_{(57)}$=0.98, p=.347, d=0.23, 1-tailed GT2] and GPT (DH) Contrast Measures [$t_{(57)}$=0.54, p=.465, d=0.13, 1-tailed GT2].

3.3.5.4. Tobacco users vs. cannabis users.

Significant differences were observed between cannabis users and tobacco users for three of the cognitive variables. The cannabis using group presented with lower scores on the Visual Scanning subtest of the TMT when compared to tobacco users [$t_{(55)}$=2.40, p=.028, d=0.55, 1-tailed Bonferroni] and the DFT Switching test [$t_{(55)}$=2.42, p=.027, d=0.60, 1-tailed Bonferroni] and these showed moderate to large effect sizes. Cannabis users took longer to complete the Place Task of the GPT (DH) [$t_{(55)}$=2.71, p=.012, d=0.88, 1-tailed GT2] and the Contrast Measure of the GPT (DH) [$t_{(55)}$=2.93, p=.007, d=0.94, 1-tailed GT2]. Both of these comparisons display large effect sizes. In all cases here the significant results indicate diminished performance by the cannabis group relative to the tobacco group.

There were no significant differences between cannabis users and tobacco users for the TMT Switching test [$t_{(55)}$=1.62, p=.166, d=0.41, 1-tailed Bonferroni] and DFT Switching Contrast [$t_{(55)}$=1.99, p=.071, d=0.60, 1-tailed HSD] outcome measures.

3.3.5.5. Controls vs. tobacco users.

There was a significant difference between controls and tobacco users on one of the cognitive variables, controls took longer to complete the Contrast Measure of the GPT (DH) [$t_{(50)}$=2.30, p=.030, d=0.59, 1-tailed HSD] and this showed a moderate effect size. The longer time represents diminished performance levels by the control group relative to the tobacco group.

There were no significant differences between tobacco users and controls for the TMT Visual Scanning [$t_{(52)}$=0.24, p=.500, d=0.06, 1-tailed Bonferroni], TMT Switching test [$t_{(52)}$=1.68, p=.145, d=0.41, 1-tailed Bonferroni], DFT Switching test [$t_{(52)}$=1.55, p=.188, d=0.38, 1-tailed Bonferroni], DFT Switching Contrast [$t_{(50)}$=1.49, p=.151, d=0.40, 1-tailed HSD] and GPT (DH) Place Task [$t_{(50)}$=1.68, p=.109, d=0.44, 1-tailed HSD] outcome measures.

3.3.5.6. Controls versus early cannabis users

The early onset cannabis using group presented with significantly lower scores than the controls on the Switching measure of the TMT [$t_{(42)}$=4.12, p<.001, d=1.18, 1-tailed Bonferroni] and on the Switching Contrast measure from the TMT [$t_{(42)}$=2.71, p=.025, d=0.83, 1-tailed Bonferroni], both of which yielded a large effect size. The early onset cannabis using group also presented with significantly lower scores on the Switching measure from the DFT [$t_{(42)}$=3.27, p=.005, d=0.90, 1-tailed Bonferroni] and the switching contrast measure from the DFT [$t_{(42)}$=3.38, p=.004, d=0.97, 1-tailed GT2], both of which yielded a large effect size.

There were no significant differences between early cannabis users and controls for the TMT Visual Scanning condition [$t_{(42)}$=1.94, p=.167, d=0.61, 1-tailed Bonferroni] and the GPT contrast measure [$t_{(42)}$=1.39, p=.329, d=0.41, 1-tailed GT2].

3.3.5.7. Controls versus late cannabis users

The late onset cannabis using group presented with significantly lower scores than the controls on the Visual Scanning measure of the TMT [$t_{(42)}$=2.51, p=.042; d=0.75, 1-tailed Bonferonni], which yielded a large effect size. The late onset cannabis using group also presented with significantly lower scores on the Switching measure from the DFT [$t_{(42)}$=3.42, p=.003, d=1.00, 1-tailed Bonferroni] and the Switching Contrast measure from the DFT [$t_{(42)}$=2.59, p=.033, d=0.78, 1-tailed GT2], both of which yielded a large effect size.

There were no significant differences between early cannabis users and controls for the TMT Switching measure [$t_{(42)}$=1.68, p=.289, d=0.48, 1-tailed Bonferroni], TMT Switching Contrast measure [$t_{(42)}$=0.14, p=.500, d=0.04, 1-tailed Bonferroni], and the GPT Contrast Measure [$t_{(42)}$=0.49, p=.499, d=0.14, 1-tailed GT2].

3.3.5.8. Tobacco users versus early cannabis users

The early onset cannabis using group presented with significantly lower scores on the Switching measure from the TMT when compared to tobacco users [$t_{(40)}$=2.62, p=.031; d=0.80, 1-tailed Bonferroni] which both yielded a large effect size. The early onset cannabis group also took significantly longer to complete the Contrast Measure of the GPT [$t_{(40)}$=3.39, p=.003; d=1.37, 1-tailed GT2], which yielded a large effect size.

There were no significant differences between cannabis users and controls for the TMT Visual Scanning condition [$t_{(40)}$=1.71, p=.272, d=0.51, 1-tailed Bonferroni], the Switching Contrast measure from the TMT when compared to tobacco users [$t_{(40)}$=2.16, p=.083; d=0.76, 1-tailed Bonferroni], the DFT Switching measure [$t_{(40)}$=1.95, p=.165, d=0.56, 1-tailed Bonferroni], and the DFT Switching Contrast measure [$t_{(40)}$=2.04, p=.118, d=0.70, 1-tailed Hochberg].

3.3.5.9. Tobacco users versus late cannabis users

The late onset cannabis using group did not present with deficits compared to the tobacco users on any of the cognitive variables.

There were no significant differences between cannabis users and controls for the TMT Visual Scanning condition [$t_{(40)}$=2.27, p=.079, d=0.66, 1-tailed Bonferroni], TMT

Switching measure [$t_{(40)}$=0.17, p=.500, d=0.05, 1-tailed Bonferroni], TMT Switching Contrast measure [$t_{(40)}$=0.56, p=.500, d=0.18, 1-tailed Bonferroni], DFT Switching measure [$t_{(40)}$=2.07, p=.127, d=0.64, 1-tailed Bonferroni], DFT Switching Contrast measure [$t_{(40)}$=1.27, p=.374, d=0.47, 1-tailed Hochberg], GPT Contrast Measure [$t_{(40)}$=1.54, p=.276, d=0.59, 1-tailed Hochberg].

3.3.5.10. Early cannabis users versus late cannabis users

There were significant differences between early and late onset cannabis users for only one of the cognitive variables. The early onset users presented with significantly lower scores on the TMT Switching Contrast measure [$t_{(31)}$=2.56, p=.037, d=0.91, 1-tailed Bonferroni], which yielded a large effect size.

There were no significant differences between early cannabis users and late cannabis users for the TMT Visual Scanning condition [$t_{(31)}$=0.49, p=.500, d=0.17, 1-tailed Bonferroni], TMT Switching Measure [$t_{(31)}$=2.25, p=.082, d=0.79, 1-tailed Bonferroni], DFT Switching measure [$t_{(31)}$=0.09, p=.500, d=0.03, 1-tailed Bonferroni], DFT Switching Contrast measure [$t_{(31)}$=0.70, p=.449, d=0.26, 1-tailed HSD], and GPT Contrast Measure [$t_{(31)}$=1.68, p=.170, d=0.75, 1-tailed HSD].

3.3.5.11. Additional ANCOVA analyses

A set of further ANCOVAs were run to control for the total amount of cannabis used. This was done as an earlier age of onset could potentially mean greater levels of cannabis use. However, these ANCOVAs were run despite the violations of at least one of the assumptions and therefore would be expected to have reduced power. These analyses are reported in Appendix A.3.11.23.

Table 3.11.

Between subject effects and descriptive statistics for the four-group cognitive data

Cognitive Variable	Control		Tobacco users		EoC Users		LoC Users		*p*-value
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
Trail Making Task									
Visual Scanning	11.57 ± 1.96[c]	[10.86-12.29]	11.36 ± 1.85	[10.71-12.20]	10.42 ± 1.82	[9.48-11.36]	10.10 ± 1.96[c]	[9.17-11.02]	**.031***
Number Sequencing	10.31 ± 2.96	[9.38-11.12]	10.18 ± 2.35	[9.25-11.12]	10.63 ± 2.01	[9.44-11.81]	9.95 ± 1.81	[8.78-11.12]	.872
Letter Sequencing	10.30 ± 3.18	[9.32-11.28]	10.28 ± 2.60	[9.26-11.30]	10.75 ± 1.77	[9.48-12.03]	10.44 ± 1.86	[9.16-11.71]	.940
Motor Speed[3]	11.16 ± 2.13	[10.54-11.77]	11.11 ± 1.47	[10.48-11.74]	10.72 ± 1.53	[9.92-11.52]	11.28 ± 1.15	[9.92-11.52]	.613
Switching	11.47 ± 1.81[b]	[10.90-12.04]	10.76 ± 1.62[d]	[10.18-11.34]	9.52 ± 1.47[bd]	[8.79-10.23]	10.68 ± 1.47	[9.96-11.41]	**.001*****
Switching Contrast	10.22 ± 2.14[b]	[9.45-10.99]	9.96 ± 1.82[d]	[9.17-10.74]	8.57 ± 1.82[bdf]	[7.61-9.52]	10.31 ± 1.98[f]	[9.35-11.26]	**.034***
Errors[KW]	12.00 (2.00)	[10.00-12.00]	12.00 (2.50)	[10.00-12.00]	12.00 (3.00)	[9.00-12.00]	12.00 (0.00)	[12.00-12.00]	.104
Verbal Fluency Task									
Letter Fluency[2]	10.70 ± 3.12	[9.56-11.85]	11.00 ± 3.42	[9.81-12.19]	10.94 ± 2.35	[9.45-12.42]	10.50 ± 2.53	[9.02-11.99]	.873
Category Fluency	12.59 ± 3.21	[11.43-13.74]	13.52 ± 3.62	[12.37-14.71]	12.94 ± 3.03	[11.44-14.45]	12.13 ± 3.10	[10.65-13.61]	.491
Switching Fluency	12.22 ± 2.93	[11.07-13.37]	12.44 ± 3.16	[11.26-13.64]	10.94 ± 2.43	[11.25-13.64]	11.56 ± 3.37	[10.07-13.06]	.403
Switching Contrast	10.07 ± 3.72	[8.76-11.39]	9.00 ± 3.50	[7.63-10.37]	7.88 ± 3.70	[6.16-9.59]	9.19 ±2.40	[7.48-10.90]	.249
Set Loss Errors[KW]	13.00 (1.00)	[13.00-13.00]	13.00 (2.50)	[11.00-13.00]	11.00 (2.75)	[11.00-13.00]	13.00 (2.75)	[12.00-13.00]	.171
Repetition Errors[KW]	11.00 (3.00)	[10.00-13.00]	13.00 (2.50)	[11.00-13.00]	13.00 (3.75)	[10.00-13.00]	11.50 (2.75)	[11.00-13.00]	.883
Design Fluency Task									
Filled Dots[r]	10.24 ± 3.15	[9.20-11.27]	10.37 ± 2.43	[9.31-11.43]	10.61 ± 2.91	[9.27-11.96]	9.23 ± 2.47	[7.91-10.56]	.457

Empty Dots[r]	10.81 ± 2.99	[9.83-11.79]	10.32 ± 2.32	[9.37-11.39]	10.54 ± 2.79	[9.26-11.81]	10.57 ± 2.72	[9.31-11.84]	.968
Switching	13.23 ± 3.10[bc]	[12.23-14.23]	12.12 ± 2.86	[11.08-13.15]	10.48 ± 3.01[b]	[9.17-11.79]	10.40 ± 2.50[c]	[9.10-11.69]	**.002****
Switching Contrast	12.30 ± 2.69[bc]	[11.43-13.17]	11.36 ± 1.91	[10.46-12.26]	9.88 ± 2.28[b]	[8.74-11.06]	10.44 ± 2.00[c]	[9.31-11.57]	**.005****
Set Loss Errors[KW]	13.00 (2.00)	[12.00-14.00]	13.00 (2.00)	[12.00-14.00]	12.00 (2.50)	[11.00-12.00]	12.00 (2.00)	[12.00-14.00]	.100
Repetition Errors[KW]	13.00 (1.00)	[12.00-13.00]	12.00 (1.00)	[12.00-13.00]	12.00 (1.00)	[12.00-13.00]	13.00 (1.00)	[13.00-13.00]	.775
Grooved Pegboard									
DH Place Task*	64.31 ± 10.43	[61.12-67.50]	60.49 ± 6.15[b]	[57.20-63.77]	67.43 ± 7.75	[63.45-71.41]	63.92 ± 6.08	[59.94-67.90]	.062
DH Remove Task*	23.03 ± 3.29	[21.76-24.29]	23.56 ± 3.12	[22.25-24.88]	22.66 ± 3.95	[21.02-24.30]	22.42 ± 3.20	[20.77-24.06]	.708
DH Contrast	41.30 ± 9.98[a]	[38.36-44.24]	36.34 ± 6.42[ad]	[33.29-39.39]	44.67 ± 5.75[d]	[40.86-48.49]	40.12 ± 6.46	[36.30-43.93]	**.009****
NDH Place Task*[2]	66.77 ± 8.88	[63.66-69.87]	65.90 ± 8.87	[62.72-69.09]	67.38 ± 6.33	[63.35-71.42]	66.03 ± 5.76	[61.92-70.15]	.930
NDH Remove Task*[3]	22.66 ± 3.75	[21.33-24.00]	22.96 ± 3.36	[21.58-24.35]	22.23 ± 3.91	[20.50-23.96]	23.53 ± 2.62	[21.80-25.26]	.997
NDH Contrast	43.11 ± 10.54	[40.02-46.20]	42.92 ± 8.07	[39.71-46.13]	45.30 ± 4.76	[41.29-49.31]	42.85 ± 5.25	[38.84-46.87]	.781
Symbol Search Task									
Scaled Score	12.39 ± 2.72	[11.25-13.53]	12.30 ± 2.86	[11.15-13.45]	13.16 ± 2.92	[11.75-14.58]	13.14 ± 2.93	[11.70-14.58]	.686
Errors[KW] *	1.00 (2.00)	[0.00-2.00]	0.00 (1.50)	[0.00-1.00]	0.00 (2.00)	[0.00-2.00]	0.50 (1.00)	[0.00-1.00]	.693
Iowa Gambling Task									
% of beneficial decks	50.22 ± 12.89	[45.92-54.52]	47.28 ± 10.65	[42.81-51.75]	46.56 ± 7.68	[40.98-52.15]	48.88 ± 11.99	[43.29-54.46]	.702

Note. See Table 3.10 for notes.

3.3.5.12. Cannabis use variables and cognitive data

Table 3.12.

Spearman's correlations between cannabis use variables and cognitive variables for the whole cannabis group (n=32).

Cognitive Variable	Age of onset	Lifetime spliffs smoked	Years of cannabis smoking	Desired Intoxication
Trail Making Task				
Visual Scanning	-.065	**-.352***	-.047	**-.300***
Switching	**.341***	-.256	**-.394***	-.266
Switching contrast	**.361***	-.079	**-.309***	-.192
Design Fluency Task				
Switching	.067	-.002	**-.317***	-.004
Switching Contrast	.209	.151	-.030	.310
Grooved Pegboard				
Place task	-.198	.070	.256	.204
Contrast	**-.372***	-.076	.239	.072

Note. * ($p<.05$) denotes a significant correlation.

To determine whether an association existed between cannabis use variables and the dependant variables in which cannabis users showed impaired performance, correlational analyses were run for the cannabis group as a whole (N=32). The cannabis use variables examined were the age-of-onset of cannabis use, number of lifetime spliffs smoked, number of years when using cannabis was reported and the typical desired level of intoxication reached on a scale from 1(sober) to 10 (most stoned you have ever been).

3.3.6. Concurrent Validity of the Grooved Pegboard

The current study introduced a new measure which has yet not been published before. The measure is a contrast condition between the Grooved Pegboard Place task and the Grooved Pegboard Remove task in which the time taken to complete the latter task is subtracted from the time taken to complete the former task. Tables 3.13 and 3.14 show the correlation matrices for the Contrast Measure of the Grooved Pegboard with several standardised tests of motor coordination, motor speed and graphomotor speed.

Table 3.13.

A correlation matrix of the Contrast Measure of the Grooved Pegboard for the dominant hand with three other tasks measuring motor processes (N=84).

	1	2	3	4	5
1. Contrast Measure	-				
2. Place Task	.885**	-			
3. Remove Task	.028	.367**	-		
4. TMT Motor Speed	-.204	-.346**	-.390**	-	

Table 3.14.

A correlation matrix of the Contrast Measure of the Grooved Pegboard for the non-dominant hand with three other tasks measuring motor processes (N=84).

	1	2	3	4	5
1. Contrast Measure	-				
2. Place Task	.889**	-			
3. Remove Task	.111	.453**	-		
4. TMT Motor Speed	-.211	-.296**	-.392**	-	

Note. The TMT Motor Speed test is only completed with the dominant hand.

The results of the Spearman's correlations show that the Grooved Pegboard Contrast measure was strongly and positively correlated with Place Task with little difference between the dominant hand (r_s=.885, p<.001, 1-tailed) and the non-dominant hand (r_s=.889, p<.001, 1-tailed). The Contrast condition was not significantly correlated with the Remove Task for the dominant hand (r_s=.028, p=.401, 1-tailed) nor the non-dominant hand (r_s=.111, p=.157, 1-tailed). It was also not correlated with the TMT Motor Speed test for the dominant hand (r_s=-.204, p=.062, 1-tailed) nor the non-dominant hand (r_s=-.211, p=.054, 1-tailed). While the Contrast condition was not

correlated with the two motor speed tasks, the Place Tasks were significantly correlated with the dominant hand Remove Task (r_s=.367, p=.001, 1-tailed), the non-dominant hand Remove Task (r_s=.453, p=.001, 1-tailed), the dominant hand TMT Motor Speed (r_s=-.346, p=.001, 1-tailed) and the non-dominant hand TMT Motor Speed (r_s=-.296, p=.006, 1-tailed). Finally the dominant hand Remove task (r_s=-.390, p<.001, 1-tailed) and non-dominant hand Remove task (r_s=-.392, p<.001, 1-tailed) were both significantly correlated with the TMT Motor Speed test. All correlations with the TMT Motor Speed test were negative as the scoring was reversed in which higher scores denoted better performances, while all Grooved Pegboard variables were scored in such a way that meant lower scores meant better performances.

3.4. Discussion

3.4.1. Concurrent Validity of the Grooved Pegboard

The current study introduced a new neuropsychological measure and therefore concurrent validity tests were run to determine what processes were being measured by this task. The Grooved Pegboard Contrast condition for both the dominant hand and the non-dominant hand involved the subtraction of the time taken to complete the Remove task from the Place task. It is thought that both of these tasks (Place + Remve) to differing degrees measure motor speed (e.g. Strauss et al., 2006) and this was confirmed by the concurrent validity tests. Both the Place task and the Remove task correlated with performance on the graphomotor speed task from the TMT. Furthermore, the Place Task and the Remove Task correlated with each other, perhaps reflecting the overlap of motor speed processes involved in the respective tasks. However the Contrast condition only correlated with the Place task and did not correlate with the Remove Task or the TMT Motor Speed task which suggests that the Contrast condition does not involve motor speed, but rather it relates to the additional processes involved in the completion of the Place task beyond motor speed. As other authors have reported that the Grooved Pegboard Place task involves motor coordination, motor programming, visuo-executive cognition and motor speed (Baser & Ruff, 1997; Strauss et al., 2006; Ashendorf et al., 2009; Bezdicek et al., 2014) the removal of this motor speed element would imply that the Contrast condition measures these cognitive and coordinative elements, the higher levels of processing involved in manual dexterity beyond simple motor speed.

3.4.2. Cognitive Data

3.4.2.1. The Trail Making Test (TMT)

Seven outcome measures from the TMT were used in the current experiment which included Visual Scanning, Number Sequencing, Letter Sequencing, Switching, Switching Contrast, Motor Speed, and the error score.

The cannabis group presented with deficits on the Visual Scanning subtest compared to the controls and the tobacco using group in addition to deficits on the Switching subtest relative to controls. After dividing the cannabis group into EoC and LoC groups it appeared that EoC users presented with deficits compared to controls and tobacco users for both the Switching and Switching Contrast variables. LoC users presented with deficits compared to controls on the Visual Scanning test.

There were no between-group effects on the Number Sequencing, Letter Sequencing, Motor Speed, or error measures for the three-group analysis or the four-group analysis.

The Visual Scanning subtest showed deficits in the LoC group when compared to the controls. This finding was supported by previous experiments finding deficits on visual scanning tasks by cannabis users who started using later in life (≥17 years; Ehrenreich et al., 1999). The data reported in this chapter did not support Ehrenreich et al's (1999) findings with regards to the EoC (≤16 years) as there were no significant differences between the EoC group and the remaining three groups in current experiment. It is likely that the deficits discovered on the Visual Scanning subtest were not due to the later age of onset, but rather due to the lifetime number of spliffs consumed which was slightly, albeit not significantly, higher in the LoC group (see Table 3.5). This interpretation is firstly due to the effect becoming non-significant after controlling for lifetime spliffs smoked and secondly due to the significant correlation between lifetime spliffs smoked and Visual Scanning performance (see Table 3.12). There was also a correlation between performance on the Visual Scanning subtest and the level of intoxication the user desires to reach. This could suggest that either greater cannabis use per session is associated with deficits in cognition, the binge hypothesis, or that a desire for greater levels of intoxication is a product of long term cannabis use which is the actual determinant of the deficits on this task. It is possible the discrepancies between the current study and Ehrenreich et al (1999) were due to the abstinence period, while

the current study enforced a 24 hours abstinence period to minimise the likelihood of acute intoxication or hangover effects, Ehrenreich et al's abstinence period was two hours to one week. If a larger proportion of these recent cannabis users, around the two hour abstinence mark, were in the EoC group then this could have led to the early onset related deficits in visual scanning. Pope et al (2003) used a more strict cannabis abstinence criteria of 28 days for their study. The authors administered one test of sustained visual attention to EoC (≤16 years), LoC (≥17 years) and controls, the Conners' Continuous Performance Test (CPT). The authors found no effect of cannabis use or the age of onset of cannabis use on this task in contrast to Ehrenreich et al (1999) and the current study. It could be that task differences led to these mixed results as the CPT involves searching for a target letter among letter distractors (i.e. representation maintained primarily in verbal working memory), while Ehrenreich et al's task involves searching for a target shape among spatial distractors (i.e. representation maintained primarily in spatial working memory), and the current task involves search for a letter among letter distractors, yet does not involve sustained attention as the task lasts for relatively little time (<60 seconds) compared to the CPT (14 minutes).

The Letter Sequencing, Number Sequencing and Motor Speed tests form part of the supplementary material primarily for determining if participants have a fundamental deficit, such as an inaccurate knowledge of the English alphabet or impaired motor speed. Medina et al (2007) found a general effect of cannabis on the combined Letter Sequencing and Number Sequencing score which was interpreted as a motor speed deficit. In contrast the three-group and four-group data did not replicate these findings. As no other tests measuring motor speed or graphomotor speed have been administered to cannabis users in an age of onset analysis, this chapter presents the first evidence that suggests these processes are not associated with the age of onset of cannabis use.

The primary executive function dependent variable, Switching, showed between group differences. Post-hoc tests revealed that the EoC users presented with deficits on this variable when compared to both the control group and the tobacco using group. The LoC group performed at a level comparable with tobacco users and controls on this task, therefore supporting the experimental hypothesis that the EoC users would be more vulnerable to cognitive impairments than the LoC users. The associated dependent variable, TMT Switching Contrast, also showed between group differences. Post-hoc

testing revealed that the EoC group showed deficits in performance when compared to the control group, the tobacco group and the LoC group. This test provided the strongest support for the experimental hypothesis within the current experiment. While previous studies have used various versions of the TMT with cannabis users, only one study has used the TMT with an age of onset analysis (Gruber et al., 2011). The authors found that performance was not impaired in either the EoC or LoC users. These discrepant results are possibly attributable to the version of the TMT used, the current study used the D-KEFS version while Gruber et al (2011) used the Trails B version (Lezak, 2004). It is unlikely that the differences were attributable to the drug use behaviours of the respective samples as both studies used the same age of onset criteria for EoC users ($\leq$15 years) and LoC users ($\geq$16 years). Furthermore, Gruber et al's (2011) study reported longer periods of cannabis use than the current study by a factor of approximately 1.5 which suggests that if a dose-related response was also present, then Gruber et al's sample would be expected to present with deficits. While the TMT Switching data contradicts that of Gruber et al's study, the deficits of EoC users relative to controls, tobacco users and LoC users on the TMT Switching Contrast data is the first of its kind and therefore cannot be directly compared to previous research. These findings suggest that early onset cannabis use is associated with deficits in set switching abilities and the contrast test suggests that it is unlikely that a contributory factor such as motor speed or semantic memory was explaining these deficits. However, when considering the TMT error scores which showed no differences between groups it appears that the deficits in set switching are not so severe that participants are locked in one particular set, but rather that cannabis use is linked with an increased amount of time to successfully switch between sets.

3.4.2.2. The Verbal Fluency Test (VFT)

Six outcome measures from the VFT were used in the current experiment including Letter Fluency, Category Fluency, Switching, Switching contrast, the percentage of repetition errors and the percentage of set loss errors. There were no between group effects on any of these variables for the three-group analysis or the four-group analysis.

The present experiment found no between group differences on VFT Letter Fluency and thus supports one previous study which showed no effect of age of onset on letter fluency as determined by a similar FAS test (Pope et al., 2003). Despite this evidence,

one study did not find any between group differences on an FAS test with a general cannabis group, yet upon splitting by age of onset, the EoC group appeared to present with deficits relative to the LoC group (Gruber et al., 2011). The EoC users in Gruber et al's (2011) study produced significantly fewer words in the time limit than did the LoC group, yet there were no significant differences between the EoC and the control group. Gruber et al (2011) and Pope et al (2003) used the same version of the FAS test and thus it remains unclear why this discrepancy occurred. The present study also found no effect of the age of onset of cannabis use on the VFT Category Fluency test. In reverse of the results reported above, Pope et al (2003) found that EoC users were impaired relative to controls on a semantic fluency test while Gruber et al (2011) found no differences on a semantic fluency test. While there are differences in group characteristics such as length of abstinence from cannabis which could explain differences in performance between these groups, this would not explain why one study found deficits in letter fluency but not semantic fluency (Gruber et al., 2011) while another found deficits in semantic fluency but not letter fluency (Pope et al., 2003). As both groups of authors administered the same test (the COWAT) these differences cannot be ascribed to test differences. Sample characteristics are the most likely explanation for these discrepancies although it is not clear what these characteristics are and how they differentially affected performance on the two fluency tests.

The use of the VFT Switching task and the VFT Switching Contrast measure are both novel tasks with regards to cannabis users and the present experiment suggests that performance is unaffected by the age of onset of cannabis use. As with the DFT and TMT, the VFT uses a switching paradigm between two different rules on the same task yet unlike these other tests the VFT failed to detect impairments on the switching contrast measure. This suggests a disassociation between the visual switching tasks and the verbal switching task although it is not clear whether it is this distinction in modality which explains the different performance between tasks. Further research needs to replicate this measure on cannabis users to determine whether the processes this task draws upon are unaffected by the age of onset of cannabis use and by cannabis use in general. Furthermore, there were no between group effects for the VFT percentage of set loss errors suggesting that the age of onset of cannabis use is not associated with cognitive flexibility within the verbal domain while the lack of between group effects

for the VFT percentage of repetition errors suggests no severe verbal working memory impairments (Delis et al., 2001).

3.4.2.3. The Design Fluency Test (DFT)

Six outcome measures of the DFT were used in the current experiment including Filled Dots, Empty Dots, Switching, Switching Contrast, repetition errors, and set loss errors. The cannabis group presented with deficits on the DFT Switching task relative to the control group and presented with deficits on the DFT Switching Contrast measure relative to the control group and the tobacco group. After dividing the cannabis group, both the EoC users and LoC users displayed deficits relative to the control group. There were no between group effects for the remainder of the dependent variables.

The two primary executive function tests from the DFT, the Switching and Switching Contrast tests, both showed between group differences. Follow-up tests showed that the EoC and LoC groups presented with impairments relative to the controls on both of these two tasks. Further examination of the effect sizes suggests that the deficits across both tasks were approximately equal suggesting that there was not an age of onset effect but just a general effect of cannabis use impairing set switching in the visual domain. Further examination of the correlational data suggests that DFT Switching performance was negatively related to the number of years an individual has smoked cannabis for but not the age of onset or other cannabis use variables. When considering the lack of between group differences for the two error scores, it appears that the deficits discovered on the DFT Switching and DFT Switching Contrast tests were not due to memory impairments or perseveration. As with the TMT data it appears that the performance on these tasks describes a difficulty in switching sets manifested in a longer time to complete the switch. This is not the first evidence that the age of onset of cannabis use is associated with performance on set switching tasks however it is the first evidence of this kind derived through the use of the DFT. These deficits by both cannabis using groups only appeared relative to control group and not relative to the tobacco group. As the control group did not differ from the tobacco group on the DFT it unlikely that tobacco use is what was mediating these deficits. Furthermore, the tobacco group did differ from the whole cannabis group, possibly suggesting that the lack of between group differences between the tobacco group and the EoC/LoC users was due to a lack of power associated with the cannabis group division.

While the primary subtests of the DFT uncovered impairments, the supplementary subtests: Filled and Empty Dots, did not highlight group differences. This is the first use of a non-verbal fluency task which purportedly measures non-verbal creativity, visual attention, and initiation (Delis et al., 2001; Suchy et al., 2010). It appears that these two subtests are unrelated to cannabis use.

3.4.2.4. The Grooved Pegboard (GPT)

Six outcome measures from the GPT were used in the current experiment which included the Place task, the Remove task, and the Contrast measure (Contrast = Place time - Remove time). The two tasks were first completed with the Dominant Hand (DH) and then with the Non-Dominant Hand (NDH). The cannabis group presented with deficits compared to the tobacco group on the GPT DH Contrast Measure, while the control group presented with deficits compared to the tobacco group on the GPT DH Contrast Measure. There was a trend towards group differences on the GPT DH Place task (p=.054) and thus it is unclear if this represents chance variations in performance across groups or an underpowered analysis hiding true effects. There were no between group effects on any task with the non-dominant hand or the Remove task with either hand. The four-group analysis found that the previously determined deficits on the GPT DH Contrast Measure were largely due to early onset cannabis use, as only the EoC group displayed deficits relative to the tobacco users, while the LoC did not differ from any group.

Bolla et al (2002) found a positive relationship between time taken to complete the GPT Place task and the weekly number of joints smoked which demonstrated a dose-related response. The present study partially supports these previous findings as the cannabis users showed a trend towards impairments relative to tobacco users. In contrast, Becker et al (2014) found that cannabis use was unrelated GPT Place task performance. As Becker et al.'s study recruited cannabis users with an age of onset below 17, a potentially high risk group for developing cognitive and motor impairments, it is not clear why none were detected. With limited research and conflicting results regarding this particular aspect of motor control performance it is unclear as to whether cannabis leads to impaired performance on the GPT Place task.

As remove task performance was not associated with cannabis use or the age of onset of cannabis use it appears that motor speed is not affected by cannabis use. This supports the findings from the TMT in which there was not an effect of cannabis use or the age of onset of cannabis use on the Motor Speed subtest (see Section 3.4.2.2). This contradicts Medina et al's (2007) findings that motor speed was affected by use of the TMT composite score for Number and Letter Sequencing. Becker et al (2014) found that finger tapping test was not impaired in cannabis users and this test arguably a purer measure of motor speed than Medina et al's measure as it does not require visual scanning or semantic memory. The current findings therefore support Becker et al (2014) that basic motor speed is unaffected by cannabis use.

The third outcome measure from the GPT is a novel modification proposed and described for the first time within this research programme. Each individual's Remove task time was subtracted from their Place task time to provide a Contrast Measure with the aim of minimising the contribution of motor speed on the Place task and provide a purer measure of the speculated cognitive component. Cannabis users in the three-group analysis, and EoC users in the four-group analysis, showed significantly higher scores on this Contrast Measure than the tobacco group suggesting a reduction in cognitive efficiency. There was no difference between cannabis users and non-smoking controls, yet the tobacco group outperformed the control group on this task. These findings suggest that tobacco use improves motor functioning while cannabis use impairs it. As the cannabis using group also showed high levels of tobacco use, it is feasible that this tobacco use ameliorated the effects of the cannabis which lead to an equilibrium in task performance, resulting in a lack of observable differences in performance between cannabis users and non-smoking controls. These deficits become apparent however, when comparing cannabis users with tobacco users, and when comparing tobacco users with non-smoking controls. A mechanism for this interpretation is that cannabis users and tobacco users were both presenting with temporarily elevated motor control due to the acute effects of tobacco use. Self-reports show that 17 of the 27 tobacco users and 17 of the 32 cannabis users used tobacco on the day of testing. It is possible that the consumption of tobacco acutely elevated performance on the GPT DH Contrast Measure which explains how tobacco users outperformed controls, how tobacco users outperformed cannabis and how no difference was uncovered between cannabis users and controls. A meta-analysis by Heishman, Kleykamp and Singleton (2010) found that

fine motor control was improved following acute tobacco administration on a range of motor tasks including the GPT supporting the acute-tobacco interpretation of the current data. If future research gathered more specific information about recent tobacco use such as the amount of hours since the last smoke or even included recent tobacco use as an exclusion criteria then this confounding variable could be removed.

The deficits discovered on the DH tasks were not re-discovered on the NDH tasks in the current study. This could be due to practice related ceiling effects occurring following the first two attempts with the dominant hand. This would entail that the groups, or specific individuals within those groups, with impaired performance improved at a faster rate than those whose performance was not relatively impaired. Conversely, Bolla et al (2002) found that non-dominant hand performance was that which was negatively affected by cannabis use which would suggest that cannabis use does not unilaterally impair motor control as different studies have now found impairments in the dominant and non-dominant hands. The authors do not mention if the dominant hand was tested and so practice effects in Bolla et al's (2002) study cannot be concluded. In contrast, Becker et al (2014) found that neither DH nor NDH place tasks were impaired by cannabis use. These three studies, including the current one, produce three conflicting accounts of how cannabis is related to GPT performance and therefore more research is needed.

3.4.2.5. The Symbol Search Test (SST)

Two outcome measures from the SST were used in the current experiment which were the age-scaled score from the number of correct responses, otherwise referred to as SST Scaled Score, and the number of errors made on this test. Unlike the three D-KEFS tests the error score used here is not age scaled and is just the number of errors committed. There were no between group differences on this variable for the three-group analysis or the four-group analysis.

This subtest from the WAIS-IV is a measure of visual processing speed, a task which requires the identification of a target abstract symbol among several non-target symbols. The present results suggest that the speed at which individuals discriminate and identify symbols is unaffected by chronic cannabis use. The present study did however discover cannabis related deficits on a measure of visual scanning which required visual

processing (see section 3.4.2.2.). The Visual Scanning subtest from the TMT required the seeking of the target symbol (the number '3') and the discrimination between these target symbols and non-target symbols (other numbers and letters). As discussed, the finding from the SST suggests that any deficits discovered on the Visual Scanning task were not related to the identification and processing of the visual stimulus.

3.4.2.6. The Iowa Gambling Task (IGT)

One outcome measure from the IGT was used in the current experiment which was the percentage of advantageous deck selections. There were no between-group effects on this variable for the three-group analysis or the four-group analysis.

In contrast to the current results, evidence of cognitive damage has been discovered by a number of previous administrations of the IGT to cannabis users and controls (Whitlow et al., 2004; Bolla et al., 2005; Fridberg et al., 2006; Verdejo-Garcia et al., 2007) which all found that cannabis use lead to impaired decision making. This is the first known study to study the age of onset of cannabis and there appeared to be no risk of early or late onset cannabis use on IGT performance.

One of the possible explanations for this deviation from consensus is down to the procedure employed within the present experiment. In order to test for physiological markers which influence decision making within the current sample, previously shown to be absent in patients with VMPFC damage (Bechara et al., 2005), the participants were attached to the Q-sensor, a portable device for measuring skin conductance responses. In concordance with the IGT administration procedure for physiological measurements, the intervals between each stimulus of the task were increased from 500ms to 4000ms and thus encouraging a greater amount of deliberation between each decision. In the short time period (500ms) traditionally used with the IGT participants may have to rely more on an impulsive system while over the longer time period (4000ms) participants may have more time to draw on resources from a reflective system (Bechara et al., 2005). To test if cannabis use leads to an impaired impulsive system while an intact reflective system, future research could involve two groups of cannabis users; each randomly assigned to an IGT with either a short inter-stimulus break or a longer inter-stimulus break.

A second explanation for the deviation from consensus is the amount of cannabis consumed by the different samples. As determined by either estimated lifetime cannabis use or years of cannabis use, the present study included a "lighter" cannabis using group when compared to these previous studies (Whitlow et al., 2004; Bolla et al., 2005; Fridberg et al., 2006; Verdejo-Garcia et al., 2007).

3.4.3. Putative Confound Data

The current sample over both analyses were matched for a large number of potential confounding variables including FSIQ, individual IQ subtests, depression, anxiety, compulsions, obsessions, sex, years of education, and educational achievement. Furthermore, where suitable these variables were included in ANCOVA analyses to control for any effects these variables may have had. The pattern of data suggests that the differences in cognitive performance were not due to any of these variables.

Other than cannabis use variables, the only putatively confounding variables which differed across the levels of the independent variables were age, alcohol use, tobacco use, and illegal drug use. Examination of correlation matrices between these confounding variables and the cognitive dependent variables in which cannabis-related deficits were discovered, suggested that only other drug use was correlated with a cognitive deficit. However, it is unlikely that other drug use was explaining these deficits as the level of drug use was negligible relative to the amount of cannabis use consumed by the group, and the relationship between other drug use and TMT visual scanning disappeared after controlling for cannabis use. This suggests that 'heavier' cannabis users are more likely to have used other drugs and it is their cannabis use, not their drug use, which is explaining the deficits in performance.

While it is possible that confounding variables not tested in the current study are mediating the relationships between cannabis use and cognition, the current data suggests that none of the 12 potentially confounding variables tested in the current study were mediating the deficits.

3.4.4. Strengths and Limitations

One of the primary limitations with the present experiment is the sex ratio. Although an equal sex ratio was achieved for the cannabis using group, there was an imbalance in

sex ratio for both the control and tobacco smoking groups with a greater amount of females taking part. Although these differences were not significant between groups the non-uniformity potentially biases the findings as sex differences have been found on a number of tasks used in the current neuropsychology battery (e.g. Bolla et al., 2002; Bryden & Roy, 2005). However, the current study only discovered performance related sex differences on two of the dependent variables and after controlling for these sex effects the main effect did not change. This suggests that although there were not identical sex ratios across groups, this confounding variable was not explaining the differences in group performance.

The severity and domain of cognitive impairments appears to be related to the stage of abstinence (Crean et al., 2010). The presence of such deficits is partially dependent on whether the individual is acutely intoxicated (0-6 hours), suffering residual effects (7 hours - 20 days) or has achieved a long period of abstinence (21 days +). The present study used a self-report assessment to determine the most recent incident of cannabis use and the cannabis use group ranged from 48 hours to 6 years suggesting that the present study includes a mixture of residual and long-term effects. Crean et al (2010) described residual effects as any effects of cannabis present between 7 hours and 20 days of abstinence, yet it is not clear how they came to this criterion. The current study puts an emphasis on a 'hangover' period, in which cognitive deficits may appear due to the intoxication the previous day. The hangover effects could be due to the lingering influence of cannabinoids within the bloodstream or through an indirect route including altered sleep patterns. The present experiment included a minimum period of 24 hour abstinence as hangover effects appear to not persist after 24 hours of abstinence (Pope, Gruber & Yurgellun-Todd, 1995). A potential limitation of the present study is that only self-report was used to ascertain the last use of cannabis whereas other experiments have included the analysis of urine samples to determine recent use (e.g. Pope et al., 2003). Furthermore, it is not clear if the deficits which were discovered represent a short term impairment or long lasting damage.

3.4.5. Future Directions

The current analysis discovered deficits by the EoC and LoC group which were related to visual scanning, set switching, and visuo-motor coordination processes. In addition to this, the set switching tasks in which deficits were uncovered all require some level of

visual processing, while the verbal set switching task which did not require such visual processes, failed to uncover deficits in the cannabis using groups. Due to this fact, it remains possible that a deficit relating to visual attention/scanning is mediating these deficits. As executive function tasks tend to recruit multiple processes and are typically not process pure, future research needs to clarify if performance decrements on a given task are a product of all contributory processes or rather reflecting a specific impairment. Within the context of the current experiment it needs to be determined whether deficits on set switching tasks are related to task set reconfiguration, visual attention, task set inhibition, the manipulation and maintenance of the task multiple sets within working memory or a non-executive process such as motor speed.

A different direction with future research concerns the outcome for the IGT. As noted earlier in Section 3.4.2.7 the current study did not replicate previously detected impairments on the IGT and a possible explanation for this is the time between stimuli presentations. Exploring the role of impulsive and reflective decision making processes by manipulating the inter-stimulus time period experimentally would provide further information into why cannabis users perform worse than controls on this task.

This was the first study to highlight the role of chronic cannabis intoxication levels and the effects that this has on cognition. The results showed that high levels of desired intoxication were associated with performance deficits on a measure of visual scanning. A method for examining this phenomenon further would be to recruit a group of cannabis users and divide them into those who aim to regularly achieve 'high' levels of intoxication with those who aim to achieve 'low' levels of intoxication, whilst matching the groups for cannabis use. In order to see if this suggestion receives further merit, a further correlational approach should be conducted to see if the findings replicate those within the current study. If the findings are replicated then the concept of 'cannabis bingeing' would be worth further exploration. This replication would help reduce the possibility that the correlation represents a type I error.

3.4.6. Conclusion

If the data presented from the current study are interpreted as being a result of cannabis use then this needs to be considered in light of the abstinence criteria. Studies with very low abstinence (from cannabis) timeframes (e.g. 4h>; Ehrenreich et al., 1999) would

have trouble attributing the deficits discovered in cognition to the acute, hangover, withdrawal or long term effects of cannabis use. Similarly, studies with slightly longer abstinence timeframes (e.g. 12h>; Gruber et al., 2011) would have trouble attributing the deficits discovered in cognition to hangover, withdrawal or long term effects of cannabis use. While certain studies employed a 28 day abstinence timeframe to ensure that any deficits discovered were due to the long term effects of cannabis (e.g. Pope et al., 2003) the current study only utilised a 24 hour abstinence timeframe. This means that if the deficits discovered in cognition in the current study are considered a product of cannabis use then they could be attributable to either withdrawal effects which last for around two-to-three weeks (Budney et al., 2003) or due to the long term effects of cannabis.

In summation, the results show that the groups differ in performance on several neuropsychological tasks and that these overall differences are explained by cannabis related impairments on tasks which involve visual scanning, set switching and visuo-motor coordination. It also appears that early onset cannabis use was mediating some but not all of the deficits found in the whole cannabis group. It appears unlikely that these deficits were mediated by group differences in the 12 confounding variables and therefore it is suggested that cannabis acts directly to impair these neurocognitive processes, although a reverse causation explanation is also possible. While it is not clear if these findings can be attributed to long-term or temporary alterations in cognition, the current findings do support previous research (Gruber et al., 2011; Fontes et al., 2011) which suggests that early onset cannabis use is associated with greater cognitive deficits than late onset use.

Chapter Four. Visual Search deficits in abstinent cannabis users: an eye-tracking approach

4.1. Introduction

This chapter describes a quasi-experiment which follows on from the conclusions reached in the neuropsychological study (Chapter Three). Namely, this study aimed to investigate whether cannabis related deficits previously found on tasks which measure both visual search and set switching are attributable to one, both or neither of these processes. This study involves a new sample of participants, the use of an eye-tracker, and two computerised tasks to test these hypotheses.

4.1.1. Visual Search Behaviours

The utility of visually searching is observed in many activities which are essential to day-to-day life. This is seen in behaviours such as driving, in which visual searching is critical for hazard avoidance and is found to be improved in more experienced drivers (Underwood, Chapman, Bowden & Crundall, 2002).

An early development in the field of visual search research was the discovery that a fixation location; a point at which gaze briefly stops, is dependent on the amount of information which can be derived from a specific area in a scene (Mackworth & Morandi, 1967). The authors suggested that eyes do not just search, they search intelligently. It appears that this intelligent eye searching can occur in the form of 'exploratory searching'; in which non-motivated searching occurs with information from the scene dictating the subsequent gaze patterns (i.e. bottom-up decisions; Janiszewski, 1998). It can also occur in the form of goal-directed searching in which motivated search strategies are activated in order to locate a specific piece of information in the visual scene (i.e. top-down decisions). These two search forms will occur in tandem as scene information will influence search strategies (Mackworth & Morandi, 1967) and prior knowledge will influence the extent to which information is gathered from the visual scene (Brucks, 1985).

Another key development in the field was Feature Integration Theory, which suggested that features of the visual scene (e.g. colour, contours etc.) are processed individually

and pre-attentively, i.e. in parallel (Treisman & Gelade, 1980). Conversely, Feature Integration Theory suggests that conjunction searches involve a serial search pattern, the goal-directed movement of visual attention across the scene until the target is located. A typical conjunction search is one which involves more than one feature, i.e. searching for a red triangle among red circles, green triangles, and green circles. Evidence appears to suggest that while serial and parallel processes are dissociable, there is not a clear dichotomy between these two processes which deviates from early accounts of Feature Integration Theory (Maioli et al., 2001). In feature searches the parallel system may explain how objects are quickly detected independent of the number of distractors (Treisman & Souther, 1985), however in conjunction searches it is likely that a combination of parallel and serial search systems are working together (Maioli et al., 2001).

There are a number of factors which determine where a visual search task is located on the serial-parallel continuum, and these same factors therefore influence how the task recruits visual attention and a focussed, goal-directed search. Feature searches which recruit a parallel system typically involve a target with one *extra* feature (e.g. target: Q, distractor: O) however searches in which involve one *less* feature, encourage a more serial-like strategy (e.g. target: O, distractor: Q; Treisman & Souther, 1985). Conjunctions (combinations of multiple features) typically encourage the recruitment of a search strategy nearer the serial end of the serial-parallel continuum (Maioli et al., 2001; Treisman, 1982). An additional method for increasing search difficulty and inducing a serial strategy involves stimulus similarity. Maximising the visual similarity between target and distractor stimuli while minimising the visual similarity between different distractors both aid in achieving this goal (Duncan & Humphreys, 1989). Increasing the set size (number of stimuli per trial) will increase the difficulty during a serial search task, yet will have little influence on search difficulty if a solely parallel search process is recruited (Maioli et al., 2001; Nakayama & Martini, 2011).

The process of serially searching a visual field can be thought of as the moving of a spotlight of visual attention across the stimulus array. This spotlight can be increased or decreased in size depending on task demands, referred to as the zoom-lens model (Eriksen & James, 1986). Typically, the acuity will depend on the size of the spotlight and this has been broken down into the 2° area of maximum acuity within the foveal

focus. When extended out to 5° there is reduced acuity (the parafoveal area) and then beyond this area there is even more degraded acuity (the peripheral area; Rayner, 1998). This spotlight, while linked to eye movements, is not synonymous with it. It is possible for a covert shift in visual attention to occur without a corresponding eye movement (Carusco, 2011; Nakayama & Martini, 2011; Posner, 1980).

The preparation stage of visual search, in which the target stimuli is identified and maintained prior to searching, typically recruits areas of the visual cortex and prefrontal cortex (Eimer, 2014). Once the search is initiated parallel search processes provide information about the whole visual scene by recruiting widespread occipital and parietal regions (Eimer, 2014; Leonards, Sunnaert, van Hecke & Orman, 2000). Visual processing resources are then allocated to a particular location within the search array of visual field, a process largely mediated by Frontal Eye Field (FEF) and parietal activity (Armstrong, Chang, & Moore, 2009; Eimer, 2014; Noudoost, Chang, Steinmetz, & Moore, 2010) two regions dense with CB_1 receptors (Eggan & Lewis, 2007). Visual cortical signals are mediated - to a degree - by dopamine and associated D_1 receptors within the FEF, which suggests that visual search and attentionally guided behaviours are mediated by dopamine (Noudoost & Moore, 2011). The identification and selection of a stimulus which matches the target representation maintained in working memory occurs last, potentially recruiting multiple occipital regions and subcortical nuclei including the pulvinar and thalamic reticular nucleus (Bundeson, Habekost & Kyllingsbæk, 2011; Eimer, 2014). Although there is temporal and functional evidence arguing for a dissociation of these four stages: preparation, guidance (parallel processing), serial processing, and selection, these stages largely recruit overlapping brain networks (Eimer, 2014).

Within visual search tasks there are a number of variables which describe different processes. The fixation count per trial is a good measure of strategic search efficiency; more efficient strategies will involve fewer fixations before locating the target or discovering that there is no target (Najemnik & Geisler, 2005). Related to this is the concept of *inhibition of return* in which the gaze direction tends to have a preference for novel areas of the visual field (Najemnik & Geisler, 2005). The number of revisits to a previously visited area could be indicative of the competencies of a temporary spatial memory store (Gilchrist & Harvey, 2000) such as visuo-spatial working memory

(Baddeley & Hitch, 1974). The fixation duration refers to the amount of time spent between saccades. During this period a number of processes occur including extraction and visual processing of the information within the foveal focus, the peripheral scanning of neighbouring stimuli, the planning of the next saccade, and the initiation of the saccade (Hooge & Erkelens, 1996; Radach & Heller, 2000; Rayner, 2009; Salthouse & Ellis, 1980).

4.1.2. Cannabis and Visual Search Tasks

Two studies have used the same task to assess the effects of cannabis on visual search performance (Ehrenreich et al., 1999; Huestegge et al., 2002). The task consisted of 100 trials, each containing 25 square stimuli. For each individual square stimulus, one of the four sides was missing, resulting in four possible stimuli randomised across each trial. The participant was asked to respond on each trial when they detected the presence or absence of the square stimuli with the top side missing. The earlier study administered the visual scanning task to controls, early onset cannabis users ($\leq$16 years old) and late onset cannabis users ($\geq$17 years old) and found that the early onset group had slower reaction times on this task than both controls and the late onset users for both target and non-target trials (Ehrenreich et al., 1999). A limitation of this study is that the abstinence period was reported at two hours to one week, suggesting a mix of acute and residual effects of cannabis on task performance. Huestegge et al (2002) by contrast, enforced a 16 hour minimum abstinence to ensure that it was only the residual effects which were being tested. This study recruited only one group of cannabis users, therefore not examining the age of onset, and a group of controls and found that the cannabis group were slower to respond on both target and non-target trials (Huestegge et al., 2002).

Huestegge et al (2002) used an eye-tracking device while administering the task. This allowed the authors to deconstruct the processes involved in task completion and to detect where the deficits were located. The eye-tracking data showed that fixation durations did not differ between groups, yet the cannabis group produced a greater number of fixations per trial before determining the presence or absence of the target. In addition to these findings, cannabis users also returned to previously inspected areas more than controls. Further investigation using a scan path analysis suggested this is because the cannabis users tended to follow the experimenter's instructions and perform

a 'reading like' search of the trial, while controls opted for a more holistic strategy in defiance of the same instructions. Overall it appears that the reaction time differences between cannabis users and controls can be at least partially attributed to an inefficient search strategy evidenced by more fixations and more re-inspections. However, the former could also be attributable to the cannabis users being more obedient and following the experimenter's instructions, while the latter could also be attributable to inefficient visual working memory, as suggested by the authors.

While the findings reported by Huestegge et al (2002) can be attributed to the residual effects of cannabis (abstinence: 16 - 40 hours), the findings by Ehrenreich et al (1999) need to be treated with caution (abstinence: 2 hours - 1 week) as the shortest abstinence period reflects intoxication. However, these studies provided some early evidence suggesting visual search behaviours are impaired in cannabis users compared to controls.

In a longitudinal study of cannabis abstinence, Hanson et al (2010) administered a number of cognitive assessments including Ruff 2 & 7 (Ruff & Allen, 1996). This test involves searching for target stimuli (i.e. 2 and 7) among numerical distractors for a serial task and then again among alphabetical distractors for a more parallel task. Although other tasks were administered, this was the only task which remained impaired in cannabis users at the end of the study. The test was administered over three occasions and on the last test, at three weeks of abstinence, cannabis users were still impaired on the accuracy score (number of errors) yet not the speed of processing score, suggesting that visual search accuracy is impaired due to chronic cannabis use. There appeared to be practice effects for both groups, but despite the improvements the cannabis users still had lower accuracy scores than controls.

In the neuropsychological study of the current thesis, a D-KEFS Trail Making Test subtest, Visual Scanning, was administered to controls and cannabis users. The findings of this study partially replicated the earlier work (Ehrenriech et al., 1999; Huestegge et al., 2002) however with a different format. The Visual Scanning test involved the search for a target symbol '3', among an alphanumeric array. This differs from the earlier task in that the target can be coded verbally, as opposed to the earlier studies which used a visuo-spatial target stimulus (i.e. a square). Furthermore, the earlier studies used a structured array while the D-KEFS task was an unstructured array of numbers and

letters. Despite these differences cannabis users also showed impairments on this visual search task relative to controls, however when the cannabis group was divided in two - only the late group presented with impairments. This is contrary to the findings reported by Ehrenreich et al (1999) who found the early onset users were the ones with impaired performance, while using the same early/late onset criteria. As discussed in Chapter Three, these deficits by the late onset group are unlikely to be due to a later age of onset, but rather reflect other group characteristics. The use of an eye-tracking device in a comparable task format to the D-KEFS Visual Scanning Test would allow the exploration of how cannabis users are impaired on the task. By breaking down the task into fixation durations, fixation count and revisit count, a clearer picture could emerge as to how cannabinoids affect the processes involved in motivated searching behaviours.

4.1.3. Set Switching Behaviours

An early account of set switching was introduced into the Working Memory model (Baddeley & Hitch, 1974) in a later amendment of the model (Baddeley, 1998), as a function of the central executive. The description at this stage included switching between strategies on a task and attending to one stimulus while inhibiting another. Set switching, or one its related constructs (e.g. attentional shifting), have since been ubiquitous in subsequent accounts of executive function (e.g. Anderson et al., 2001; Banich, 2009; Delis et al., 2001; Powell et al., 2004).

Following on from the inclusion of set switching as a central executive process (Baddeley, 1998) it has been determined that working memory is a key contributor to performance on many commonly used assessments of set switching. On the Trail Making Test (TMT) verbal working memory representations and maintained and updated, as the target symbol switches back and forth through number and letters (Delis et al., 2001). Construct validity testing has confirmed the role of working memory in the TMT (Sánchez-Cubillo et al., 2009) by the use of correlation and regression analyses. Inhibition has also been implicated in set switching tasks using similar methods (Langenecker et al., 2007; Sánchez-Cubillo et al., 2009) and by the use of an n-2 paradigm. The n-2 paradigm involves a switching task in which a switching between two tasks (A-B-A) leads to greater switch costs than switching between three tasks (A-B-C; Mayr & Keele, 2000). This is suggestive of a residual inhibitory effect on a

process which has previously been disengaged, a phenomenon dubbed *backward inhibition*.

The presentation modality also plays a clear role in the completion of a task. The set switching conditions of visual based tasks such as the D-KEFS TMT and the D-KEFS Design Fluency Test (DFT) both require visual scanning and visual attention resources (Delis et al., 2001; Sánchez-Cubillo et al., 2009; Suchy et al., 2010). In comparison, the set switching condition of the D-KEFS Verbal Fluency Test (VFT) recruits declarative memory and working memory resources, in addition to the central process of set switching (Delis et al., 2001). It is unlikely though that visual attention would contribute any unique variance to purely verbal test such as the VFT and therefore it appears that it is the visual processes which primarily differentiate the two categories of tests. This role of visual attention in the TMT, in addition to working memory and inhibitory processes (Delis et al., 2001) can make it difficult to determine which process(es) are impaired when a particular population shows impairments on the task.

4.1.4. Cannabis and Set Switching

The association between chronic cannabis use and set switching deficits remains unclear. The TMT is a commonly used test of this construct, although different versions are often used (e.g. Medina et al., 2007; Gruber et al., 2011) which differ in the spatial density and arrangement of the stimuli and therefore the results cannot be completely comparable. It is for these reasons that the differences between tasks are most likely due to differing degrees of difficulty rather than the recruitment of different cognitive processes. These differences in versions perhaps explain why the D-KEFS version of the TMT (Delis et al., 2001) uncovered impairments in a group of cannabis users (Medina et al., 2007) yet the Halstead-Reitan battery version (Reitan & Wolfson, 1985) did not uncover such impairments (Bolla et al., 2002; Gruber et al., 2011). Gruber et al (2011) did find a trend for impairments ($p<.10$) with the whole cannabis group, but after dividing the group into early and late onset users, the trend was not present for either group. Partially supporting the results of Medina et al (2007) and Gruber et al (2011); the analysis in neuropsychological study (Chapter Three) found a trend for impaired performance by cannabis users on the set switching component of the TMT (D-KEFS). When an age of onset analysis was conducted the Set Switching subtest and switching contrast conditions showed that early onset cannabis users were impaired relative to

controls, late onset users and tobacco users. This is in contrast to Gruber et al (2011) who did not find an effect of age of onset, however this could again be due to the version of the TMT used. This explanation is speculative however, as the differences between the versions have not been directly analysed.

Two other assessments of set switching derived from the D-KEFS battery (Delis et al., 2001) were administered in the neuropsychological study reported in Chapter Three. The first was from the VFT in which participants were asked to switch between semantic categories in a semantic fluency paradigm. The second was from the DFT in which participants had to switch between connecting filled or empty dots while creating novel patterns. The cannabis users were impaired on two assessments of set switching from the DFT, while not impaired on any measure from the VFT (Chapter Three). This pattern was upheld after conducting an age of onset analysis, in which early and late onset cannabis users were both impaired on the DFT, yet both groups performed comparably with controls on the VFT.

Data reported in the neuropsychological study suggested that cannabis users' set switching performance was impaired on tasks (TMT, DFT) which involved both motor speed (Schear & Sato, 1989; Delis et al., 2001) and visual attention (Delis et al., 2001; Suchy et al., 2010) in addition to the key set switching process. In contrast, the VFT, on which performance was not impaired in cannabis users, does not have a visual or motor component to it. Therefore it is possible that either motor speed or visual attention abnormalities were explaining the poorer task performance by cannabis users relative to controls. It is unlikely that motor deficits were explaining these deficits as two separate tests to assess motor speed were unaffected in cannabis users, however visual attention was impaired as assessed by the Visual Scanning component of the TMT. It could be that the higher order process, set switching, is intact in cannabis users, and it is visual attention problems which are leading to the task deficits. The two options are not mutually exclusive, due to the impaired performance on the Set Switching Contrast conditions from both the TMT and DFT, it is likely that set switching processes are also impaired.

To the current authors' knowledge, there is no research examining set switching tasks in cannabis users while using an eye-tracker. This is therefore the first study to use this approach.

4.1.5. Aims and Hypotheses

The principle aim of the current study was to extract the contribution of visual search and executive function processes to task completion by using an eye-tracking methodology to better elucidate the processes diminished by cannabis use. The present study utilised a computerised adaptation of the TMT, containing a more process pure visual search component followed by a visual search and set switching component.

Based on the data collected in the neuropsychological study, it was hypothesised that early onset cannabis users would be impaired on the set switching component of the computerised task while general cannabis users would show impairments on the visual search component. Furthermore, it was predicted that cannabis users would have more fixations per trial and greater revisits as measured by the eye-tracker, in accordance with previous research (Huestegge et al., 2002).

4.2. Method

4.2.1. Participants

The CannaForm was completed by 182 individuals recruited by opportunity and purposive sampling methods and this ended up in a total of 35 participants who took part in the experimental stage. Individuals were approached by the experimenter on a university campus or at a public location in a northern English city centre and asked to complete a lifestyle questionnaire. Additional cannabis users were recruited using snowball sampling and in liaison with a local cannabis activist group. The administrators of the activist group put out a notification asking individuals with a history of cannabis use and limited other drug use to contact the email address of the researcher if they were interested in taking part in psychological research. After contact by the potential participants, the experimenter sent an electronic version of the information sheet to the participant and awaited confirmation that they consented to take part (see Appendices A.4.1.1 and A.4.1.2). The demographic information of the participants can be seen in Table 4.2. One cannabis user who took part in the neuropsychological study also took part in this study, however the rest of the participants were new to this study.

Participants were excluded from the study if they met any of the following criteria: 1) brain trauma or history of neurological disease; 2) learning disabilities or genetic disorders which impact cognition; 3) non-native English speakers; 4) chronic alcohol use (>37 units per week); 5) alcohol use within the past 24 hours; 6) lifetime other drug use (>15 total uses); 7) any illegal drug use (other than cannabis) in the past week; 8) impaired vision. Inclusion criterion for the cannabis groups was at least 50 lifetime uses. Participants were asked to abstain from cannabis use for at least 24 hours before testing to ensure participants were not suffering from the acute intoxication or 'hangover' effects of cannabis. This was confirmed via questionnaire on the day of testing. These criteria were extended from the last study to include an assessment of vision due to the use of eye-tracking in the current study.

4.2.2. Design

The current study employed a quasi-experimental design in which participants were allocated to groups based on pre-existing criteria. The independent variable for the first analysis was labelled cannabis use and consisted of two levels: non-smoking controls, and cannabis users. The independent variable for the second analysis was labelled the age of onset of cannabis use and consisted of three levels: non-smoking controls, early onset cannabis users and late onset cannabis users. There were 22 Dependent Variables (DVs) which were the outcome measures derived from the two computerised tasks and the eye-tracking metrics. See Table 4.9 for the full list of dependent variables.

Separate analyses keeping the same IV were also conducted on IQ (DVs = full scale, verbal IQ, performance IQ) and mental health (DVs = anxiety, depression, obsessions, compulsions, motivation) to ascertain whether the groups were matched for intelligence and mental health estimates.

4.2.3. Materials

In order to assess whether an individual could be included into the study or needed to be excluded, the CannaForm was administered. To ensure participants task performance was unaffected by impaired vision, the visual spatial and object perception was assessed using the Visual Object Space Perception battery (VOSP; Warrington & James, 1991). If a participant failed one or more of the four VOSP subtests then they would be

retrospectively excluded from taking part, however no participants displayed impaired vision.

The Tobii T120 eye tracker was used to monitor gaze. As no suitable computerised version of the TMT exists and no other standardised test was available to investigate the hypotheses, two tasks were created for this experiment. The tasks created for use with the eye-tracker were the computerised analogue to the TMT Visual Scanning Task (hereinafter called Tobii VST) and the computerised analogue to the TMT Number/Letter Switching Test (hereinafter called Tobii SST). Both tasks involved the participant responding to the presence or absence of a target symbol in an array of alphanumeric distractors totalling 20 stimuli per trial (see Figure 4.1). Each trial was self-terminating and would only move on once the participant has responded. For the Tobii VST the target symbol was the letter 'F' and for the Tobii SST the target symbol alternated between the letter 'U' and the number '5' over consecutive trials.

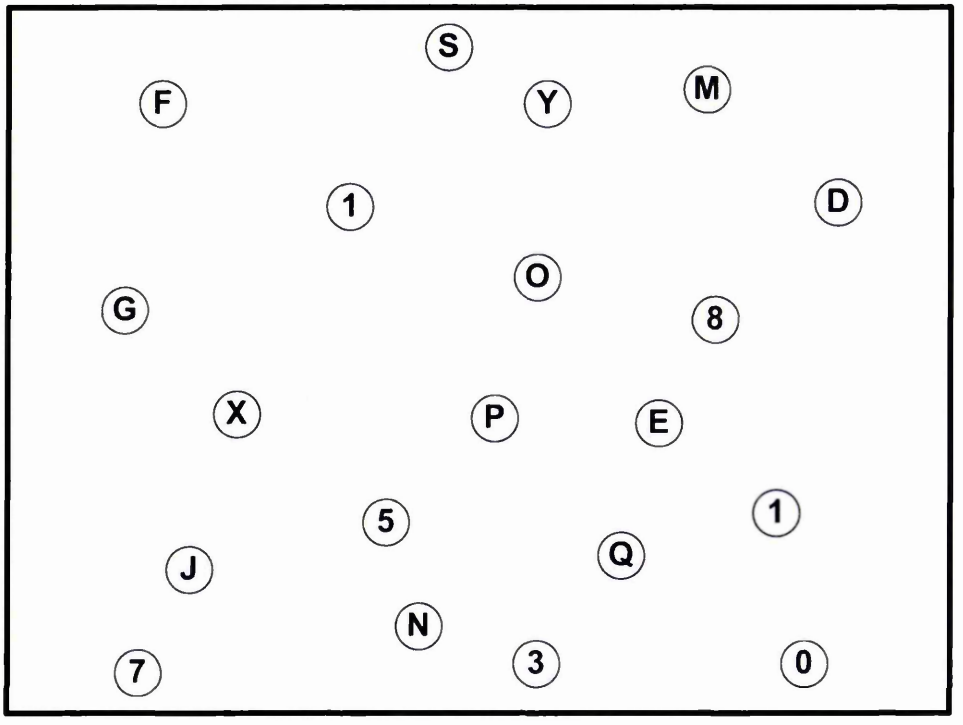


Figure 4.1. A sample target trial taken from the Tobii VST

To ensure high validity a systematic approach to task design was utilised for both tasks. For every aspect of the stimuli: the set number, the stimuli dimensions, the entire trial dimensions, the stimuli content (i.e. alphanumeric symbols), and the spatial density, a

predetermined criteria was selected. These criteria were that where possible the task would replicate the TMT Visual Scanning test, the task would replicate previous eye-tracking visual search tasks (i.e. Huestegge et al., 2002), or the task would be in accordance with theoretical accounts of visual search and visual attention (e.g. Najemnik & Geisler, 2005). This method ensured that similar cognitive processes to those recruited in the TMT Visual Scanning test would be recruited for this task and that a serial search strategy would be required. See the appendeces (Section A.2.2) for a more detailed account of the task construction.

For the Tobii SST there was an additional role of switching between two stimuli. From a face validity perspective there were some differences between the Tobii SST and the set switching task from the TMT. The Tobii SST involves switching between two symbols (i.e. U, 5, U, 5, etc), while the TMT version involves switching between two categories in which the symbols ascend through their respective categories (i.e. 1, A, 2, B, 3, C, etc.) The continuity of the switching symbol in the SST reduces the demand on working and long term memory resources during the task. To confirm face validity with a content validity approach described by Monsell (2003) the current analysis determined if there was a switch cost between the non-switch trials in the Tobii VST and the switch trials of the Tobii SST (see Section 4.3.6). This method confirmed that set switching processes were recruited by the Tobii SST. As both the Tobii VST and Tobii SST require response with a single button press while the TMT tasks involve a grapho-motor response format, the current tasks also reduce demands on the motor system.

During the Tobii VST the participants were instructed to press one button when they see a target symbol in the array and press a second button when they think the target symbol is not in the specific array. They were told to do this as fast as possible without making any errors. During the Tobii SST the participants were instructed that the rules had changed and now the target symbol would switch back and forth between trials. They were asked to press a button if they see target symbol (for that trial) in the array and press a second button when they think the target symbol is not in the specific array

In addition to the primary tasks, a number of other measures were administered to account for potential cofounding variables. The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was administered to test for anxiety and depression. The Clark-Beck Obsessive Compulsive Inventory (CBOCI; Clark & Beck, 2002) was

administered to test for obsessions and compulsions. The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) was administered to test for IQ estimates. In addition to these tasks used in the neuropsychological study, the Apathy Evaluation Scale (AES; Marin et al., 1991) was administered to test for motivation. The rationale for selecting these tasks can be found in the Methodology chapter.

Hair samples were also collected during this study and were kept in foil, sealed inside a plastic container.

4.2.4. Procedure

Following the recruitment process the participants were administered the CannaForm in one of three ways including self-report by the participants, face-to-face interview with the experimenter reading out the questions and over the phone interviews, with the experimenter reading out the questions. The method of administration was based on the particular recruitment strategy. Self-report and face- to-face interviews were selected when the individuals were approached in person by the experimenter. If the participant could complete the questionnaire at that point in time, an interview method was employed. If the participant had no free time or several participants were approached at once, then the self-report method was employed and the completed questionnaires were handed directly back to the researcher at an agreed time. The telephone interviews only took place when an individual responded to the notification put onto the local cannabis activist group's Facebook group or associated websites. Questionnaire debriefing occurred after the participants had completed this stage.

Those individuals who met the inclusion criteria and who did not violate the exclusion criteria were contacted and a time arranged for cognitive testing. The participant arrived at the eye-tracking laboratory and was given the information sheet for a second time to ensure they were happy to continue. The order of the tasks was counterbalanced by blocks (IQ test, mental health questionnaires, and eye-tracking tests). After the tests and questionnaires were administered a hair sample (approximately 100mg) was collected and placed in foil and sealed in a plastic container. Debriefing then took place. All data collected during the study was labelled with the participant's unique code to ensure anonymity and sealed in a locked cabinet.

4.2.5. Data Analysis

The present study collected data from two categories of outcome measures: behavioural data and eye-tracking data. For both types of data, target trials and non-target trials were analysed separately. Behavioural data included Reaction Times (RTs), number of errors, and the time taken to complete the whole task. The first stage in preparing the RT data was to remove the RTs for error trials as there is normally an additional process involved in the trial where an error has occurred - i.e. the reason the error occurred. The median reaction time across the correct trials was calculated for each participant and then subject to the normality protocol described in earlier chapters which included checking for outliers, skewness statistics, kurtosis statistics, histograms, and Shapiro-Wilks tests. Subsequent transformations were made when the normality protocol suggested a variable deviated from normality and winsorising methods were used when outliers greater than ±3 z-scores from the mean were detected. These transformation methods were the square root of X ($\sqrt{x}$), base 10 logarithm of X ($log10(x)$), inverse of X (x^{-1}), square of X (x^2) and cube of X (x^3). The number of errors and total time taken variables did not need to be converted into median scores as the total score was used for each of these two variables.

In order to determine fixation metrics the Area Of Interests (AOIs) for each stimuli needed to be created. As stated by Goldberg and Helfman (2010; p.2) when discussing the process of defining the AOIs, "there are no rules or best practice guidelines to aid this effort." As processing can occur - albeit at a degraded level of acuity - beyond the foveal focus, the amount of "padding" around each stimulus needs to be considered. Based on the empirically discovered foveal and parafoveal focus angle (i.e. Rayner, 1998), and by observing the amount of space around each stimulus (Goldberg & Helfman, 2010), AOIs were given 1.2cm "padding".

The number of unique fixations was calculated by using the median number of unique fixations per trial across all correct trials for each participant. The unique fixations were taken for target trials and non-target trials separately to conform to standard protocol (e.g. Huestegge et al., 2002). The number of revisits was calculated by subtracting the number of unique fixations from the sum of the fixations per trial. Instead of taking the median across all trials this value was kept as a sum total across the entire task as the number was too low for the median analysis and would therefore have yielded a floor

effect. It was considered to look at revisits for target trials and non-target trials however instead target stimuli and non-target stimuli were observed as it was thought this would be more informative for this metric. The fixation duration was also examined for target and distractor stimuli and was calculated by taking the median across every correct trial.

This process of the normality protocol and data treatment was conducted for both the Tobii VST and the Tobii SST. In order to control for salient confounds, a list of 12 variables (age, sex, years of education, GCSE grades, anxiety, depression, obsessions, compulsions, motivation, other drug use, weekly alcohol use, and tobacco use) were tested for the four ANCOVA assumptions described earlier in the thesis (independence of treatment and covariate effects, associations between the covariate and the dependent variable, the association must be linear, and there must be homogeneity of regression). If a variable could be controlled for it was analysed using the ANCOVA method. The remaining variables were analysed using *t*-tests and Mann Whitney U tests for the two group comparisons (controls vs. cannabis users) and analysed using ANOVAs and Kruskal-Wallis tests for the three group comparisons (controls vs. EoC users vs. LoC users) if data were parametric or non-parametric, respectively.

For demographic, drug use, mental health, and IQ data, the groups were compared with chi-square tests for categorical data, *t*-tests and Mann Whitney U tests for the two group comparisons (controls vs. cannabis users) and ANOVAs and Kruskal-Wallis tests for the three group comparisons (controls vs. EoC users vs. LoC users) if the data were parametric or non-parametric, respectively.

Table 4.1.

Between subject effects and descriptive statistics for the two-group demographic data.

Demographic Variable	**Control *n*=13**	**Cannabis users *n*=22**	***p*-value**	***Test statistic***	***Effect size***	***df***
Sex $^{\chi^2}$	4m	11m	.262	1.26	-	-
Age ^{MW}	19.00 (2.50) [18-26]	19.50 (3.50) [18-35]	.169	141.50	0.20	33
Nationality $^{\chi^2}$	13 BR	20 BR; 1 BG; 1 ZI	1.00	1.19	-	-
First Language	13 ENG	22 ENG	-			
Years of education ^{MW}	14.00 (1.00) [13-18]	14.00 (1.50) [10-17]	.861	183.50	1.42	33
Educ. Achievement (GCSE a-c)	9.67 ± 1.30 [7-12]	8.95 ± 3.40 [0-16]	.492	0.48	.015	1,31

Note. *n*= number of participants; m= male; BR= British; BG=British-German; Zimbabwean-Irish=ZI; ENG= English; GCSE a-c= general certificate of secondary education grades a-c. For continuous data the descriptive statistics are presented as mean ± standard deviation [range] when parametric, and median (interquartile range) [range] when non parametric. χ^2= chi-square, KW=Kruskal-Wallis; AN=ANOVA; MW=Mann-Whitney; TT=t-test. ANC=ANCOVA.

4.3. Results

4.3.1. Demographic Data

Data from the CannaForm pertaining to demographic characteristics were collected and analysed to determine whether relevant factors differed between the three groups.

There were three continuous variables which potentially could be analysed through ANOVA method and therefore assumptions were tested for both the two-group analysis (see Table 4.1) and three-group analysis (see Table 4.2). The normality protocol of assessing histograms, the Shapiro-Wilk's test, skewness statistics and kurtosis statistics suggested that there were deviations from normality for the age and years of education variables. The five transformation methods described in section 4.2.5 were implemented and the normality protocol suggested that the data could not be made parametric and therefore Kruskal-Wallis tests were used. The educational achievement (GCSE's) variable showed to be normally distributed and with no outliers and therefore was analysed using the ANOVA method.

Across all two-way (see Table 4.1) and three-way (see Table 4.2) analyses there were no between group differences suggesting that the groups were matched for sex, age, nationality, educational achievement, and years of education.

Table 4.2

Between subject effects and descriptive statistics for the three-group demographic data.

Demographic Variable	**Control *n*=13**	**EoC *n*=12**	**LoC *n*=10**	***p*-value**	***Test statistic***	***Effect size***	***df***
Sex $^{\chi 2}$	4m	6m	5m	.533	1.26	-	2
Age ^{KW}	19.00 (2.50) [18-26]	20.00 (4.75) [18-35]	19.50 (3.25) [18-23]	.252	2.76	-	2
Nationality $^{\chi 2}$	13 BR	12 BR	8 BR; 1 BG; 1 ZI	.076	4.56	-	2
First Language	13 ENG	12 ENG	10 ENG	-	-		
Years of education ^{KW}	14.00 (1.00) [13-18]	14.00 (2.00) [10-17]	14.00 (1.00) [14-17]	.981	0.04	-	2
Educ. Attainment (GCSE a-c)	9.67 ± 1.30 [7-12]	8.00 ± 3.41 [0-12]	10.22 ± 3.11 [5-16]	.159	1.96	.116	2,30

Note. See table 4.1 for notes

Table 4.3

Between subject effects and descriptive statistics for the two-group drug use data.

Drug Use Variable	**Control** ***n*=13**		**Cannabis users** ***n*=22**		***p*-value**	***Test statistic***	***Effect size***	***df***
	Median (IR)	Range	Median (IR)	Range				
Days of drinking (p/w)^{MW}	2.00 (1.00)	[0-4]	1.75 (3.19)	[0-5.5]	.785	138.00	0.30	31
Tobacco (LT)^{MW}	0.00 (3.63)	[0-72]	711.38 (4,629.00)	[0-12,045]	**.003**	193.50	2.92	31
Cannabis (LT)^{MW}	0.00 (0.75)	[0-5]	540.00 (1,806.90)	[90-25,550]	**<.001**	252.00	4.76	31
Cannabis (YoU)	-	-	4.00 (4.00)	[1-9]	-			
Cannabis (AoO)	-	-	15.23 ± 1.78	[12-19]	-			
Cannabis (Intox)	-	-	6.11 ± 2.41	[0-10]	-			
Cannabis (time since last use)	-	-	8.50 (53.25)	[2-712]	-			
Amphetamines (LT)	-	-	0.00 (0.00)	[0-1]	-			
Cocaine (LT)	-	-	0.00 (0.00)	[0-6]	-			
Mushrooms (LT)	-	-	0.00 (0.25)	[0-10]	-			
Ecstasy (LT)^{MW}	0.00 (0.00)	[0-1]	0.50 (4.00)	[0-40]	**.031**	191.50	2.51	31
Other Drug Use* (LT)^{MW}	0.00 (0.00)	[0-2]	1.50 (7.13)	[0-45]	**.018**	197.00	2.68	32

Note. p/w= *per* week; LT= lifetime use; AoO= age of onset in years; YoU=Years of Use; Intox=desired level of intoxication reached on a scale from 0 (sober) to 10 (wasted); time since last use is reported in days. Significant omnibus effects (p<.05) are noted in bold. Omnibus tests were analysed using ANOVA unless labelled with ^{kw} which indicates a Kruskal-Wallis test. For parametric data the mean ± standard deviation are presented instead of the median (interquartile range. * other drug use indicates all recreational drug use excluding cannabis, tobacco and alcohol. Drug use data is omitted for the controls were there is insufficient data or no drug use to determine average amounts.

4.3.2. Drug Use Data

When a testing date and time was arranged the participants were asked to abstain from alcohol use for twenty-four hours and recreational drug use for one week prior to the testing time. All participants reported their last alcohol and drug use on the testing day which showed respective uses within the accepted timeframe for all participants. The aim was to recruit participants with less than 15 uses of cannabis use and tobacco use for the control group however this criterion was violated for three and five of the participants, respectively (see Table 4.3). These participants were not excluded due to the low level of use. It was also aimed to have less than 15 episodes of other drug use (total episodes of drug use; not including cannabis, alcohol or tobacco) across all three groups. This criterion was met for the control group however was violated for two of the participants from the cannabis group/early onset cannabis group (see Tables 4.3 and 4.4). The amounts were still relatively small (16 and 45 uses) when compared to the amount of cannabis each participant had consumed (3,636 and 1,008 uses, respectively) and therefore the participants were not excluded.

The normality protocol suggested that there were deviations from normality for all of the drug use variables seen in Tables 4.3 and 4.4, with the exception of the desired cannabis intoxication level, years of cannabis use, and age of cannabis onset. The transformation protocol could not generate normality and therefore these variables were analysed using the Kruskal-Wallis test. Results of the three way analysis which were significant suggested follow-up comparisons were necessary to determine which groups differed. These post hoc tests are now discussed.

4.3.2.1 Controls vs. EoC users.

There were four significant Kruskal-Wallis tests which dictated follow-up Dunn's comparisons. These tests showed that EoC users had higher levels of tobacco use than controls [$t_{(23)}$=13.04, p=.001, r=0.69, 1-Tailed Dunn's], higher levels of cannabis use than controls [$t_{(23)}$=17.83, p<.001, r=0.91, 1-Tailed Dunn's], higher levels of ecstasy use than controls [$t_{(23)}$=8.25, p=.026, r=0.48, 1-Tailed Dunn's], and higher levels of total other drug use than controls [$t_{(23)}$=9.33, p=.013, r=0.53, 1-Tailed Dunn's].

4.3.1.2 Controls vs. LoC users.

Further follow-up tests showed that LoC users had higher levels of cannabis use than controls [$t_{(21)}$=14.72, p<.001, r=0.73, 1-Tailed Dunn's], however the two groups did not differ in total tobacco use [$t_{(21)}$=14.72, p<.001, r=0.73, 1-Tailed Dunn's], total ecstasy use [$t_{(21)}$=6.96, p=.084, r=0.40, 1-Tailed Dunn's], or total other drug use [$t_{(21)}$=7.22, p=.079, r=0.40, 1-Tailed Dunn's].

4.3.1.3 EoC users vs. LoC users.

Further follow-up tests showed that the two groups did not differ on any of the four variables including total cannabis use [$t_{(20)}$=3.11, p=.500, r=0.16, 1-Tailed Dunn's], total tobacco use [$t_{(20)}$=8.10, p=.360, r=0.43, 1-Tailed Dunn's], total ecstasy use [$t_{(20)}$=1.29, p=.500, r=0.08, 1-Tailed Dunn's], or total other drug use [$t_{(20)}$=2.12, p=.500, r=0.13, 1-Tailed Dunn's].

In addition to the four Kruskal-Wallis test follow-ups, seven further Mann-Whitney U and independent t-tests were run just between the EoC and LoC using groups. This showed that the EoC group initiated cannabis use significantly earlier than the LoC group [$t_{(20)}$=5.67, p<.001, d=2.41, 1-Tailed t-test], had significantly more years of cannabis use than the LoC group [$t_{(20)}$=1.84, p=.042, d=0.86, 1-Tailed t-test] although there was no difference in desired levels of intoxication between the two groups [$t_{(20)}$=0.86, p=.201, d=0.36, 1-Tailed t-test] or time since last cannabis use [$U_{(20)}$=40.00, p=.234, z=0.73]. There was also no differences between the two groups in total amphetamine use [$U_{(20)}$=59.00, p=.447, z=0.13], total cocaine use [$U_{(20)}$=54.00, p=.254, z=0.73], or total magic mushroom use [$U_{(20)}$=58.00, p=.423, z=0.18].

4.3.1.4 Considerations

While some of the differences between groups were statistically significant for various drug use variables the two tables (4.3 & 4.4) should be consulted to examine descriptive statistics because a statistically significant difference does not necessarily imply substantive or real world significance. Cannabis users were shown to use significantly more other drugs than controls; however this effect only represents a median difference of 2.50 total lifetime uses and therefore is unlikely to explain any group differences in cognitive performance reported in section 4.3.5.

Table 4.4

Between subject effects and descriptive statistics for the three-group drug use data.

Drug Use Variable	**Control** ***n*=13**		**EoC** ***n*=12**		**LoC** ***n*=10**		***p*-value**	***Test statistic***	***Effect size***	***df***
	Median (IR)	Range	Median (IR)	Range	Median (IR)	Range				
Days of drinking (p/w)^{KW}	2.00 (1.00)	[0-4]	1.25 (2.50)	[0-4]	2.00 (2.94)	[0.25-5.50]	.394	1.86	.058	2
Tobacco (LT)^{KW}	0.00 (3.63)^{b}	[0-72]	1,952.50 (10,512.00)^{b}	[1-12,045]	15.50 (1,382.25)	[0-5,200]	**.002**	12.22	.394	2
Cannabis (LT) ^{KW}	0.00 (0.75)^{a,b}	[0-5]	864.00 (2,712.00)^{b}	[108-25,550]	432.00 (722.50)^{a}	[90-3,636]	**<.001**	23.24	.726	2
Cannabis (YoU)	-	-	5.45 ± 2.25	[2-9]	3.56 ± 2.16	[1-8]	**.042**	1.84	0.86	20
Cannabis (AoO)	-	-	14.00 ± 1.04	[12-15]	16.75 ± 1.23	[16-19]	**<.001**	5.67	2.41	20
Cannabis (Intox)	-	-	5.70 ± 1.83	[3-10]	6.60 ± 3.00	[0-10]	.201	0.86	0.36	20
Cannabis (last use in days)^{MW}	-	-	10.00 (25.00)	[2-60]	7.0 (221.00)	[2-712]	.234	40.00	0.73	20
Amphetamines (LT)^{MW}	-	-	0.00 (0.00)	[0-1]	0.00 (0.00)	[0-1]	.447	59.00	0.13	20
Cocaine (LT)^{MW}	-	-	0.00 (0.00)	[0-6]	0.00 (0.25)	[0-1]	.254	54.00	0.73	20
Mushrooms (LT)^{MW}	-	-	0.00 (0.75)	[0-3]	0.00 (0.25)	[0-10]	.423	58.00	0.18	20
Ecstasy (LT) ^{KW}	0.00 (0.00)^{b}	[0-1]	0.00 (5.38)^{b}	[0-40]	0.50 (3.25)	[0-4]	**.040**	6.44	.195	2
Other Drug Use (LT) ^{KW}	0.00 (0.00)^{b}	[0-2]	2.50 (7.38)^{b}	[0-45]	0.50 (8.25)	[0-16]	**.023**	7.51	.227	2

Note. See table 4.3 for notes. ^{a} ^{b} & ^{c} indicate significant (p<.05) differences between the groups following a significant Kruskal-Wallis test.

Table 4.5

Between subject effects and descriptive statistics for the two-group mental health data.

Mental Health Variable	**Control** ***n*=13**		**Cannabis users** ***n*=22**		***p*-value**	***Test statistic***	***Effect size***	***df***
	Mean ± SD	95% CI	Mean ± SD	95% CI				
HADS								
Anxiety[r]	5.69 ± 2.93	[3.92-7.46]	8.10 ± 3.99	[6.28-9.91]	**.042**	1.78	0.69	32
Depression[r]	2.54 ± 2.85	[0.82-4.26]	3.67 ± 2.63	[2.47-4.87]	.066	1.54	0.41	32
CB-OCi								
Obsessions	8.92 ± 5.20	[5.78-12.07]	11.20 ± 6.19	[8.30-14.10]	.141	1.10	0.40	31
Compulsions[r]	5.46 ± 3.99	[3.05-7.87]	5.30 ± 3.76	[3.54-7.06]	.426	0.06	0.04	31
AES								
Motivation	42.08 ± 5.99	[38.46-45.70]	40.67 ± 7.98	[37.04-44.30]	.294	0.55	0.20	32

Note. HADS=Hospital Anxiety and Depression Scale. CB-OCi=Clark-Beck Obessive and Compulsive Inventory. AES=Apathy Evaluation Scale. All tests are t-tests with 1-tailed hypotheses. HADS scores: 0-7= normal; 8-10=borderline; 11-21=abnormal (Zigmond & Snaith, 1983).

4.3.3. Mental Health Data

Data from the HADS (Zigmond & Snaith, 1983), the CBOCI (Clark et al., 2005), and the AES (Marin et al., 1991) were collected to determine whether the groups differed on measures of depression, anxiety, obsessions, compulsions, and motivation. The possible scores on the two HADS tests ranged from 0-21 with higher scores indicating higher levels of anxiety or depression. The possible scores on the CBOCI ranged from 0-42 for the obsessions scale and from 0-33 for the compulsions scale with higher scores indicating more severe symptoms of OCD. In contrast to the other two questionnaires, higher scores on the AES reflected greater levels of motivation (maximum possible score 54), while lower levels suggested apathy (minimum possible score 0).

The five variables were subject to the outlier, normality, homogeneity of variance, and transformation protocols. Normal, transformed, and un-transformable variables can be seen in Tables 4.5 and 4.6.

One of the two-group (see Table 4.5) analyses found a group difference, namely that cannabis users displayed significantly higher levels of anxiety than controls. In contrast, none of the three-group (see Table 4.6) analyses found any significant differences for any of the mental health variables. This suggests that the groups were matched for all mental health variables except anxiety within the two-group analysis.

Table 4.6

Between subject effects and descriptive statistics for the three-group mental health data.

Mental Health Variable	**Control** ***n*=13**		**EoC** ***n*=12**		**LoC** ***n*=10**		***p*-value**	***Test statistic***	***Effect size***	***df***
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI				
HADS										
Anxiety[r]	5.69 ± 2.93	[3.92-7.46]	8.83 ± 5.02	[5.64-12.03]	7.11 ± 1.73	[5.76-8.47]	.196	1.72	.100	2,31
Depression[r]	2.54 ± 2.85	[0.82-4.26]	4.58 ± 2.97	[2.70-6.47]	2.44 ± 1.51	[1.28-3.60]	.116	2.31	.130	2,31
CB-OCi										
Obsessions	8.92 ± 5.20	[5.78-12.07]	12.64 ± 7.76	[7.42-17.85]	9.44 ± 3.05	[7.10-11.79]	.270	1.37	.084	2,30
Compulsions[r]	5.46 ± 3.99	[3.05-7.87]	5.55 ± 3.91	[2.92-8.17]	5.00 ± 3.77	[2.10-7.90]	.958	0.04	.003	2,30
AES										
Motivation	42.08 ± 5.99	[38.46-45.70]	40.58 ± 10.03	[34.21-46.96]	40.78 ± 4.55	[37.28-44.27]	.864	0.15	.009	2,31

Note. See table 4.5 for notes. *Additional note.* All tests are ANOVAs.

Table 4.7.

Between subject effects and descriptive statistics for the two-group IQ data.

IQ Variable	**Control** ***n*=13**		**Cannabis users** ***n*=22**		***p*-value**	***Test statistic***	***Effect size***	***df***
	Mean ± SD	95% CI	Mean ± SD	95% CI				
FSIQ	108.08 ± 10.59	[101.67-114.48]	109.24 ± 7.65	[105.76-112.72]	.357	0.37	0.13	32
Vocabulary^{L}	53.92 ± 7.86	[49.17-58.67]	56.95 ± 6.03	[54.20-59.70]	.093	1.35	0.43	32
Block Design	53.69 ± 8.61	[48.49-58.89]	53.33 ± 7.45	[49.94-56.72]	.449	0.13	0.04	32
Similarities	53.69 ± 6.37	[49.84-57.54]	55.05 ± 6.17	[52.34-57.86]	.271	0.62	0.22	32
Matrix Reasoning	56.92 ± 6.93	[52.73-61.11]	55.62 ± 5.66	[53.04-58.20]	.277	.060	0.21	32

Note. L=Log transformation. FSIQ=Full Scale Intelligence Quotient. All tests are t-tests with 1-tailed hypotheses.

4.3.4. IQ Data

The estimates of IQ derived from the WASI were collected and analysed to determine whether the three groups differed on measures of FSIQ and each of the four subtests. An interpretation by the test authors breaks up performance into extremely low (69 and below), borderline (70-79), low average (80-89), average (90-109), high average (110-119), superior (120-129) and very superior (130 and above) categories (Wechsler et al., 1999). The subtest possible scores (age-scaled) are 20-73 for the Vocabulary subtest, 24-73 for the Block Design subtest, 20-71 for the Similarities subtest, and 20-69 for the Matrix Reasoning subtest. Higher scores on all of the subtests indicate better performance.

The five variables were subject to the outlier, normality, homogeneity of variance, and transformation protocols. Normal, transformed, and un-transformable variables can be seen in Tables 4.7 and 4.8.

None of the two-group (see Table 4.7) or the three-group (see Table 4.8) analyses found any significant differences for any of the IQ variables. This suggests that the groups were matched for levels of IQ, although there was a trend for cannabis users to perform better on the vocabulary subtest.

Table 4.8.

Between subject effects and descriptive statistics for the three-group IQ data.

IQ Variable	**Control** ***n*=13**		**EoC** ***n*=12**		**LoC** ***n*=10**		***p-value***	***Test statistic***	***Effect size***	***df***
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI				
FSIQ	108.08 ± 10.59	[101.67-114.48]	110.50 ± 5.65	[106.91-114.09]	107.56 ± 9.84	[99.99-115.12]	.709	0.35	.022	2,31
Vocabulary[L]	53.92 ± 7.86	[49.17-58.67]	57.83 ± 6.48	[53.72-61.95]	55.78 ± 5.54	[51.52-60.04]	.329	1.09	.066	2,31
Block Design	53.69 ± 8.61	[48.49-58.89]	55.08 ± 6.99	[50.64-59.52]	51.00 ± 7.79	[45.00-56.99]	.503	0.70	.043	2,31
Similarities	53.69 ± 6.37	[49.84-57.54]	55.17 ± 6.04	[51.33-59.01]	54.89 ± 6.70	[49.74-60.04]	.829	0.19	.012	2,31
Matrix Reasoning	56.92 ± 6.93	[52.73-61.11]	55.92 ± 4.29	[53.19-58.65]	55.22 ± 7.38	[49.55-60.89]	.815	0.21	.013	2,31

Notes. See Table 4.7 for notes. *Additional note.* All tests are ANOVAs.

Table 4.9.

Between subject effects and descriptive statistics for the two-group cognitive data.

Cognitive Variable	Control *n*=13		Cannabis users *n*=22		*p*-value	*Test statistic*	*Effect size*	*df*
	Mean ± SD	95% CI	Mean ± SD	95% CI				
Task Data								
VST								
Total time	294.49 ± 31.51	[275.45-313.53]	322.87 ± 43.87	[303.38-342.37]	**.025**	2.03	0.74	33
Reaction time (T-T)[U]	1.53 (0.31)	[1.44-1.94]	1.81 (0.65)	[1.52-2.07]	.052	95.50	1.62	33
Reaction time (NT-T)[r]	2.78 ± 0.56	[2.44-3.11]	3.29 ± 0.69	[2.99-3.60]	**.016**	2.25	0.81	33
Omission errors[r]	6.46 ± 5.58	[3.09-9.83]	4.68 ± 2.73	[3.47-5.89]	.172	0.96	0.41	33
Comission errors[U]	0.00 (0.00)	[0.00-0.00]	0.00 (0.00)	[0.00-0.00]	.135	130.00	1.10	33
SST								
Total time	313.07 ± 34.25	[292.37-333.77]	346.94 ± 49.16	[325.14-368.73]	**.013**	2.19	0.80	33
Reaction time (T-T)[IV]	1.64 ± 0.32	[1.45-1.84]	1.89 ± 0.44	[1.70-2.08]	**.037**	1.85	0.65	33
Reaction time (NT-T)	3.33 ± 0.58	[2.91-3.75]	3.67 ± 0.79	[3.33-4.00]	.228	1.52	.052	1,28
Omission errors[r]	5.69 ± 3.61	[3.51-7.88]	4.41 ± 2.68	[3.22-5.60]	.119	1.20	0.40	33
Comission errors[U]	0.00 (0.00)	[0.00-0.00]	0.00 (0.00)	[0.00-0.00]	.286	131.50	0.56	33
Eye-Tracking Data								
VST								
Fixation duration on target[r]	0.26 ± 0.04	[0.24-0.29]	0.28 ± 0.06	[0.25-0.31]	.355	0.88	.030	1,29
Fixation duration on distractors	0.20 ± 0.02	[0.19-0.21]	0.20 ± 0.01	[0.19-0.20]	.565	0.34	.012	1,28
Unique fixation count (T-T)[r]	3.38 ± 1.02	[2.77-4.00]	3.90 ± 1.42	[3.26-4.55]	.145	1.08	0.42	32
Unique fixation count (NT-T)[r]	8.04 ± 2.44	[6.57-9.51]	9.17 ± 2.71	[7.93-10.40]	.114	1.23	0.44	32
Revisits* on target[r]	8.00 ± 2.45	[6.52-9.48]	11.57 ± 5.38	[9.12-14.02]	**.015**	2.28	0.85	32
Revisits* on distractors[r]	53.77 ± 28.78	[36.38-71.16]	79.81 ± 48.46	[57.75-101.87]	.055	1.65	0.65	32
SST								
Fixation duration on target[r]	0.31 ± 0.08	[0.27-0.36]	0.32 ± 0.06	[0.29-0.35]	.363	0.35	0.12	32
Fixation duration on distractors	0.20 ± 0.02	[0.19-0.21]	0.20 ± 0.01	[0.19-0.20]	.079	1.45	0.49	32
Unique fixation count (T-T)[U]	3.00 (2.50)	[2.00-5.00]	4.00 (1.00)	[3.00-4.00]	.178	111.00	0.92	32

Unique fixation count (NT-T)[L]	8.77 ± 2.20	[7.44-10.10]	9.76 ± 2.53	[8.61-10.91]	.161	1.01	0.35	32
Revisits* on target[L]	8.77 ± 2.45	[7.29-10.25]	11.29 ± 5.94	[8.58-13.99]	.121	1.19	0.44	32
Revisits* on distractors[r]	63.54 ± 29.25	[45.86-81.22]	107.81 ± 59.25	[80.84-134.78]	**.006**	2.64	0.97	32

Notes. T-T=Target Trials; NT-T=Non-target Trials. IV=Inverse transformation. *In contrast to the unique fixation count in which descriptive data is presented *per trial*, the descriptive data for the revisits is presented for the whole task, a sum of all trials completed. U=Mann Whitney U.

4.3.5. Cognitive Data

4.3.5.1. ANOVA Assumptions

The 22 variables were subject to the outlier, normality, homogeneity of variance, and transformation protocols. Normal, transformed, and un-transformable variables can be seen in Tables 4.9 and 4.10.

4.3.5.2. ANCOVA Assumptions

In addition to the basic ANOVA assumptions described in section 4.3.5.1 there are additional assumptions necessary for the ANCOVA. This analysis attempted to take into account the relative effects of anxiety (Eysenck et al., 2007), depression (Delis et al., 2001), obsessions and compulsions (Lawrence et al., 2006), motivation (Musty & Kaback, 1995), FSIQ (Ardila, Pineda & Rosseillo, 1999), alcohol use (Brown, Tapert, Granholm & Delis, 2000), tobacco use (Jacobsen et al., 2005) years of education, educational attainment (Hooper et al., 2004) and age (Taylor et al., 2011) on cognitive test performance. The assumption of independence of treatment and covariate effects states that the covariate must not be significantly related to the independent variables. The ANOVA results from the Demographic Data, Mental Health Data and IQ Data analysis showed that three of these variables: anxiety, tobacco use and other drug use, were all related to the independent variable while the remaining variables met the first assumption of independence of treatment and covariate effects.

Secondly, the variables must be correlated with the given dependent variable. See Appendix A.4.12 for the table of correlations between potential confounding variables and the cognitive dependent variables. Thirdly, in such situations where a relationship is present between the dependent variable and the potential covariate, the relationship must be linear. These relationships were checked using scatter graphs. Finally, homogeneity of regression slopes was tested by looking for a significant interaction effect between the potential covariate and the independent variable. Any potential covariate which violated this assumption was not included in the ANCOVA.

In such cases where a potential confounding variable met all the assumptions then an ANCOVA was run. In situations where no potential confounding variable was related to the dependent variable or a violation occurred then an ANOVA was run. After checking

assumptions VST fixation duration on distractors was analysed while controlling for educational achievement and age, VST fixation duration on targets was analysed while controlling for compulsions, VST omissions was analysed while controlling for FSIQ and SST non-target reaction time was analysed while controlling for depression and alcohol use. The remaining variables were unrelated to the potential confounding variables or violated assumptions for the anlaysis.

For the two-group analysis independent *t*-tests were used when no covariates needed to be controlled. ANCOVAs were used in situations where covariates needed to be controlled. For the three-way analyses there was only one significant main effect (see Table 4.10) and therefore only one series of post-hoc tests was conducted.

4.3.5.3 Post-Hoc Tests

There were two significant main effects between the three groups for the number of revisits on target stimuli during the VST task and the number of revisits on distractors during the SST task. Post-hoc tests showed that early onset cannabis users made significantly more VST target revisits than controls [$t_{(23)}$=3.94, p<.001, d=1.41, 1-tailed Tukeys HSD] and late onset users [$t_{(20)}$=3.32, p=.003, d=1.30, 1-tailed Tukeys HSD] on the VST. In contrast, there were no differences between controls and late onset users [$t_{(21)}$=0.39, p=.461, d=0.21, 1-tailed Tukeys HSD].

On the SST, post-hoc tests showed that early onset cannabis users made significantly more distractor revisits than controls [$t_{(23)}$=2.83, p=.011, d=1.04, 1-tailed Tukeys HSD]. In contrast, there were no differences between controls and late onset users [$t_{(21)}$=1.63, p=.124, d=0.95, 1-tailed Tukeys HSD] or late onset users and early onset users [$t_{(20)}$=1.08, p=.266, d=0.56, 1-tailed Tukeys HSD] on the VST.

4.3.5.4. Correlational Analysis

In order to further explore the nature of the cannabis related impairments, the tests which identified cognitive impairments in cannabis users or showed a trend towards group differences were selected and then correlated with cannabis use variables within the entire cannabis using group (See Table 4.11). This showed that only one cannabis use variable was correlated with one dependent variable, the age of onset negatively

correlated with the number of revisits to target stimuli on the VST [r=-.438, p=.023, n=22, 1-tailed].

4.3.5.5. Quartile Analysis

In order to test how performance changed over the course of the test the 80 trials for the Tobii VST and Tobii SST were broken down into its constituent components. The trials were first halved into the target trials and non-target trials to observe these effects separately. Secondly the 40 trials per category were broken down into quartiles representing 10 trials for each quartile for target and non-target trials. Of these 10 trials all error trials were removed so that for each participant an estimate for each quartile could be assessed for only the trials on which they responded correctly. These remaining trials formed an estimate of how each individual performed over the time course of the task and thus provided a measure of sustained attention as opposed to selective attention (e.g. Hanson et al., 2010). The means and standard errors of these estimates for cannabis users and controls can be seen in Figure 4.2 for the Tobii VST and Figure 4.3 for the Tobii SST. This quartile analysis was not broken down into early and late onset users as there was not an age of onset effect on target or non-target reaction times.

Table 4.10.

Between subject effects and descriptive statistics for the three-group cognitive data.

Cognitive Variable	Control *n*=13		EoC *n*=12		LoC *n*=10		*p*-value	*Test statistic*	*Effect size*	*df*
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI				
Task Data										
VST										
Total time	294.49 ± 31.51	[275.45-313.53]	328.33 ± 43.78	[300.51-356.14]	316.33 ± 45.62	[283.70-348.97]	.119	2.28	.125	2,32
Reaction time (T-T)^{KW}	1.53 (0.31)	[1.44-1.94]	1.92 (0.73)	[1.36-2.10]	1.76 0.67)	[1.52-2.49]	.260	2.69	.046	2
Reaction time (NT-T)^{r}	2.78 ± 0.56	[2.44-3.11]	3.36 ± 0.77	[2.87-3.85]	3.20 ± 0.61	[2.77-3.64]	.090	2.61	.140	2,32
Omission errors^{r}	6.35 ± 5.58	[4.16-8.54]	4.69 ± 3.18	[2.39-6.98]	5.25 ± 2.21	[2.61-7.89]	.593	0.53	.034	2,30
Comission errors^{KW}	0.00 (0.00)	[0.00-0.00]	0.00 (0.00)	[0.00-0.00]	0.00 (0.00)	[0.00-0.00]	.537	1.25	.032	2
SST										
Total time	313.07 ± 34.25	[292.37-333.77]	356.49 ± 51.68	[323.66-389.33]	335.47 ± 45.89	[302.64-368.29]	.063	3.02	.159	2,32
Reaction time (T-T)^{IV}	1.64 ± 0.32	[1.45-1.84]	1.95 ± 0.54	[1.61-2.29]	1.81 ± 0.25	[1.61-2.01]	.197	1.71	.097	2,32
Reaction time (NT-T)	3.33 ± 0.58	[2.91-3.75]	3.85 ± 0.93	[2.92-3.74]	3.34 ± 0.52	[2.79-3.89]	.164	1.93	.125	2,27
Omission errors^{r}	5.69 ± 3.61	[3.51-7.88]	4.92 ± 3.50	[2.69-7.14]	3.80 ± 1.03	[3.06-4.54]	.353	1.08	.063	2.32
Comission errors^{KW}	0.00 (0.00)	[0.00-0.00]	0.00 (1.00)	[0.00-1.00]	0.00 (0.00)	[0.00-0.00]	.322	2.27	.043	2
Eye-Tracking Data										
VST										
Fixation duration on target^{r}	0.26 ± 0.04	[0.24-0.29]	0.27 ± 0.06	[0.23-0.31]	0.29 ± 0.06	[0.25-0.33]	.483	0.75	.051	2,28
Fixation duration on distractors	0.20 ± 0.02	[0.19-0.21]	0.20 ± 0.01	[0.19-0.21]	0.19 ± 0.01	[0.19-0.21]	.499	0.71	.050	2,27
Unique fixation count (T-T)^{r}	3.38 ± 1.02	[2.77-4.00]	3.72 ± 1.37	[2.85-4.69]	4.05 ± 1.54	[2.95-5.15]	.513	0.68	.042	2,31
Unique fixation count (NT-T)^{r}	8.04 ± 2.44	[6.57-9.51]	9.41 ± 2.87	[7.48-11.34]	8.90 ± 2.64	[7.01-10.79]	.455	0.81	.050	2,31
Revisits on target^{r}	8.00 ± 2.45$^{a\,b}$	[6.52-9.48]	14.36 ± 5.90^{a}	[10.40-18.33]	8.50 ± 2.37^{b}	[6.81-10.19]	**<.001**	8.93	.365	2,31
Revisits on distractors^{r}	53.77 ± 28.78	[36.38-71.16]	91.73 ± 60.43	[51.13-132.32]	66.70 ± 28.23	[46.50-86.90]	.165	1.91	.110	2,31
SST										
Fixation duration on target^{r}	0.31 ± 0.08	[0.27-0.36]	0.32 ± 0.07	[0.27-0.36]	0.32 ± 0.06	[0.28-0.36]	.929	0.07	.005	2,31
Fixation duration on distractors	0.20 ± 0.02	[0.19-0.21]	0.20 ± 0.02	[0.19-0.21]	0.19 ± 0.01	[0.19-0.20]	.257	1.42	.084	2,31

Unique fixation count (T-T)^{KW}	3.00 (2.50)	[2.00-5.00]	4.00 (1.00)	[3.00-4.00]	3.25 (2.25)	[3.00-5.00]	.398	2.27	.043	2
Unique fixation count (NT-T)^{L}	8.77 ± 2.20	[7.44-10.10]	10.18 ± 2.71	[8.36-12.00]	9.30 ± 2.36	[7.61-10.99]	.375	1.01	.061	2,31
Revisits on target^{L}	8.77 ± 2.45	[7.29-10.25]	13.54 ± 7.03	[8.82-18.27]	8.80 ± 3.22	[6.49-11.11]	.068	2.93	.159	2,31
Revisits on distractors^{r}	63.54 ± 29.25^{a}	[45.86-81.22]	123.00 ± 75.71^{a}	[72.14-173.86]	91.10 ± 28.99	[70.36-111.84]	**.026**	4.09	.209	2,31

Note. See Table 4.9 for notes. KW=Krusal-Wallis.

Table 4.11.

A table of correlation coefficients to explore which cannabis use variables which may mediate the performance deficits by cannabis users

Cognitive Variable	Age of onset	Lifetime spliffs smoked	Years of cannabis smoking	Desired Intoxication	Time since last Use
	P	Rho	P	P	Rho
Task Data					
VST					
Total time	-.116	.077	-.152	-.136	-.039
Reaction time (T-T)	-.087	.112	-.094	-.083	-.267
Reaction time (NT-T)^{r}	-.117	.104	-.189	-.304	-.146
SST					
Total time	-.209	.207	.295	-.157	-.130
Reaction time (T-T)^{IV}	.085	.060	-.216	.042	.195
Eye-Tracking Data					
VST					
Revisits on target^{r}	**-.438***	.030	.280	-.315	-.273
Revisits on distractors^{r}	-.257	.238	.083	-.324	-.151
SST					
Revisits on target^{L}	-.265	-.062	.272	-.093	-.296
Revisits on distractors^{r}	-.207	.311	.323	-.211	-.296

Notes. P= Pearson's correlation coefficient; Rho= Spearman's correlation coefficient. This analysis was performed on just the cannabis users n=22. r=root transformed. IV=inverse transformation. L=log transformed.

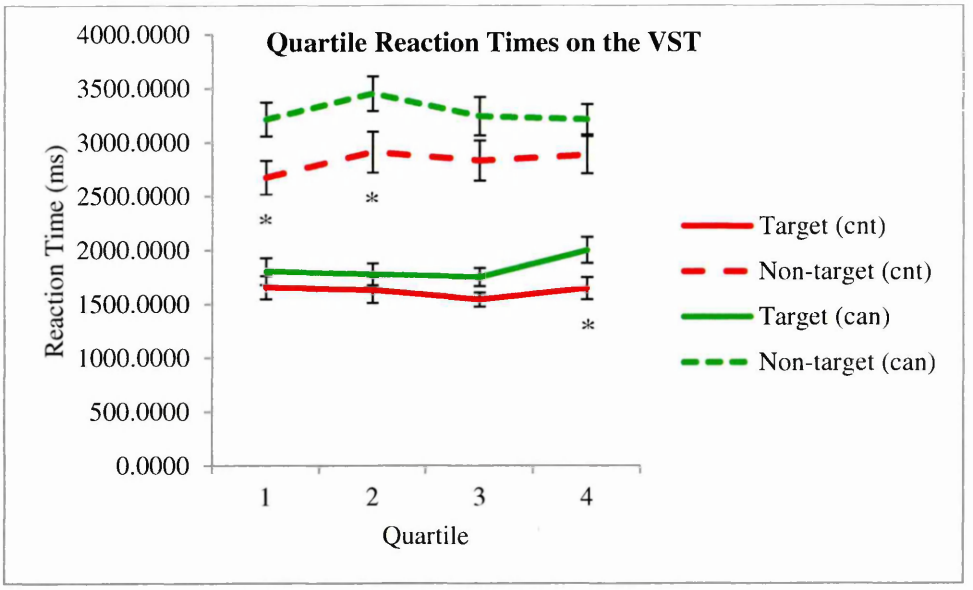


Figure 4.2. The mean reaction times across the four quartiles of the VST for target and non-target trials, for both cannabis users (can) and controls (cnt). Error bars represent standard errors. The * below a comparison indicates between group differences for that specific quartile.

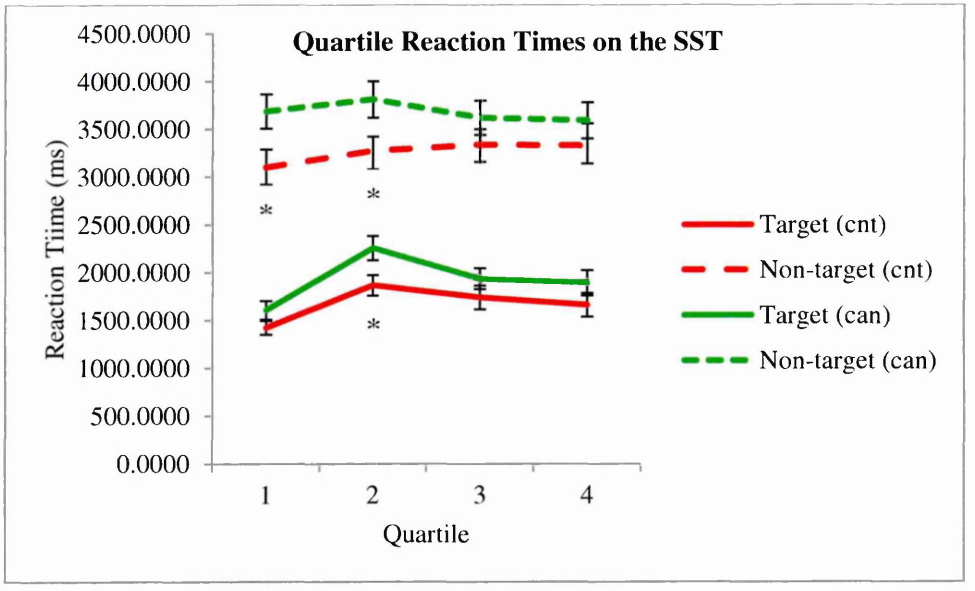


Figure 4.3. The mean reaction times across the four quartiles of the SST for target and non-target trials, for both cannabis users (can) and controls (cnt). Error bars represent standard errors. The * below a comparison indicates between group differences for that specific quartile.

4.3.6. Validity and Reliability

In order to test which variables of the Tobii SST recruited set switching processes a subtraction of a switch trial from a non-switch trial (e.g. SST total time – VST total time) was conducted as described in Monsell (2003) to determine if a switch cost was present. As many of the variables were transformed using different transformation methods the transformed data could not be compared and therefore Wilcoxon tests are used to test all non-parametric variables while related sample *t*-tests compared all parametric data. Any significant results suggest that there was a switch cost, and therefore set switching processes, involved for that specific cognitive variable on the Tobii SST.

Table 4.12.

P-values for the comparisons between the Tobii SST and the Tobii VST for each dependent variable.

Cognitive Variable (SST-VST)	Controls	Cannabis users (total group)
Task Data		
Total time	**.023**	**.004**
Reaction time (T-T)	.254	.392
Reaction time (NT-T)	**.007**	**<.001**
Omission errors	.238	.272
Comission errors	.079	.051
Eye-Tracking Data		
Fixation duration on target	**.010**	**.003**
Fixation duration on distractors	**.021**	.056
Unique fixation count (T-T)	.321	.255
Unique fixation count (NT-T)	.095	.012
Revisits on target	.082	.463
Revisits on distractors	**.050**	**.003**

Internal reliability of the Tobii VST and Tobii SST was tested using Cronbach's alpha for both the target trials and the non-target trials. Missing data were corrected using

multiple imputations with five iterations. The median Cronbach's alpha score across the five iterations was used as a pooled iteration was not possible.

The analysis showed that both tests reached levels of reliability suitable for cognitive testing ($\alpha > .80$; Kline, 1999). The score for the target trials of the VST was in the "good" range ($\alpha = .84$) while the score for the non-target trials of the VST was in the "excellent" range ($\alpha = .98$). The score for the target trials of the SST was in the "good" range ($\alpha = .84$) while the score for the non-target trials of the SST was in the "excellent" range ($\alpha = .97$).

4.4. Discussion

4.4.1. Validity and Reliability

The construction of the two Tobii tasks was orchestrated to ensure that visual scanning processes contributed to task performance. This was done by systematically creating task components based on previous visual search tasks (Delis et al., 2001; Huestegge et al., 2002) and by using concepts derived from visual search theory (e.g. Najemnik & Geisler, 2005). Confirming that the search strategy in both tasks that was nearer the *serial end* of the serial-parallel continuum was done by examining the reaction times across the trials with previous studies which have used serial and parallel tasks (Maoili et al., 2001). Given the number of distractors per trial and the reaction times per trial, these data suggests that a more serial-like search strategy with a parallel element was recruited, rather than a solely parallel strategy. The validity of the SST was also examined by a method discussed by Monsell (2003) for determining the role of set switching processes.

The switch cost analyses suggested a clear switch cost was present on the Tobii SST for the total time taken to complete the task, the reaction time for the non-target trials, the fixation duration time on the target stimuli, the number of unique fixations on the non-target stimuli, and the number of revisits on the distractors. There was concordance between the cannabis users and the controls for this approach. This method does not specify what processes are involved in the switch cost however task-set reconfiguration,

backward inhibition and working memory are likely candidates as discussed in Section 4.1.3 of this chapter.

Results of Cronbach's alpha tests of reliability showed that the reaction times for the target and non-target trials across the VST and SST were not only suitable for cognitive testing purposes (i.e. $\alpha>.80$; Kline, 1999) but for the non-target trials the reliability scores were near to perfect ($\alpha=.97$ & $\alpha=.98$). This suggests that for each of the respective four groups: VST target, VST non-target, SST target, and SST non-target, each of the individual trials were largely measuring the same underlying cognitive processes as the other trials within the same test.

4.4.2. Cognitive Data

4.4.2.1. The Tobii Visual Search Task (VST)

There were 11 dependent variables derived from the VST divided between five task variables and six eye-tracking metrics. The cannabis users took significantly longer than the controls to complete the VST and had a significantly slower reaction time for the non-target trials, but not the target trials. While error rates were not significantly different between groups the cannabis users reported fewer omission errors when observing descriptive statistics and confidence intervals, possibly suggesting a more cautious strategy. The cannabis users also had significantly more revisits to the target stimuli than the controls. Although the effect was not significant, there was a trend ($p<.10$) for cannabis users to have slower reaction times on the VST target trials and make more revisits to distractor stimuli. In the second (three-group) analysis, the only significant main effect was for the number of revisits to target stimuli in which early onset cannabis users made significantly more revisits than both controls and late onset users.

Of all the possible 12 putatively confounding variables which were examined, very few were correlated with the dependent variables. Of the ones which were, all were controlled for on the VST except for the influence of anxiety on the number of revisits to distractor stimuli, the influence of FSIQ on the number of omission errors (for the two group comparison only), and the influence of tobacco on the number of commission errors. These last two variables did not display significant differences across the groups

however the former variable, revisits to distractor stimuli, nearly reached statistical significance and it could be that this was due to the higher levels of anxiety in the cannabis group. In contrast, all the VST variables which were significantly different across the groups were not correlated with any of the confounding variables and therefore the deficits are best explained by cannabis use. Interestingly, only one of the cannabis variables was associated with the dependent variables in the correlations analysis. The age of onset of cannabis use was negatively and moderately correlated with the number of revisits to the target stimuli which suggests that the earlier an individual starts using cannabis, the more revisits they make and thus the worse the performance on the task.

The current study found that cannabis users were slower to respond on non-target trials and there was a strong trend towards cannabis users taking longer to respond to target trials. This replicates the findings from Huestegge et al (2002) however the current study did not find that early onset cannabis users took longer to respond on these measures than controls and late onset users, and therefore not supporting the data by Ehrenreich et al (1999). This could be due to Ehrenreich et al's much more recent abstinence criteria (two hours +) and therefore the effects discovered could be an acute intoxication effect by the early onset group driving their data. Also the cannabis users took longer to complete the whole VST task in the current study, supporting the slower findings of cannabis users on the Visual Scanning subtest of the TMT in Chapter Three of the current thesis.

The fixation duration data in the current study supports previous work done by Huestegge et al (2002) who also found no group effects on these variables. Huestegge et al (2002) also used a measure of total fixation count and the number of revisits to measure search efficiency however the current study adopted a modified approach. While revisits were also analysed here, the total fixation count was not analysed as the fixation count would also include the number of revisits. Instead the current study adopted the measure of the unique fixation count, which has the benefit of being completely separable from fixation revisits. This unique fixation count did not highlight any between group differences however it is not known if the same would be true for Huestegge et al's data. The current study found that revisits were made more frequently

by the cannabis users, a finding which also supports the previous study by Huestegge et al (2002).

One candidate for explaining the revisits to stimuli is visuo-spatial working memory deficits. Theories on the role of working memory in visual search tasks have been controversial (Horowitz & Wolfe, 1998), however by the use of statistical models and dual-task paradigms a role of spatial working memory has been demonstrated (Gilchrist & Harvey, 2000; Woodman & Luck, 2004). As spatial working memory appears to have a role in visual search completion it remains a possibility that this cognitive domain is impaired in cannabis use which led to the deficits discovered in the current sample of cannabis users. This was also the interpretation made by Huestegge et al (2002) after their comparable finding. Related to this concept of memory deficits, is the concept of accuracy checking in which cannabis users may have a reduced level of certainty about areas they have previously checked and are re-checking the search areas. This explanation is partially supported by the lower, albeit not significantly different, levels of omission errors in the cannabis using group.

An alternate explanation for the revisits is fixation instability. In fixation stability tasks a participant is required to fixate on a single stationary stimuli without moving their gaze. Previous studies have identified that certain populations have difficulty maintaining stable gaze such as those with schizophrenia (Barton, Pandita, Thakkar, Goff & Manoach, 2008; Benson et al., 2012). Given the role of dopamine in top-down control of saccades and visual signals (Noudoost & Moore, 2011) and altered dopaminergic function in cannabis users and individuals with schizophrenia (Bloomfield et al., 2014), it could be that these two groups share an eye-movement symptom, specifically the inability to control a steady fixation without making small saccades from an initial fixation point. This could be easily tested by the use of a stability fixation test and a comparison of cannabis users and controls.

The quartile analysis suggests that the cannabis-related slower non-target trial reaction times and slower overall task performance are largely driven by the first half of the task, although the slowest target trial reaction times occurred at the end of the task. Slower reaction times at the start could suggest that cannabis users took longer to learn how to efficiently search the stimulus array (Najemnik & Geisler, 2005). Given the evidence of a slower first half performance on the SST as well as this VST, the association with

cannabis appears to be robust. These findings would be compatible the accuracy checking explanation of revisits but not the working memory or fixation instability explanation. While it may it may be possible to alter a strategy by reducing the time spent accuracy checking, it is less likely that participants could increase their fixation stability or reduce their working memory deficits. It is possible however, that the quartile data and the revisit data do not represent the same underlying performance deficit, therefore a fixation instability or working memory deficit may still be viable.

The slower reaction times at the end of the task suggest an effect of sustained attention (Kim et al., 2006) however as this is a solitary finding over both tasks, it could represent a type I error. If sustained attention was impaired in cannabis users then it would be expected to see slower reaction times on the last quartile for target and non-target reaction times across both tasks, an effect which was not found.

4.4.2.2. The Tobii Switching Search Task (SST)

There were 11 dependent variables derived from the SST divided between five task variables and six eye-tracking metrics. The cannabis users took significantly longer than the controls to complete the SST and had a significantly slower reaction time for the target trials, but not the non-target trials. Similar to the VST, the cannabis users displayed marginally, albeit not significantly, fewer omission errors suggesting a more cautious strategy. The cannabis users also had significantly more revisits to the distractor stimuli than the control group. The age of onset only showed one significant effect – early onset users made more revisits to distractors than controls while there was no difference between late onset users and controls. This result initially supported the age of onset hypothesis however after controlling for the effects of anxiety the effect was no longer significant – albeit still suggested a trend ($p<.10$). There was also a trend for the age of onset effect on the revisits to targets variable.

The 12 confounding variables were also tested for ANCOVA assumptions and implemented where possible. The effects of alcohol use could not be parcelled out of the number of unique fixations on non-target trials however there were no between group differences here so this had little impact on the overall findings. In contrast, anxiety's effects on the number of distractor stimuli revisits could not be controlled in the two group analysis. It is possible that anxiety mediated performance on this variable.

Anxiety was also related to performance on SST non-target reaction times and could not be controlled for while depression and alcohol use could not be controlled for on the SST omission errors variable however as there were no between group differences here this is likely to have little impact on the overall findings.

Results of the analysis for the SST did not highlight an effect of cannabis on fixation duration times, a finding replicated in the previous VST task and the task by Huestegge et al (2002). As with the VST, the increased number of revisits by cannabis users could be explained by working memory deficits, increased accuracy checking or fixation stability deficits.

As the quartile analysis partially replicated the findings from the VST – slower first half performance – it is likely that there was a change in strategy or a learning effect. While this finding may be unrelated to the revisits, it would be compatible with increased levels of accuracy checking by the cannabis users, similar to the VST.

The purpose of introducing a switching component was to investigate whether the contribution of set switching processes were also impaired. To determine this all of the dependent variables which demonstrated a clear switch cost identified in Table 4.12 were examined. Both the VST and SST total times were elevated in cannabis users and thus impaired set switching cannot be determined. The reaction times for non-target trials displayed a clear switch cost however counter to the predicted direction this variable was not impaired in cannabis users on the SST, but was on the VST. Fixation duration on targets also displayed a clear switch cost however this variable did not uncover any cannabis related deficits on the VST or SST. Finally, the revisits on distractors displayed a clear switch cost and this was impaired in cannabis users for the SST but not the VST. This mixed pattern of results suggests that the additional switching requirement of the SST did not lead to an increased level of deficits in cannabis users. Given the clear impairments on tasks the TMT, a task which recruits set switching processes in a visual search paradigm (Chapter Three; Medina et al., 2007) it was expected to see impairments on this task. It is possible that the difference in switching type is responsible as the current task – the SST – utilised a continual switch between two symbols while the TMT involves sequential changing the target symbol, increasing demands on working and long term memory. Alternatively it could be that

previously discovered deficits on the TMT are actually due to the visual search requirements of the task as demonstrated in this study.

4.4.3. Putative Confound Data

The two groups (cannabis vs. controls) and the three groups (EoC vs. LoC vs. controls) were matched for a large number of potential confounding variables including FSIQ, individual IQ subtests, depression, compulsions, obsessions, motivation/apathy, sex, age, alcohol use, years of education, and educational achievement. In contrast, there were differences between cannabis users and controls in levels of anxiety, tobacco use, other drug use, and cannabis use variables. The levels of other drug use were negligible and therefore unlikely to influence cognition. Levels of tobacco use were not negligible however this variable was unrelated to any of the cognitive variable in which cannabis users had impaired performance and thus tobacco use is an unlikely factor to explain performance levels. It appears that the main predictors of performance deficits are the age of onset of cannabis use, membership within the cannabis using group, and levels of anxiety which were significantly higher in the cannabis group, although not in the EoC or LoC groups. While the age of onset of cannabis use and anxiety could only explain deficits on two of the variables, cannabis use in general can explain deficits on the majority of variables.

While anxiety has been linked with impaired attentional performance (Eysenck et al., 2007) there is also evidence suggesting that inducing anxiety via threat of shocks can improve certain aspects of attentional processes (Robinson, Letkiewics, Overstreet, Ernst & Grillon, 2011). Examination of scatter-plots in the current study suggested a ✓-shaped relationship between task performance and anxiety on the three variables that anxiety was linked with. The number of revisits to distractor stimuli on the VST and SST, and the reaction time on non-target trials during the SST were all linked with anxiety and lower scores indicated better performance on these variables. This suggests that as self-reported anxiety levels increased, performance improved up to a degree. After a critical point was reached, any further increases in self-reported anxiety led to decreases in task performance (see Appendix A.4.11). The role of anxiety mediating some of these deficits is supported by the average levels of anxiety by each group. The average level of anxiety in the control group (approximately 5.68) is nearer the bottom point of the ✓-curve, whereas the average level of anxiety by the cannabis users

(approximately 8.10) is further up the slope of the ✓-curve, indicating diminished performance. While the relationship between cannabis use and anxiety is not clear within the current study, there is clear evidence for anxiety mediating at least three of the cannabis-related deficits in task performance.

4.4.4. Limitations

The current study used two tasks – the VST and SST - have not been previously tested for validity or reliability. Therefore interpreting the results were more problematic than standardised tests with norm referenced data. To negotiate this problem the current study used two methods to determine validity. Firstly the tasks were developed as computerised analogues to a standardised and widely used neuropsychology task, the D-KEFS Trial Making Test (TMT). The VST maps closely on the task set out of the TMT Visual Scanning test while the SST has slightly more differences to its paper based analogue, the TMT Number-Letter Switching test. An additional measure of validity was accomplished by determining if a *switch cost* was present, a frequently used measure of determining the role of set switching processes in tasks (Monsell, 2003). This test demonstrated the role of set switching in a number of the SST dependent variables. In order to check internal reliability, Cronbach's alpha was calculated for the VST and SST and the results suggest that it is highly reliable. While these approaches helped determine the validity and reliability of the tasks, the lack of norm-referenced data means that the performances by the two groups cannot be examined relative to the general population.

4.4.5. Future Research

The current data showed that on tasks requiring visual search processes there is an increased level of revisiting to previously searched areas, a slower reaction time, and a slower overall performance by cannabis users. It is unclear what was mediating these deficits beyond the cannabis use and anxiety. If a further unknown confounding variable was mediating performance on these tasks then studies addressing this unknown confound are needed.

Given the role of visual search behaviours in everyday activities the implications of visual deficits on such activities should be explored. Approximately 74% of adults in Britain aged 17 or above hold a full driving licence and approximately 11% of adults

aged 16 or above have been involved in a motor vehicle accident within the past three years (Department for Travel, 2013) which suggests that if cannabis could affect such a prevalent and dangerous activity, then evidence of this risk factor needs to be identified. The role of visual search has previously been implicated in driving competencies (Underwood et al., 2002) and as cannabis use has been associated with impairments of visual search behaviours demonstrated in this study and in previous work (see Chapter Three; Ehrenriech et al., 1999; Hanson et al., 2010; Huestegge et al., 2002) a mechanism by which chronic cannabis use can affect driving abilities has been discovered. Although the role of cannabis and driving performance has received much attention this has primarily centred on acute cannabis use (Hartman & Huestis, 2013). As there is now clear evidence of visual search deficiencies in abstinent cannabis users, this has implications for hazard perception and could be tested by using the current Driver and Vehicle Licensing Agency (DVLA) hazard perception test. Incorporating eye-tracking into such a study would allow in more in-depth analysis of how of individuals locate and process hazardous visual information in a driving context.

4.4.6. Summary

The main finding of this study is that cannabis use is related to slower overall visual search performance, slower reaction times, and that the performance decay is partially explained by an increased number of revisits to stimuli. Possible explanations for this occurrence are impaired spatial working memory in which cannabis users return to previously searched areas at a greater rate than controls, fixation instability in which cannabis users have trouble maintaining a fixation without initiating saccades or accuracy checking, in which cannabis users are adopt a more cautious visual search strategy. As the pattern of deficits in the current study could not be attributable to set switching the current study suggests that tasks which are thought to measure this process, i.e. the TMT, may in fact just be detecting visual search deficits in cannabis users.

This study also examined the age of onset of cannabis use and how this relates to cognitive performance. Of all the analyses run there was negligible evidence for an age of onset effect, with only two variables appearing to be related to the age of onset. Although this variable did appear in the predicted direction, namely that early onset

cannabis users present with worse performance than late onset cannabis users, relative to controls, these isolated findings could just be type I errors.

While interpretations of cannabis-related impaired performance on cognitive tasks have included neurotoxicity (e.g. Meier et al., 2012), altered functional activity in the brain (e.g. Kanayama et al., 2004), or withdrawal effects (e.g. Schreiner & Dunn, 2012) it is not clear what underlying mechanism is linking cannabis use to impaired performance within this study. Although the lack of correlation between the time since last cannabis use and cognitive performance suggests the withdrawal explanation is unlikely, this does not provide evidence for permanent damage. The mechanism may be unclear but the current study provides further evidence of a link between cognitive deficits and non-acute cannabis use.

Chapter Five. What Mediates the Relationship between Executive Function and the Age of Onset of Cannabis use? Testing a New Cannabis Questionnaire

5.1. Introduction

The current research programme developed a new cannabis questionnaire, hereinafter called the Cannabis Use and Lifestyles Form (CannaForm). This chapter will discuss the development of the questionnaire and then present data on the predictors of cannabis use and the age of onset of cannabis use as a method of testing the CannaForm's utility.

The proposition that cannabis use has a causal role in cognitive impairments has received changing levels of support since the research began. In response to a key publication by Solowij et al (2002), Pope (2002; p.1173) stated that "The consensus across studies is strong enough to discount the likelihood that this finding can be explained by any combination of confounders", referring to the long term effects of cannabis use. Despite this claim a publication in the subsequent year reported that cognitive deficits in cannabis users disappeared after controlling for verbal IQ (Pope et al., 2003). Contrary to Pope's (2002) statement, it is clear that confounding variables play a large role in quasi-experimental studies (see Table 5.1). In order to understand the true long term effects of cannabis these variables need to be considered. The current study aims to test the utility of the CannaForm by testing whether lifestyle variables previously found to be related to executive function are related to cannabis use and additionally, if they are related to the age of onset of cannabis use. The relationship between cannabis use/lifestyle variables and executive function will not be discussed here, however only variables with this association will be investigated (see Eysenck et al., 2007; Grimley & Banner, 2008; Jacobsen et al., 2005; Romine & Reynolds., 2005; Yonker et al., 2005).

Table 5.1.

A table displaying how different studies have addressed confounding variables when examining cognition in cannabis users

Author	Gender	Age	Education	IQ	Mental Health	Alcohol Abuse	Alcohol Use	Other Drug Use*	Tobacco Use	Recent Drug[a] Use
Pope et al (1996)	S	GM	GM, S	S	Ex	Ex	-	Ex	-	U
Pope et al (2001)	GM, S	GM, S	D	S	Ex	Ex	GM	Ex	D	U
Solowij et al (2002)	GM, S	D	GM	S	Ex	Ex	-	Ex	-	U
Pope et al (2002)	GM, S	GM, S	D	S	Ex	Ex	-	Ex	-	U
Bolla et al (2002)	GM	GM	D	GM, S	Ex	Ex	Ex, GM	-	-	U
Pope et al (2003)	GM, S	S	D	S	Ex	Ex	-	Ex	-	U
Whitlow et al (2004)	GM	GM	S	GM	Ex, GM	Ex	GM	-	S	U
Medina et al (2007)	GM	GM	GM, D[b]	GM	Ex, GM, D[c], S	-	S	D	D	U
McHale et al (2008)	R	GM	-	-	-	-	Ex	Ex	S	Q
Fontes et al (2011)	D	GM	GM	GM, Ex	Ex	-	-	-	-	U
Gruber et al (2011)	R, S	GM	-	GM	Ex, GM	Ex	Ex	Ex	-[d]	U
Grant et al (2012)	GM	GM	GM	-	Ex	-	GM	Ex	GM	-
Becker et al (2014)	S	GM	GM[e]	GM, S	Ex	-	S	Ex	D, Ex[f]	Q
Thames et al (2014)	S	S	GM	S	Ex	D, GM	S	Ex	-	U

Note. - = not reported/not enough information provided; S = statistically controlled for; Ex = exclusion criteria; GM = groups matched; D = differences between groups and no reported attempts to account for this; R = reported descriptive information; U = urine tests; Q = questionnaire; IQ = Intelligence Quotient;* the studies differed quite widely on their exclusion criteria for other drug use. [a] any illegal drug inclusive of cannabis however widely different criteria was used over these studies. The majority of the statistical studies controlling for IQ violated assumptions for covariate tests. [b] years of

education did not differ but school achievement did differ; [c] anxiety did not differ but depression did differ; [d] no subjects met criteria for nicotine dependence; [e] controlling for sex; [f] cannabis users were excluded if they were daily tobacco smokers yet the group did still use tobacco.

5.1.2. Lifestyle Variables

Section 1.5 of the current thesis identified a list of 12 putative confounds as a way of considering factors which need to be controlled when conducting quasi-experimental research on cannabis and cognition. This list included IQ, education, sex, mental health, tobacco use, brain trauma, learning disabilities, familiarity with the English language, alcohol use, drug use and recent alcohol/drug use. When conducting quasi-experimental or correlational research the number of potential confounding variables is practically limitless, therefore time, costs and other pragmatic considerations dictate that only the most salient putative confounds should be considered. Typically, putative confounds are associated with cannabis use in general, however this also examines if established confounds differ according to the age at which an individual initiates cannabis use. In order to assess the prevalence of confound measures, Table 5.1 shows the frequency of confounds considered by studies administering neuropsychological assessments of executive function. The methods for dealing with confounds varied widely however they approximately fitted into the categories of: (1) creating exclusion criteria to avoid the confound having an effect, (2) 'matching' the groups to distribute the effects of the confounding variable evenly across groups and (3) statistically accounting for the variable by methods such as an analysis of covariance. The different methods employed within each of these three categories differ in validity, and therefore it is essential that this is considered when comparing different studies based on the codes presented in Table 5.1. On occasions the groups were not matched for a particular variable (e.g. Education; Pope et al., 2001). In such circumstances the difference between groups is reported and thus the results can be interpreted in light of this confound. The following confounds were picked based on associations with cannabis and executive function, however it is the association with cannabis variables which will be discussed as that is the focus of this study.

5.1.2.1. Sex as a Confounding Variable

Assessing sex differences in cannabis use has produced a range of different outcomes. Without controlling for any other variables there are no noticeable differences in trying cannabis at least once between the two sexes (Home Office, 2008; Tu et al., 2008). Furthermore, a logistic regression analysis which controlled for numerous other variables found that males were 1.17 times more likely to have used cannabis at least

once however this odds ratio was not statistically significant (McCrystal & Percy, 2011).

Despite no sex differences being apparent for at least one use of cannabis, males are reportedly 2.3 times as likely to have used cannabis in the past year as females (Home Office, 2008) and over 1.8 times as likely to use cannabis heavily (Tu et al., 2008). Tu et al (2008) also found that males were more likely than females to start using cannabis at a younger age.

These heterogeneous cannabis use patterns across the sexes suggest that if cannabis does have a causal impact on cognitive integrity then it is likely that such effects will also be varied across the sexes. In addition to varied cannabis use behaviours, there is also strong evidence that male and female brain maturation trajectories are not synchronised. Males appear to be one to two years behind, with female frontal grey matter peak volumes occurring at around age 11 and males around age 12.5 (Giedd et al., 1999). Despite showing marginally different ages at which frontal volumes reach their peak (9.5 vs. 10.5), the finding of males trailing females by one to two years was also found by Lenroot et al (2007). There now appears to be three lines of evidence suggesting that males are more at risk to the effects of cannabis 1) of those who do use cannabis, males are more likely to use it heavily, 2) males are more likely to use cannabis early in life and 3) neuromaturational processes are likely to be at an earlier stage in males than females at the same point in time (e.g. 12 years old). These last two points are built on the premise that cannabis use at earlier stages in development is potentially more damaging to the structure and function of the brain, a position argued for in section 1.3.

5.1.2.2. Education as a Confounding Variable

The majority of research investigating the link between educational variables and cannabis use has been done outside of the UK. In Australia and New Zealand, cannabis use has been found to be related to school attendance and attitudes towards school (Jones & Heaven, 1998), while the age of onset of cannabis use has been related to high school completion, university enrolment and university completion (Horwood et al., 2010). In the United States of America (USA) cannabis use has been associated with school drop-out rates (Mensch & Kandel, 1988; Lynskey et al., 2003a) and educational

achievement (Novins & Mitchell, 1998). The UK has not been part of the main body of research within this field and as schooling systems and cannabis strains differ widely across countries there are problems extrapolating findings from one country to another. One UK based study investigating schizophrenic symptoms and cannabis in the general population found that individuals with undergraduate degrees or postgraduate degrees were less likely to have used cannabis than those with GCSEs or no educational qualifications (Freeman et al., 2013). A Northern Ireland based study found a trend for GCSE grades predicting whether or not an individual had previously used cannabis and thus partially supporting Freeman et al's (2013) results (McCrystal & Percy, 2011).

All of these studies have discovered an association between cannabis use and a particular educational variable yet establishing causation is problematic. The use of epidemiological approaches has helped establish timelines (e.g. Lynskey et al., 2003a) and suggests that early onset cannabis tends to precede school drop outs. Several explanations have been proposed for how cannabis use could lead to poorer educational outcomes including amotivation, cognitive deficits, and an early transition into 'adult roles' (Lynskey & Hall, 2000). The evidence for cannabis induced amotivation is mixed (Musty & Kaback, 1995; Barnwell, Earleywine & Wilcox, 2006) and therefore seems the least likely route to explain the poorer educational outcomes. Lynskey and Hall (2000) suggested that regular cannabis use could lead to the deterioration of scholastic functioning via the acute effects of cannabis however they highlighted that there was limited evidence of longer lasting cognitive impairments. Since this study there have been numerous advances in this area and several studies highlight long lasting impairments (Pope et al., 2001, 2002, 2003; Medina et al., 2007; Hanson et al., 2010). These deficits appear in domains such as memory, attention, and executive function, key predictors of scholastic achievement (Riding et al., 2003; Grimley & Banner, 2008). The third explanation is that cannabis use leads to the early transition into 'adult roles' such as leaving school early. It also includes the social setting in which cannabis takes place which includes surrounding themselves with 'delinquent peers' (Fergusson & Horwood, 1998). The use of twin studies has helped explain some of the association between cannabis use and education. Verweij, Huizink, Agrawal, Martin and Lynskey (2013) recruited over 3000 mono- and di-zygotic twins to explore the influence of environment and genes on cannabis and education. The authors found that the link between cannabis use and school leaving was primarily due to genetic and shared-

environmental factors, leaving little explanatory power for cognitive impairments, non-shared environment and amotivation. In contrast, Horwood et al (2010) argue that based on a dose-related effect for the age of onset and frequency of use, in addition to controlling for numerous confounding variables, the best explanation is a causal effect of cannabis use on poorer educational outcomes. The authors concede that they could not control for genetic influences, and given the results by Verweij et al (2013) it appears possible that genetics are the best candidate for explaining the results.

It is also likely that the extent to which these variables are involved will depend upon the outcome being assessed, whether it is early school leaving (e.g. Verweij et al., 2013) or educational achievement (e.g. McCrystal & Percy, 2011). It is also possible that there is a dual causation effect implying that not only does cannabis lead to poorer educational outcomes, but early school leaving/lower grades leads to cannabis use (Lynskey & Hall, 2000).

5.1.2.3. Drugs as Confounding Variables

An early exploration into the association between cannabis and other legal and illegal recreational drugs found that the use of other drugs was highly related to cannabis and that the onset of use progressed from 'softer' to 'harder' drugs (Kandel, 1975). These associations remain after controlling for other variables, for example Patton, Coffey, Carlin, Sawyer and Lynskey (2005) found that in Australia, the use of cannabis was highly related to the use of tobacco even after adjusting for alcohol use, physical activity, mental health, sex, and parental smoking habits. The authors found similar adjusted relationships between alcohol use and cannabis use, and to a lesser extent with alcohol use and tobacco use. The widely popularised explanation for the progression of drug use is known as the *gateway hypothesis*. This causal explanation is that the use of 'softer' drugs can directly lead to the use of 'harder' drugs through either pharmacological or psychological means (Kandel et al., 2006). Despite widespread public endorsement for the gateway hypothesis, such as commercials containing testimonials of cannabis related gateway effects (Yzer, Cappella, Fishbein, Hornik & Ahern, 2003), the evidence in support of the gateway hypothesis is controversial and varies from drug-to-drug. There is still some dispute regarding which drug is the gateway drug with tobacco (Prince vaan Leeuwen et al., 2014), alcohol (Kirby & Barry, 2012) and cannabis (Secades-Villa, Garcia-Rodriguez, Jin, Wang & Blanco, 2015)

being prime candidates. As these studies vary in country of origin there remains the possibility that cultural differences result in different progression patterns through the drug spectrum. Such cultural differences include attitudes towards drugs and the availability and cost of specific drugs (Agrawal et al., 2012). Furthermore, the extent to which genes and upbringing affect the association depends on the individual drug. It appears that tobacco use and cannabis use could be highly influenced by genes (Maes et al., 2004; Verweij et al., 2010) while the association between cannabis use and other illegal drugs is only partially due to familial influences (Lynskey et al., 2003b). While a causal explanation is possible, the access hypothesis seems another viable alternative. This explanation for the high comorbidity of drug use behaviours suggests that drug users, by the act of purchasing an illegal drug (e.g. cannabis), have access to a wide range of other illegal drugs from the same source (Macoon, 2006). This would only be applicable to countries in which cannabis is illegal and would not be an explanatory factor for the link between tobacco/alcohol and illegal drugs. Although there is some evidence that the use of certain drugs increases the likelihood of *abusing* other drugs (e.g. Cadoni, Pisanu, Solinas, Acquas & Di Chiara, 2001) there is a lack of causal evidence suggesting a link between drug (A) *use* and drug (B) *use*.

5.1.2.4. Mental Health as a Confounding Variable

Cannabis use has been associated with a large number of different mental health diagnoses and it is the purpose of this section to identify the associations between these factors. Correlational and regression analyses have shown that increased use of cannabis use is associated with a number of mental health categories, including: depression - as determined by DSM-IV criteria (Rey, Sawyer, Raphael, Patton & Lynskey, 2002), anxiety - as determined by DMS-IV criteria (Patton et al., 2002), obsessive compulsive disorders - as determined by diagnostic interview (Crum & Anthony, 1993), schizophrenia - as determined by the International Classification of Diseases 8th revision (ICD-8) criteria, administered by a psychiatrist (Zammit, Allebeck, Andreasson, Lundberg & Lewis, 2002) and eating disorders - as determined by the Diagnostic Survey for Eating Disorders - Revised (DSED-R; Weiderman & Pryor, 1996). To assess the causal nature surrounding cannabis use and this large number of various mental health diagnoses is beyond the scope of this chapter, yet the primary goal was to highlight the association between these variables.

In addition to the mental health of the individual, the mental health of family members could be a risk factor for drug use. Research has shown a link between parental mental health and the quality of family-child relationships via meta-analyses for fathers (Wilson & Durbin, 2010) and mothers (Lovejoy, Graczyk, O'Hare & Neuman, 2000). Butters (2002) found that poor family relations, characterised by less parental involvement and parental monitoring, was associated with an increase in cannabis use and problem cannabis use after controlling for confounds including socio-economic status. Furthermore, a large number of mental health conditions have a genetic component (Levinson, 2006; Lichentstein et al., 2009; Martin, Ressler, Binder & Nemeroff, 2009) and therefore young individuals with diagnosed parents may be displaying undiagnosed symptoms which could lead to self-medication with certain drugs (e.g. cannabis; Swift, Gates & Dillon, 2005). These two mechanisms could suggest that individuals with parents who have mental health conditions could be at an increased risk for cannabis use.

5.1.3. Aims and Hypotheses

The present study had three major aims. (1) To develop a new cannabis questionnaire; (2) to test whether a relationship exists between potential confounding variables and cannabis use in order to replicate previous findings; and (3) to determine whether a relationship exists between confounding variables and the age of onset of cannabis use. This will add to the literature by assessing if some confounding variables are more strongly associated with early onset users than late onset users. Logistic regression was used to investigate these relationships. It is hypothesised that all variables put into the analysis will be related to cannabis use and that these variables will be associated with early onset cannabis use greater than late onset cannabis use.

5.2. Method

5.2.1. Participants

The participants for the current survey were 329 individuals recruited by opportunity sampling methods. The sample included 256 females (78.0%) and 72 males (22.0%), with one participant not reporting their sex. The majority of the sample was in their late teens and early twenties. The median age was 19.00 (interquartile range=2.00; range=18-50). The majority of the participants were recruited from university campus

grounds and student accommodations. Individuals were approached by the experimenter and asked to complete a lifestyle questionnaire. Although a large number of non-student participants were recruited as part of the other stages of this research, only the participants recruited opportunistically were included in this analysis which left a sample of 100% students.

5.2.2. Design

The current study takes the form of a cross-sectional survey based design. For the first logistic regression analysis, the dichotomous criterion variable was whether or not an individual has used cannabis (coded as '1' and '0', respectively). For the second logistic regression, the dichotomous criterion variable was whether or not an individual initiated cannabis use before the age of 16 (coded as '1' and '0', respectively). The predictor variables across both regression models were the years of education (continuous), educational achievement (continuous; total number of GCSEs grades A*-C), sex (dichotomous - male or female), a history of mental health or learning disorders (dichotomous - yes or no), estimated total lifetime tobacco use (continuous), age (continuous), other drug use (continuous), and number of days per week that alcohol is consumed (continuous).

5.2.3. CannaForm Development

The first stage in development was determining what information was required from the questionnaire (Rust & Golombok, 1989). Although the primary purpose of this questionnaire was to identify inclusion and exclusion criteria for the quasi-experimental studies discussed in Chapters Three and Four the CannaForm also was designed to answer broader questions relating to many aspects of cannabis research. As a starting point, the cannabis questionnaire by Solowij (1998) was examined to determine what sort of questions could be asked. Elaborating on this template, the primary researcher and his three supervisors determined which questions were kept in order to collect information on the following topics: age, sex, education, mental health, neurological health, alcohol use, tobacco use and illegal drug use. Within the bracket of illegal drug use, cannabis use was considered the primary research interest and therefore the sub topics of cannabis use were also considered: age of onset, frequency of use, length of

use, lifetime use, recent use, methods of administration, strains of cannabis used, and desired intoxication levels.

Following the identification of the topics of interest, the wording of questions, the response format and the ordering of questions was then decided (Rust & Golombok, 1989). Once the final draft of the first version was created, the CannaForm was piloted on two self-reported "heavy cannabis users" recruited opportunistically. Verbal feedback was given to the primary researcher and necessary alterations were made. The new CannaForm v1.0 (see Appendix A.2.1.1) was then used for the first study described in Chapters Three and Five in which 378 participants were recruited. Following inspection of these 378 questionnaires, certain questions were identified which needed altering based on responses which indicated a poor wording of the associated question, several questions were added based on additional information which was required, and redundant questions which were not needed were removed. These changes were made and the creation of a markers guide for the CannaForm (see Appendix A.2.1.5).

At this stage two further self-reported "heavy cannabis users" were purposively recruited through a local cannabis activist website to pilot the most recent version of the questionnaire. Minor alterations were made to the CannaForm based on suggestions from these cannabis users which resulted in the CannaForm v2.0 (see Appendix A.2.1.2). This version of the CannaForm was then used during the data collection for the eye-tracking study.

Throughout the whole process a number of additional changes were considered yet not implemented due to the ongoing data collection of a large sample reported in this chapter. The predetermined amalgamation of the data from the two large samples that completed the CannaForm v1.0 and v2.0 necessitated that certain questions could not be altered throughout the process. This ensured that a question (e.g. total drug use) analysed in the current chapter - in which the samples were combined - was not answered in two different ways due to an altered question. After the data collection was complete all other changes were made, leading to the most up-to-date version of the CannaForm which has yet to be trialled (see Appendix A.2.1.3).

5.2.4. Procedure

Following the recruitment stage, participants were administered the CannaForm in one of three ways including self-report by the participants, face-to-face interview with the experimenter reading out the questions and over the phone interviews, with the experimenter reading out the questions. The interview format enabled consistent responses as the experimenter could collect the necessary information while self-reporting frequently led to questions not being completed to sufficient levels of detail. The method of administration was based on the particular recruitment strategy. Self-report and face to face interviews were selected when the individuals were approached in person by the experimenter. If the participant could complete the questionnaire at that point in time, an interview method was employed. If the participant had no free time or a larger amount of participants were approached at once, then the self-report method was employed and the completed questionnaires were handed directly back to the researcher at an agreed time. The telephone interviews only took place when an individual responded to the notification put onto the local cannabis activist group's Facebook group or associated websites. This mixture of methods could lead to different responses and inconsistent reporting as previously shown for self-report vs. interview methods (Tourangeau & Yan, 2007). As the CananForm has yet to be subjected to inter-administration reliability testing it is not clear how responses would differ, however other questionnaires on illicit drug use typically find that individuals report marginally higher levels of use on self-report questionnaires as opposed to face-to-face interviews (Tourangeau & Yan, 2007). These limitations need to be considered when interpreting the results.

Each participants was then debriefed either with a paper or electronic copy of the debrief sheet, however selected participants were also contacted, where suitable, to take part in follow up experiments described in Chapter Three and Four.

5.2.5. Data Analysis

5.2.5.1. Logistic Regression

The logistic regression model was built primarily based on the Hosmer and Lemeshow (2000) method with additional suggestions from Field (2013) and Menard (2002). Once a target variable was determined (cannabis use), any predictor variables which have

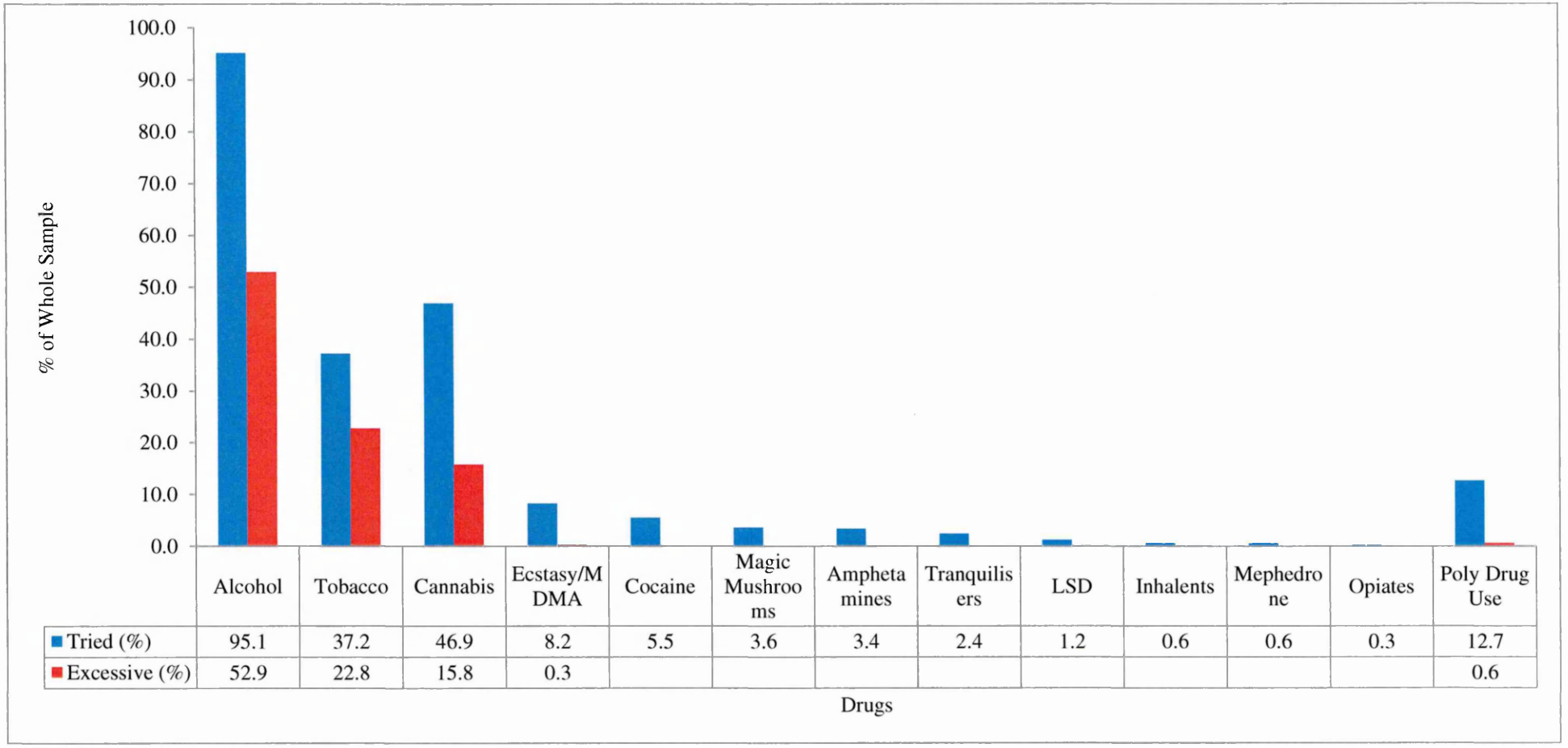
scientific interest (i.e. derived from the hypotheses) and impose a direct effect or have a confounding effect should be considered. Any other variables were disregarded due to overfitting and poorer generalizability. Once potential predictors had been identified a range of assumptions were explored. Firstly contingency tables were examined to check if there was incomplete information among the dichotomous predictor variables with the outcome variable (Field, 2013). If this violation occurred the categories were either collapsed if the interpretation was not adversely affected by this or another variable to assess the same underlying construct was found. Univariate logistic regression analyses were then run to test whether any of potential predictors were associated with the outcome variable ($p<.25$; Hosmer & Lemeshow, 2000). The model was then built in a hierarchical fashion by starting with the strongest predictor and adding each subsequent potential predictor to determine if it added a significant proportion of explained variance to the model. Suggestions on model building typically encourage parsimony by not including non-significant predictors (Hosmer & Lemeshow, 2000; Field, 2013) and therefore any non-significant variables in the adjusted model were left out of the final model however the univariate relationship can be seen in the unadjusted model. Although there were multiple methods of assessing the same variable (i.e. days per week of alcohol use and units per week of alcohol use), only one was selected in such circumstances to reduce the risk of multicollinearity and overfitting, and to aim for parsimony. Therefore the selection of which variable was chosen, was made based on proportion of variance explained and theoretical importance. Once the final model was chosen residuals (Cook's Distance, DF beta to the Constant and the Standardised Residuals) were examined based on suggestions by Field (2013) and Menard (2002). Any outliers identified by examining the residuals were removed, and the model was re-run to determine if an improvement in pseudo-R^2 was noticeable. To check the Goodness of fit and the associated over-dispersion assumptions, the Hosmer and Lemeshow test was examined to determine if the observed data differed from the predicted data (Hosmer & Lemeshow, 2000). A non-significant chi-square from this test suggested a good fit of the data. Furthermore, dividing the chi-square figure by the association degrees of freedom provides an index to assess over-dispersion. A value near to 1.00 is considered normal (Menard, 2000) while a value approaching 2.00 could be problematic (Field, 2013). Finally, Variance Inflation Factor (VIF) and Tolerance

statistics were observed to see if any violations of multicollinearity were present. Violations were apparent when VIF>10 and Tolerance <.01 (Meyers et al., 2013).

5.3. Results

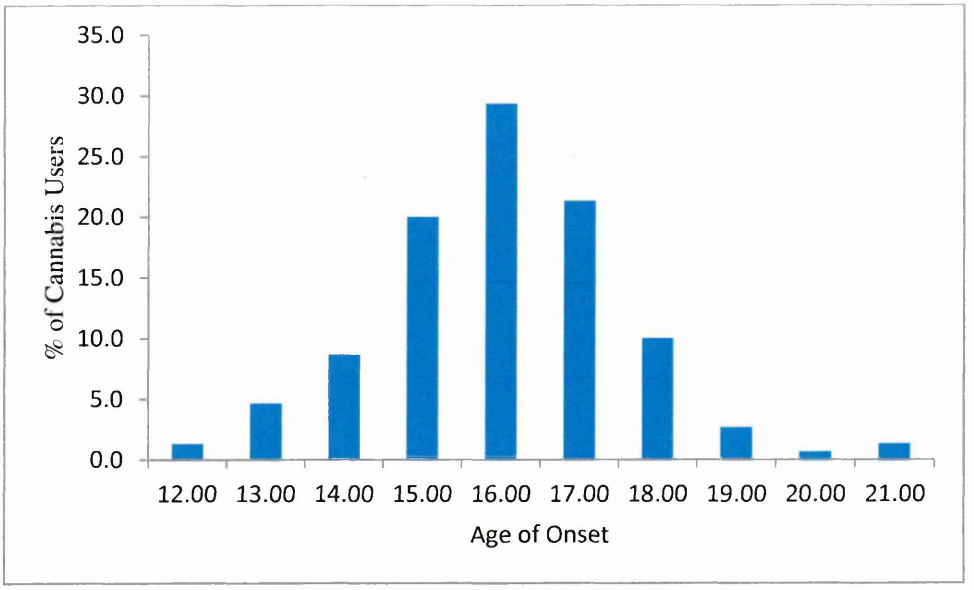
5.3.1. Drug Use Data

Figure 5.1 shows the percentage of the current sample which have tried different drugs at least once in their lifetimes. These data should not be interpreted as being representative of the general population as the data sampling methods were opportunistic.. Figure 5.1 also shows the percentage of the sample which has used each drug *excessively*. The excessive drug use data was determined by UK guidelines on safe limits for alcohol: more than 14 weekly units for women and more than 21 units for men were considered excessive. The excessive criteria for the other drugs was largely arbitrary, the main distinction was to separate those who had just used a few times and those who had used it regularly. In this context the term *excessive* should not be taken literally as no clear guidelines have been created regarding what constitutes safe or excessive illegal drug use. Therefore, for tobacco and all illegal drugs excessive use was determined by more than 100 lifetime uses.



	Alcohol	Tobacco	Cannabis	Ecstasy/MDMA	Cocaine	Magic Mushrooms	Amphetamines	Tranquilisers	LSD	Inhalents	Mephedrone	Opiates	Poly Drug Use
Tried (%)	95.1	37.2	46.9	8.2	5.5	3.6	3.4	2.4	1.2	0.6	0.6	0.3	12.7
Excessive (%)	52.9	22.8	15.8	0.3									0.6

Figure 5.1. The percentage of the sample which have used tried and used a drug excessively in their lifetimes. LSD=Lysergic Acid Diethylamide; MDMA= 3,4-Methylenedioxy-*N*-methylamphetamine. Excessive alcohol use is defined as >14 units a week for women and >21 units a day for men. Excessive tobacco and cannabis use is defined as >100 lifetime uses for both sexes.



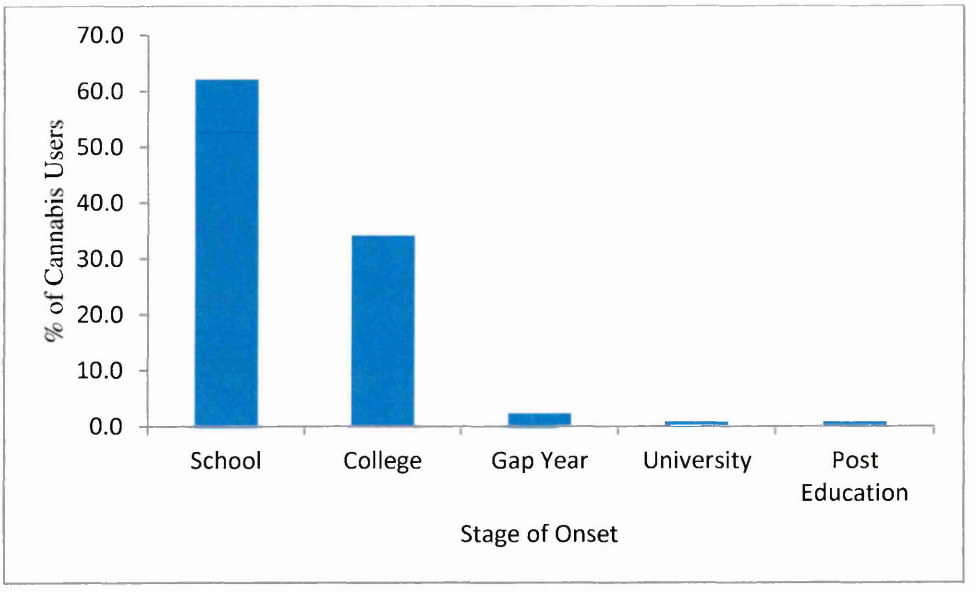


Figure 5.2. Two graphs displaying the percentage of cannabis users within the current sample who started using cannabis at various stages and ages in life.

The majority of individuals started using cannabis at school (62.1%), college onset was less prevalent at 34.1%, followed by gap year at 2.3%, university at 0.8% and post-education at 0.8% (see Figure 5.2). When considering the age of onset, it is clear that the majority starting using around age 16 (*M*=16.02 years; SD=1.58; range=12-21 years).

5.3.2. Predictors of Cannabis use - Logistic Regression Model

5.3.2.1. Building the model

As discussed in the data analysis section of the method, the current analysis used the Hosmer and Lemeshow (2000) method for constructing a logistic regression model. The criterion variable (Y_{lr}) was whether the individual had used cannabis at least once in their lifetime, or never at all. The potential predictors were sex, age, mental health (presence/absence; type), family's mental health (presence/absence; type), developmental disorders (presence/absence; type), tobacco use (use/no use; quantity of use; dependence/no dependence), other drug use (use/no use; number of different drugs), alcohol use (days per week of drinking; units consumed per week), educational achievement (total number GSCEs; number of GCSEs grades A*-C), years in education, and nationality. The model building procedure led to the selection of seven predictor variables.

The final model included the criterion variable (Y_{lr}), which was whether the individual had used cannabis at least once in their lifetime, or never at all. The explanatory variables which were considered for the model were (X_1) sex (male/female), (X_2) history of mental health problems (yes/no), (X_3) family history of mental health problems (yes/no), (X_4) years of education (continuous), (X_5) GCSE grades A*-C (continuous), (X_6) history of tobacco use (yes/no) and (X_7) days of alcohol use per week (continuous).

5.3.2.2. Assumptions

There were 329 participants originally tested for the model, 48 were left out due to missing data leaving 281. All potential predictors were associated with the outcome variable in a univariate logistic regression model ($p<.25$). The hierarchical model building procedure suggested that age, years of education and mental health were not associated with the outcome variable. Cook's distance, standardised residuals and DF beta to the constant were checked and 6 cases were identified as outliers based on criteria outlined by Field (2013). Following Hosmer and Lemeshow's (2000) guidelines, the cases were removed from the model and the analyses re-run. The Negelkerke pseudo R^2 was noticeably improved after the removal of these outliers and therefore they were not re-entered into the model. As there were only five predictor variables and now 275 cases in the final model, the assumption of overfitting was not

violated (Meyers et al., 2013). Linearity of the logit was tested for all continuous variables and was not violated. Goodness of fit statistic was checked and this fell within the ideal range [$\chi^2_{(8)}$=9.36, p=.313] (Hosmer & Lemeshow, 2000). The dispersion value came to ϕ=1.17 and was near enough to 1.00 to suggest there were no problems (Menard, 2002; Field, 2013). Collinearity diagnostics were checked and tolerance levels were all larger than 0.1 and VIF levels were all smaller than 10, suggesting that collinearity assumptions were not violated (Meyers et al., 2013).

5.3.2.3. Running the Model

The finalised model was run in a forced entry manner. The logistic regression analysis showed that the combined predictor variables were significantly related to cannabis use [$\chi^2_{(5)}$=125.59, p<.001, Cox & Snell R^2=.367, Negelkerke R^2=.489]. Further examination of the variables in the equations (see Table 5.3) suggests that sex is a significant predictor of cannabis use with males being approximately 5.09 times as likely to use cannabis as females. Tobacco use is a larger predictor with individuals who have used tobacco being approximately 12.08 times as likely to use cannabis as those who have not used tobacco. Alcohol use is also a significant predictor of cannabis use with every additional day of alcohol use per week conferring a 1.95 times greater risk of trying cannabis. Educational achievement was negatively related to cannabis use, with every additional GCSE grade conferring a reduction in likelihood of trying cannabis with an odds ratio of 0.82. Individuals who reported having a family member with mental health problems were approximately 2.95 times as likely to use cannabis. All remaining variables report in Table 5.3 under the unadjusted odds ratio column were not significantly related to cannabis use after controlling for covariates and were therefore not included in the final model (Hosmer & Lemeshow, 2000, Field, 2013).

Table 5.3.

Adjusted and unadjusted odds ratios for cannabis use predictor variables.

	Unadj. OR	*p*-value	Adj. OR	*p*-value
Sex	3.65 (2.05, 6.50)	**<.001**	5.09 (2.28, 11.38)	**<.001**
Age	1.19 (1.05, 1.35)	**.004**		
Individual's MH	1.59 (0.82, 3.08)	.085		
Family's MH	2.51 (1.35, 4.69)	**.002**	2.95 (1.25, 6.98)	**.006**
Years of Ed.	1.17 (1.01, 1.35)	**.016**		
GCSEs	0.84 (0.75, 0.94)	**.002**	0.82 (0.70, 0.96)	**.007**
Tobacco Use	9.26 (5.38, 15.91)	**<.001**	12.08 (6.02, 24.24)	**<.001**
Days of Alcohol Use	1.73 (1.39, 2.16)	**<.001**	1.95 (1.42, 2.67)	**<.001**
Disabilities	1.91 (0.72, 5.05)	.097		

Note. OR= odds ratio; 95% confidence intervals are reported in brackets; MH= mental health; Ed.= education. All *p*-values reported are 1-tailed.

5.3.3. Predictors of the Age of Onset of Cannabis Use - Logistic Regression Model

5.3.3.1. Analysis selection

The proposed method for analysis was going to be a multiple regression with the age of onset of cannabis use serving as the continuous criterion variable. Subsequent assumption testing suggested that normality and linearity were violated thus a multiple regression could not be run. As the current research programme has used an age of onset split of ≤15 and ≥16 years the most appropriate solution for this problem seemed to be converting the continuous criterion variable into a dichotomous variable using a median split and running a logistic regression. The disadvantages of this method is that not all studies use the same early/late criteria and therefore an early onset group described here may not the same as those described in other studies. The advantages of choosing the logistic regression is that it is not subject to the same assumptions which have already been shown to be violated, furthermore it allows continuity between the term early onset used in this chapter and those described in the other experimental chapters.

5.3.3.2. Building the Model

The potential predictor variables were selected in a similar manner to the first logistic regression. The criterion variable (Y_{lr}) was the age at which an individual first used cannabis. The potential predictors were sex, age, mental health (presence/absence; type), family's mental health (presence/absence; type), developmental disorders (presence/absence; type), tobacco use (use/no use; quantity of use; dependence/no dependence), other drug use (use/no use; number of different drugs), alcohol use (days per week of drinking; units consumed per week), educational achievement (total number GSCEs; number of GCSEs grades A*-C), years in education, and nationality.

The explanatory variables which were used for this analysis were: (X_1) age, (X_2) sex, (X_3) GCSE grades, (X_4) years of education, (X_5) mental health, (X_6) lifetime tobacco use, (X_6) lifetime other drug use and (X_7) weekly alcohol use.

5.3.3.3. Assumptions

There were 180 participants originally tested for the model, 31 were left out due to missing data leaving 149. Only three of the potential predictors were associated with the outcome variable in a univariate logistic regression model ($p<.25$). The hierarchical model building procedure suggested that only a history of drug use and GCSE grades provided a significant contribution to the model. The remaining non-significant predictors were left out of the final model. Cook's distance, standardised residuals and DF beta to the constant were checked and 0 cases were identified as outliers based on criteria outlined by Field (2013). As there were only two predictor variables and now 142 cases in the final model, the assumption of overfitting was not violated at 30:1 (Meyers et al., 2013). Linearity of the logit was tested for all continuous variables and was not violated. Goodness of fit statistic was checked and this fell within the ideal range [$\chi^2_{(6)}=2.55$, $p=.863$] (Hosmer & Lemeshow, 2000). The dispersion value came to $\phi=0.33$ which suggests a slight underdispersion (Menard, 2002; Field, 2013). Collinearity diagnostics were checked and tolerance levels were all larger than 0.1 and VIF levels were all smaller than 10, suggesting that collinearity assumptions were not violated (Meyers et al., 2013).

5.3.3.4. Running the Model

The finalised model was run in a forced entry manner. The logistic regression analysis showed that the combined predictor variables were significantly related to cannabis use [$\chi^2_{(2)}$=8.13, p=.017, Cox & Snell R^2=.056, Negelkerke R^2=.076]. Further examination of the variables in the equation (see Table 5.4) suggests that drug use is a significant predictor of the age of onset of cannabis use with illegal (non-cannabis) drug users being approximately 2.32 times as likely to be an early onset cannabis user. Educational achievement was a significant predictor of the age of onset of cannabis use, with every additional GCSE grade conferring a reduction in likelihood of being an early onset user with an odds ratio of 0.84.

Table 5.4.

Adjusted and unadjusted odds ratios for the age of onset of cannabis use predictor variables.

	Unadj. OR	***p*-value**	**Adj. OR**	***p*-value**
Sex	0.78 (0.38, 1.63)	.258		
Age	0.98 (0.89, 1.08)	.340		
Individual's MH	1.35 (0.56, 3.26)	.253		
Family's MH	1.44 (0.65, 3.18)	.184		
Years of Ed.	1.03 (0.86, 1.23)	.382		
GCSEs	0.84 (0.70, 1.02)	**.037**	0.84 (0.69, 1.02)	**.036**
Tobacco Use	1.03 (0.51, 2.12)	.463		
Days of Alcohol Use	1.10 (0.81, 1.48)	.275		
Disabilities	2.37 (0.69, 8.20)	.086		
Drug Use	2.39 (1.13, 5.05)	**.011**	2.32 (1.09, 4.98)	**.015**

Note. See table 5.3 for notes.

5.4. Discussion

5.4.1. The CannaForm

The current study introduces a new cannabis questionnaire which was trialled on a large sample. Face validity was confirmed by self-reported heavy cannabis and other drug users who completed the questionnaire at two separate stages in development. The exclusion criteria, inclusion criteria, drug use data, and demographic data used throughout Chapters Three and Four, were all collected from this questionnaire. Furthermore, the data reported in the current chapter suggests that the CannaForm can be utilised to answer broader research questions relating to cannabis use.

5.4.2 The Age of Onset of Cannabis Use

The current study highlights that the majority of cannabis use occurs during the school years however as the median age of the participants at time of testing was 19 the non-cannabis users may go on to use cannabis post-education later in their lives. The key finding was that the majority of cannabis users start using cannabis around the age of 16, a time when in full time education. Given the well documented acute effects of cannabis on memory (Ranganathan & D'Souza, 2006), hangover effects of cannabis on a range of cognitive variables (Pope et al., 1996), and the longer lasting effects on learning and other cognitive variables (Schreiner & Dunn, 2012) the use of cannabis could interfere with educational development both in school and out (i.e. homework; revision etc.)

5.4.3. Lifestyle Confounds and Cannabis Use

The first logistic regression model assessed how a number of variables were related to the use of cannabis. The model found that being male, having a family history of mental health problems, having a history of tobacco use, and having a greater frequency of alcohol use were associated with an increased risk of using cannabis. In contrast, having a greater number of GCSEs was associated with a reduced risk of using cannabis. While age and years of education were significantly related to cannabis use in the univariate model, after controlling for confounding variables the significant effect was removed. The presence of mental health and learning disabilities was not related to cannabis use at any stage of the analysis. It should be noted that this was just a minimum of one use

of cannabis, and these variables were not tested to determine if they predict regular cannabis use or abuse.

5.4.2.1. Sex

Previous studies observing the effects of sex on cannabis use have reported little or no difference between males and females (Home Office, 2009; McCrystal & Percy, 2011; Tu et al., 2008). In contrast to these studies the current analysis found the males were 5.09 times more likely to use cannabis than females while controlling for a number of other variables seen in Table 5.3. While the Home Office (2008) and Tu et al (2008) just reported the unadjusted percentages, the current study controlled for alcohol use, mental health, tobacco use and a number of other variables. In contrast, McCrystal and Percy (2011) used a similar logistic regression model and thus the differences between their study and the current one is unlikely to be due to the controlling of confounding variables. The between study differences could be due to the sampling method as the current study primarily was opportunistic and it is possible there was a gender bias in this recruitment method which led to the disproportionately high percentage of cannabis user being male. The greater proportion of females in this study would not affect the outcome as the odds ratios are calculated based on the percentage of the groups (i.e. sex) which belong to a level of the criterion variable (e.g. cannabis use).

Tu et al (2008) also found that males were more likely to be early users of cannabis while the current study found no sex effects on the age of onset of cannabis use. It is possible that the sampling method explained these differences as the current study reported a disproportionately high number of females and those from university. Further research needs to address this question to determine if males are at a higher risk for initiating cannabis use at a younger age.

5.4.2.2. Education

Two educational predictor variables were utilised in the regression models: the years an individual has spent in education, which was only included in the cannabis use model, and the number of GCSE grades, which was used in both models. The years of education variable was not a significant predictor of cannabis use or the age of onset of cannabis use. In contrast, there was a clear effect of educational achievement. The

number of GCSEs was a significant predictor of both cannabis use and early onset cannabis use, with increased GCSEs conferring a protective factor for both.

In contrast to the current study, three other studies have found such an association (Lynskey et al., 2003a; McCrystal & Percy, 2011; Verweij et al., 2013). Possible explanations for this lack of a relationship between years of education and cannabis use is that the majority of the sample were recruited from universities and thus the number of years in education reflects a small subset from the entire range educational possibilities. School drop outs, non-university attendees, post-graduates were all under-represented within the sample. As Horwood et al (2010) identified that cannabis users are more likely to drop out of university than non-cannabis users it could be that such a relationship would have been found if a follow-up was conducted to determine how many of the original sample went on to complete their degrees. It is not possible to determine why the number of GCSEs conferred a protective risk to the age of onset of cannabis use from this study. Possible explanations include familial or genetic influences, peer influences, amotivation, and cognitive/intelligence impairments (Lynskey et al., 2003a; Horwood et al., 2010; Verwiej et al., 2013). Alternatively, another explanation which has not received any empirical investigation is whether the acute effects of regular cannabis use are influencing the educational problems. While intoxicated it would be harder to focus and absorb information due to the transient cognitive impairments (e.g. Hart et al., 2001). It is possible that cannabis use is a time-consuming hobby which reduced the amount of spare time and individual can spend learning. This explanation is consistent with evidence that educational achievement is more affected among the frequent cannabis users.

The current study assessed educational achievement by the number of GCSEs gained by each participant. McCrystal and Percy (2011) used a similar logistic regression model to that in the current study and the model included an assessment of achievement. McCrystal and Percy chose a categorical approach to assessing GCSE grades (A-C vs. D & lower) while the current study used the number of GCSEs to assess achievement. These differing methods did yield a different outcome with the current study finding a significant effect while McCrystal and Percy only report a trend for an association between achievement and cannabis use ($p<.10$). This could be due to the varying methods of assessing this construct.

The current study also found that a greater number of completed GCSEs was associated with a reduced chance of the individual being an early onset (prior to age 16) cannabis user. While early onset cannabis use is frequently associated with leaving school early, this association with GCSE grades is a novel finding in the literature. GCSE grades have been examined with cannabis use before (McCrystal & Percy, 2011) yet this association with the age of onset of cannabis use extends these findings. The use of a twin study, such as that done by Verweij et al (2013), could help determine whether the association between early onset cannabis use and educational achievement is due overlapping familial factors or due to a causal connection between the two variables.

5.4.2.3. Drug Use

The current study found that alcohol use and tobacco use were predictors of cannabis use in the first regression model. Other drug use was considered as a predictor but violated one of the assumptions due to it being *too good* of a predictor; no participants had used another drug without using cannabis. In the second regression model other drug use was included and was a significant predictor of the age of onset of cannabis use. Unlike the association with cannabis use, tobacco use and alcohol use were not related to the age of onset of cannabis use.

The association between cannabis use and other drug use (not reported in the model) builds on previous findings by (Agrawal et al., 2004). The association between other drug use and the age of onset of cannabis also supports previous research in this area which suggests that early onset cannabis users are more likely to use any other illegal drugs (Secades-Villa et al., 2014). While the current study used a dichotomous estimate of age of onset of early (≤15 years old) and late (≥16 years old) cannabis users, Secades-Villa et al (2014) used a continuous predictor variable. Despite these methodological differences both studies found that early onset use is associated with a greater likelihood of using other illegal drugs after controlling for confounding variables. Unlike Secades-Villa et al's study, a temporal sequence of drug use was not established for the current cohort meaning that it cannot be determined if early onset cannabis use preceded other drug use. This limits the ability to derive causal interpretations from the current data.

The association between tobacco use and cannabis use found in the current study supports previous work highlighting a link between tobacco use and cannabis use. A large proportion of research in this field has found associations between tobacco *use* and cannabis *dependence* (Prince vaan Leeuwen et al., 2014) or cannabis *use* and tobacco *dependence* (Patton et al., 2005) and thus the current findings do not directly support these findings, but rather add to them. As a small proportion of the current sample reported tobacco (1.9%) or cannabis (5.9%) dependence it is unlikely that it was dependence which was explaining the association.

The association found between alcohol frequency and cannabis use also builds on previous findings in the literature. Some studies have found links between alcohol use and cannabis use (Kirby & Barry, 2012) although the link between alcohol use and cannabis disorders disappears after controlling for covariates (Prince vaan Leeuwen et al., 2014). The current study used a different approach to measuring the association. Alcohol frequency was measured by the number of days per week when drinking alcohol and an increased frequency conferred a greater risk for cannabis use but had no effect on the age of onset of cannabis use.

5.4.2.4. Mental Health

The first analysis included two mental health predictors to identify the association with cannabis use. The mental health of the individual was not included in the final model as it was not significantly related to cannabis use however the mental health of family members was related to cannabis use. Despite previous research highlighting a link between multiple mental problems and cannabis use (Degenhardt et al., 2001; Rey et al., 2002; Patton et al., 2002; Moore et al., 2007) the current study did not replicate this relationship. This is likely due to a combination of methodological and sample characteristics. While the current sample was young in age it is unlikely that this solely explains the lack of association as Patton et al (2002) recruited a younger sample. The difference emerges when considering the assessment procedure, Patton et al (2002) used clinical interviews to assess mental health while the current study assessed whether an individual has met with a therapist or equivalent. This leaves the possibility that a number of individuals in the current sample may have had mental health problems but were yet to consult professional help. Furthermore, the current study conflated all mental health problems into one variable while other studies selectively test for specific

conditions, as different mental health problems carry difference risk and protective odds ratios for the onset of cannabis use (Rey et al., 2002) this method could be hiding specific condition associations.

Despite the individual's mental health not being associated to cannabis use, the family's mental health was associated. If an individual had a family member with mental health problems, they were 2.95 times as likely to use cannabis after controlling for confounding variables. It is not clear if this association represents self-medication due to undiagnosed symptoms (e.g. Swift et al., 2005), an inherited genetic vulnerability for a particular mental health condition, or if the increased use of cannabis represents a product of diminished parental involvement with the child precipitated by parental mental health problems (e.g. Butters, 2002).

The learning disabilities variable was also included tested however no relationship with either cannabis use variable was found. Based on these data it seems that the individual's mental health, learning (dis)abilities, and familial mental health are not related to the age of onset of cannabis use. While this is the first study the current authors know of which observes relationships between learning disabilities and familial mental health with the age of onset of cannabis use, some research has already highlighted the potential link between early onset cannabis use and mental health. Green and Ritter (2000) found an association between early onset cannabis use ($\leq$16 years) and depression however this association was not significant after controlling for confounding variables. Building on this work, Lynskey et al (2004) found that major depressive disorder diagnoses were not related to early onset cannabis use ($\leq$17 years) however suicidal attempts were. Less is known about the age of onset of cannabis and other specific mental health problems reported in the CannaForm (e.g. eating disorders) and the current study could not contribute to this new knowledge. It was attempted to break down the analysis into different mental health problems however this violated the assumptions of incomplete data and so all mental health problems were conflated into one variable.

5.4.4. Limitations

The administration of the CannaForm has the potential for reduced reliability. As the CannaForm was completed in both a structured interview and self-report format it is

possible that there were differences in responses which were mediated by the particular format (e.g. Tourangeau & Yan, 2007). The interview format allowed for questions to be explained in more detail, such that if a participant did not understand a question, the experimenter was there to help. Additionally, there is also the potential for bias with the interview format which is not present during the self-report format. These benefits and limitations of the two administration formats could influence the manner in which a participant responds to a particular question.

5.4.5. The Future of the CannaForm

The current chapter displayed its utility for addressing drug use behaviours. The development of the CannaForm has been discussed in the current chapter however there are changes which are to be implemented beyond this research programme.

Firstly, a reliability study in which the questionnaire will be administered and marked by two separate experimenters in order to test the inter-rater reliability of the CannaForm. Additionally, the participants will also complete the CannaForm in a self-report procedure which will then be compared to the structured interview approach to test the reliability of the CannaForm during different administration procedures. The Validity of the CannaForm's alcohol and drug use sections could be tested by also administering the Customary Drinking and Drug Use Record (Brown et al., 1998) or a similar questionnaire.

5.4.6. Recommendations for Confounding Variables

The current study found that a number of variables were related to cannabis use and two were also related to the age of onset of cannabis use. These two variables were other drug use and educational achievement. While other drug use is often controlled for in such studies, educational achievement is not (see Table 5.1). Especially among age of onset studies it would be advisable for studies to start controlling for this variable if it meets the necessary assumptions to do so. For general cannabis use it would be advisable to control for sex, family's mental health, tobacco use, educational achievement, and alcohol use. This is not an exhaustive list however it does represent the first guidelines for identifying salient confounding variable within a singular study. The benefits of this approach are that some variables may have a relationship with cannabis use, yet not after controlling for other variables such as seen in Table 5.3.

Chapter Six: General Discussion

6.1. Introduction

The purpose of this thesis was to extend the literature on the relationship between early onset cannabis use and executive function. The current chapter discussed the contribution of the current research to the existing literature and summarises possible research directions which could follow.

Table 6.1.

A table describing the three studies of this thesis.

Study	Method	Main Findings
Neuropsychology Study (Chapter Three)	Quasi-experimental, neuropsychological tasks, questionnaires	Cannabis related deficits in visual scanning, set switching, and visuo-motor coordination Early onset cannabis related deficits in set switching and visuo-motor coordination
Eye-Tracking Study (Chapter Four)	Quasi-experimental, eye tracker, computerised tasks, questionnaires	Cannabis related deficits in visual scanning Cannabis related increases in anxiety Very little evidence for early onset cannabis related deficits
Survey Study (Chapter Five)	Correlational, questionnaire	Cannabis use is predicted by sex (males at risk), the presence of familial mental health conditions, more alcohol use, tobacco use, and lower educational achievement Early onset cannabis use is predicted by other drug use and lower educational achievement

6.2. Results

6.2.1. Summary of Results

The neuropsychological study (Chapter Three) involved the administration of a battery of neuropsychological tasks to cannabis users, tobacco users, and matched controls. The results showed that the cannabis using group performed at a significantly lower level on multiple tasks when compared to the tobacco users and controls. These tasks included the Trail Making Test (TMT) Visual Scanning test, the TMT Switching test, TMT Switching Contrast measure, the Grooved Pegboard Test (GPT) Contrast Measure, the Design Fluency Test (DFT) Switching test, and the DFT Switching Contrast test. The only ambiguous finding was on the GPT, in which the tobacco group out-performed the controls and the cannabis users while there was no difference between the cannabis users and controls. As cannabis users also used a large amount of tobacco this finding is best explained by a beneficial effect of tobacco on the GPT which hid the damaging effect of cannabis on this task, and made the tobacco users complete the task faster than the controls. This tobacco-related beneficial effect is most likely an acute and transient benefit by the use of tobacco just before the cognitive testing. There were no group differences on the remaining list of dependent variables examined in the neuropsychological chapter.

The second analysis of the neuropsychological study involved the same data set with a different independent variable. The cannabis users were divided into early onset (age of onset $\leq$15) and late onset (age of onset $\geq$16) groups while the tobacco and controls groups remained the same. This study showed that while the late onset users displayed some cognitive impairments, the early onset group was displaying greater and more widespread deficits. The GPT Contrast Measure, the TMT Switching subtest, and the TMT Switching Contrast score appeared to show a vulnerability to early onset cannabis use. The remaining variables which highlighted cognitive impairments in cannabis users relative to the control group or tobacco group did not show an age of onset effect. Further correlational analyses suggested a range of cannabis variables which were related to cognition. Earlier onset cannabis use was related to greater cognitive impairments, greater lifetime cannabis use was related to greater cognitive impairments, longer use of cannabis was related to greater cognitive impairments, and the desire to reach higher levels of cannabis intoxication was related to greater cognitive

impairments. These cannabis use variables were not related to all cognitive variables and some appeared more severe than others.

The eye-tracking study (Chapter Four) involved a new sample of participants and a focus which shifted to eye-tracking. As earlier findings from the neuropsychological chapter could not determine if cannabis was affecting set switching or visual processes, two new tasks (VST & SST) were created for use with the eye tracker to address this problem. While this study displayed clear main effects of cannabis use on task performance, there was not a clear role for the age of onset, quantity of cannabis use, or any other cannabis related variables. Furthermore, anxiety was found to be correlated with several variables in which the whole cannabis using group displayed impairments, and levels of anxiety were significantly higher in the cannabis group. This calls into question a causal role of cannabis on this task and suggests that an anxiety could have been mediating some, but not all, of the detected cognitive deficits.

The survey study (Chapter Six) aimed to determine what factors could be mediating the relationship between cannabis use, the age of onset of cannabis use, and cognition. This study found a range of variables related to cannabis use. Males, more frequent alcohol users, individuals with familial mental health problems, individuals with fewer GCSEs, and tobacco users were all at an increased risk of using cannabis. Other drug use was also related to cannabis use but could not be included in the regression model as it violated one of the model assumptions by being "too" related to cannabis use (i.e. no participants used other illegal drugs if they did not use cannabis). Despite all these variables which are associated with cannabis use, only fewer GCSEs and other drug use increased the risk of using cannabis at an early age. Most studies control for other drug use by means of exclusion criteria however controlling for education achievement is less prevalent. Given the relationship between GCSEs and the age of onset of cannabis use, and the previously discovered relationship between educational achievement and cognition (e.g. Riding, 2000; Grimley & Banner, 2008), controlling for education achievement where appropriate is now essential when observing the effect of the age of onset of cannabis use on cognition. In the neuropsychological study and the eye-tracking study, educational achievement and other drug use were controlled for, which increases the likelihood that the results can be ascribed to a causal role of cannabis use.

6.2.2. Updated Literature

6.2.2.1. Cannabis and Cognition

The results from the two quasi-experimental studies have implications for the current level of understanding within four primary areas. Firstly, there is strong evidence presented within the thesis that cannabis use is strongly associated with cognitive performance and a causal link between these two variables could not be eliminated (see Section 6.3). This adds to the growing body of literature identifying such a relationship (for reviews see Crean et al., 2010; Schreiner & Dunn, 2012).

6.2.2.2. The Age of Cannabis Onset and Cognition

Unlike the relationship between cannabis and cognition, the relationship between early/late onset cannabis use and cognition is sparse and inconsistent. This research makes a large contribution towards understanding this relationship. The neuropsychology study (Chapter Four) found strong support for early cannabis onset leading to a greater degree of cognitive deficits and this therefore supports work done by Gruber et al (2011) and Fontes et al (2011). The early work in this field had methodological limitations (i.e. Ehrenriech et al., 1999) and later work found that the association was removed after controlling for IQ (Pope et al., 2003) however following the neuropsychological study reported within this thesis, in addition to the more recent research (Fontes et al., 2011; Gruber et al., 2011), there is strong evidence that an early age of onset is associated with greater cognitive deficits. Although there was support for the age of onset hypothesis from the eye-tracking study, it was not as strong as that from the neuropsychological study.

These findings suggest that there may be a developmentally vulnerable period for cannabis use and although it is too early to determine for certain, it appears that some cognitive processes are more vulnerable than others.

6.2.2.3. The Specificity of Impairment

Section 1.4 of the Literature Review discussed the evidence for cannabis impairments in distinct executive function components. Several components such as inhibition, abstract/conceptual reasoning, working memory, and strategic planning were likely to

contribute to performance on a number of the tests used however there was no direct measurement of these processes and therefore they will not be discussed. The current thesis used four tests to measure set switching over two quasi-experimental studies. Using the set switching subtests from the TMT and DFT, the current study supported previous research identifying set switching impairments in cannabis users (Medina et al., 2007; Thames et al., 2014) and therefore did not support the studies which found no effect of cannabis on set switching (Bolla et al., 2002; Gruber et al., 2011). In contrast the set switching dependent variables from the VFT in the neuropsychological study and the SST in the eye-tracking study appeared to be unrelated to cannabis use and therefore supported Bolla et al (2002) and Gruber et al's findings (2011). Furthermore, the set switching measures from the TMT and DFT found evidence of an age of onset effect, with early cannabis users displaying greater deficits than late onset users, a finding which does not support Gruber et al (2011) who did not find such an effect on a different version of the TMT. The results of the current thesis suggest set switching is potentially impaired, although evidence from the eye-tracking study suggests that deficits in visual scanning could be explaining the deficits in set switching tasks.

Verbal fluency was measured with two different tests, one of phonemic/letter fluency and one of semantic/category fluency. The current findings support the majority of previous research which found no effect of cannabis on verbal fluency performance (Pope et al., 2001; Medina et al., 2007; Gruber et al., 2011). Despite this Gruber et al (2011) found that early onset cannabis users displayed impairments on the task, McHale and Hunt (2008) found that cannabis users were impaired on a written variant of the task, and Becker et al (2014) found that cannabis users outperformed controls on this task. The current research supports the majority of the work in this area which suggests cannabis use is not related to verbal fluency performance. While McHale and Hunt's (2008) finding is probably explained by methodological differences as discussed in section 1.4.5, the remaining inconsistencies are likely due to sample characteristics although it is not clear what these may be.

The current test used the IGT to measure decision making abilities, the same measure used by all other studies described here. Despite several studies which found impaired performance on this task (Bolla et al., 2005; Whitlow et al., 2004) not all research has found these results. Becker et al (2014) found a trend towards impairments while

Verdejo-Garcia et al (2007) found although there were no group differences, there was a dose-response effect as determined by correlating performance with number of spliffs smoked. The current study did not find any group differences between cannabis users and controls and is the first study to report that there was no age of onset effect. Possible explanations for these results are discussed in section 3.4.

The neuropsychology study (Chapter Three) used two measures of non-verbal creativity derived from two subtests of the DFT. This is the first use of such tests within the cannabis-cognition literature and the results suggest that this cognitive construct is not associated with cannabis use or the age of onset of cannabis.

Within the current research programme there were two tests used which primarily measure visual scanning including a D-KEFS standardised test within the neuropsychological study and another created for use within the Tobii eye-tracker. Both tasks support findings which show that cannabis use is related to impairments in visual scanning abilities (Ehrenriech et al., 1999; Hanson et al., 2010; Huestegge et al., 2002). Despite these group differences the current study found that there was no age of onset effect on visual search abilities, a finding which contradicts Ehrenriech et al's results (1999). The limitations of their study which have been highlighted multiple times suggest that the group differences which they found may not be due to the long term effects of cannabis, which would explain this lack of concordance.

Two categories of motor skills were tested in the current study, motor speed (GPT Remove and TMT Motor Speed) and visuo-motor coordination (GPT Place and GPT Contrast Measure). There was no effect of cannabis or the age of onset of cannabis use on either of these indicators of motor speed which supports previous research (Becker et al., 2014; Fitzgerald, Williams & Daskalakis, 2009). In contrast to these more basic skills, higher level visuo-motor coordination skills showed evidence of being impaired in cannabis users and early cannabis users relative to tobacco users but not controls. Possible explanations for this are discussed at length in the discussion section of Chapter Three. These deficits support previous research identifying a dose-response effect of spliffs on GPT Place performance (Bolla et al., 2002) however another two studies did not find differences between cannabis users and controls (Becker et al., 2014; Fitzgerald et al., 2009). This does not contradict the findings reported in Chapter Three as it was the tobacco users who outperformed cannabis users. Future research

aimed at clarifying the relationship between cannabis use and visuo-motor performance needs to account for tobacco use.

The final cognitive domain assessed in the current research programme was visual processing speed as determined by the SST. The current study found no effect of cannabis use or the age of onset of cannabis use on this variable. Both Meier et al (2012) and Thames et al (2014) used a combination of the SST and a second test to create an information processing composite score which was found to uncover deficits in cannabis users in both studies thus contradicting the current findings. It could be that the second test used to create the composite score in these studies was the one uncovering deficits and the SST itself was not related to cannabis use, potentially supporting the current data.

6.2.2.4. Predictors of Cannabis

The final area which the current thesis provided updated knowledge was on the relationship between the age of onset of cannabis use and several putative, salient confounding variables. The survey-based study found that early onset cannabis use was associated with other drug use and educational achievement. This supports previous work on the relationship between the age of onset of cannabis use and educational achievement (Lynskey et al., 2003; Horwood et al., 2010) however adds to this work by using GCSE performance as an indicator of educational achievement; a novel method due to the majority of previous research occurring outside of the UK. The current analysis found that sex was not related to the age of onset of cannabis use thus conflicting with previous research by Tu et al (2008). The findings also showed that early onset cannabis users are more likely to use other illegal drugs, a finding which supports previous results (Secades-Villa et al., 2014). As the majority of research regarding the predictors of cannabis use, or the age of onset of cannabis use, has been done outside the UK, cross-cultural differences may have an influence on such predictors. This could be explaining the contradictory results found between the current research and that of Tu et al (2008). This study was solely conducted on university students with a large female bias at a ratio of approximately 3:1, and this needs to be considered when generalising the results.

6.2.3. Original Contributions

The first and predominant goal of the current thesis was to extend the body of knowledge about the relationship between the age of onset of cannabis use and executive function. The GPT, SST, DFT, and IGT were novel methods of assessing how the age of onset of cannabis use affects cognition. Furthermore, the DFT had never been used to examine cognitive deficits in cannabis users before, unlike these other tests. Due to limited evidence on the age of onset hypothesis several tests were also included for replication purposes which included the TMT and the VFT. Both of these tests included subtests, the TMT Visual Scanning test and the VFT Category Switching test, which were novel cognitive assessment in both fields: age of onset of cannabis and cannabis use in general. This battery of neuropsychological tests extended the data on the relationship between the age of onset of cannabis use and executive function and other cognitive domains.

In the eye-tracking study two new visual search tests were run and while this use of visual search is not an original contribution to the age of onset literature, the use of an eye-tracker is an original contribution as it has not been used to address the age on onset of cannabis use before. This means that the current thesis extended the body of knowledge on how the age of onset of cannabis use affects cognition by using new measures of already tested cognitive processes (e.g. TMT Visual Scanning test), new measures of un-tested cognitive processes (e.g. all DFT subtests), and new techniques for measuring cognitive processes (e.g. eye-tracking).

There was also a large focus on the specificity of impairments. This also required the use of dependent variables yet to be tested on cannabis users or early onset cannabis users. The use of D-KEFS tests allowed for contrast conditions to be analysed and while this practice is recommended by studies examining construct validity (e.g. Sanchez-Cubillo et al., 2009) it is not always employed by studies examining the relationship between cannabis use and cognition. Typically the process involves administering a test which measures one set of cognitive functions (e.g. VFT Category Fluency), then administering a second test with a small change which recruits additional cognitive processes (e.g. VFT Category Switching, and finally subtracting the score on test one from the score on test two. This approach has received support for increasing specificity and thus aiding the interpretation of deficits (e.g. Arbuthnott & Frank, 2000; Sanchez-

Cubillo et al., 2009) and has been incorporated and standardised in the D-KEFS. In addition to using the D-KEFS, such an approach was conducted with the GPT for the first time in the current study. Tests of validity suggested that this approach increased specificity for higher cognitive/visuo-motor coordination demands of the GPT by reducing the involvement of basic motor skills. The eye-tracking study also used a similar approach by use of the Tobii VST and Tobii SST. These two tests differed by means of a switching component demonstrated by isolating a switch cost (i.e. Monsell, 2003) on a number of the dependent variables. This process of comparing the group differences in performance on the VST and SST aided in attributing the deficits to specific cognitive constructs. Although this was not set out to be a primary aim of the research programme, the neuropsychological study and the eye-tracking study reported in this thesis used existing methods (e.g. TMT Switching Contrast) and contributed new methods (e.g. GPT Contrast Measure) for increasing specificity and aided in identifying which specific cognitive constructs were at risk for impairment.

The current thesis also developed and trialled a new tool for assessing cannabis use: the CannaForm. This new tool provides a unique and in depth assessment of cannabis use behaviours such as method of administration, frequency of use, how use changes over time, and the desired level of intoxication. While other cannabis specific questionnaires do exist they either lack depth (e.g. Solowij, 1998) or do not assess the desired domains (e.g. Heishman et al., 2001; Lee et al., 2009). General drug use questionnaires contain questions on cannabis use yet also lack the desired depth on cannabis use (e.g. Brown et al., 1998). This thesis therefore contributes a new tool specifically for research in which cannabis use is the focus.

6.3. Does Long Term Cannabis Use Cause Executive Function Deficits?

As discussed in Chapter Three, Hill (1965) suggested a method of determining causation by means of a checklist. The failure to meet one criterion does not imply causation is not true, and by extension, meeting the criteria does not necessarily mean causation is true as shown by counterfactual examples (Höfler, 2005). The list of these guidelines for inferring causation will now be discussed with regards to the specific effects found in the current studies (Chapters Three, Four and Five) and how these studies aid causal interpretations in the general literature.

6.3.1. Strength of the Association

The first criterion discussed in the Methodology Chapter (Section 2.1.1) was on the strength of the association. This is discussed below with regards to the severity of the impairments however here it will be discussed with regards to causation. The effect sizes between the controls and the cannabis users were large as determined by general guidelines on interpreting effect sizes (Cohen, 1988). Although the effect sizes were mixed across different dependent variables for both studies (Chapters Three and Four), the significant results suggests moderate to large effect sizes, with the majority being large. When considering the age of onset of cannabis use, particularly in Chapter Three, the effect sizes were larger between the early onset group and the controls, than between the late onset group and the controls. The current findings which concern the strength of the association criterion lend support for the notion that the relationship between cannabis use and cognition is causal. This factor alone however, is not sufficient justification for a causal interpretation.

6.3.2. Consistency

The second criterion for causation is consistency. The neuropsychological and eye-tracking studies found cannabis related impairments in cognition and both found evidence of early onset related deficits in cognition. These early onset findings were much more pronounced in the first study (Chapter Three) than in the second study (Chapter Four). However, this adds support to the general literature on cannabis use for a causal interpretation as two new studies reported within the current thesis have found support for cannabis related impairments in cognition. The literature on general cannabis and cognition use is now extensive and a recent meta-analysis found a clear effect of cannabis use and cognitive impairments on a wide range of cognitive and motor faculties (Schreiner & Dunn, 2012). In contrast, there is little research on the age of onset of cannabis use and therefore the findings reported in the current thesis which address this cannabis use variable are perhaps more crucial for furthering understanding. Chapter Three adds further consistency to the age of onset of cannabis literature (Pope et al., 2003; Gruber et al., 2011; Fontes et al., 2011) while Chapter Four, the eye-tracking study reported in this thesis, suggests a small possibility of an age of onset effect however the results lack intra-study consistency as only one dependent variable showed an age of onset effect.

As with the first criterion, studies reported in Chapters Three and Four meet the criterion of consistency for general cannabis use and to varying degrees meet the same criterion for early onset cannabis use. This increases the possibility that cannabis use and early onset cannabis use can be said to have a causal influence on cognition.

6.3.3. Specificity

The criterion of specificity suggests a specific cause should have a specific effect. The specific effects of cannabis appear to be wide ranging with a recent meta-analysis finding cannabis related deficits in attention, abstraction/executive, forgetting/retrieval, learning, motor, and verbal/language domains (Schreiner & Dunn, 2012). The authors grouped processes known to be differentially affected by cannabis use into these domains to aid the meta-analytic process however the effects of cannabis can be examined in a more precise level of specificity. An example of this grouping by the authors is the placing of the Iowa Gambling Task – a measure of decision making – into the "attention" domain. Comparing intra-study specificity can be done as both studies reported in the current thesis used multiple dependent variables which recruit over-lapping cognitive processes.

Within the neuropsychological study there were two measures of motor speed, three measures of set switching, and two measures of verbal fluency. There were also additional measures of motor speed and visuo-motor coordination when considering that the GPT was completed with both hands. All measures of motor speed derived from the TMT and GPT suggest that cannabis use is unrelated to this domain. The three measures of set switching, or six if including contrast measures, were not all related to cannabis use. However, the set switching measures from the visual domain including TMT and DFT subtests were all impaired while the verbal set switching measures from the Verbal Fluency Test (VFT) were not impaired. Therefore there is evidence of intra-study specificity when considering that there is a dissociation between verbal and visual set switching tasks. There was not a clear effect of cannabis on visuo-motor coordination tasks as only the dominant hand was impaired in the cannabis users on the GPT Contrast Measure. This could be explained by the differential recruitment of cognitive and motor processes over dominant and non-dominant hands on the GPT (Strenge, Niederberger & Seelhorst, 2002). Furthermore, the two measures of verbal fluency; phonemic/letter fluency and semantic/category both were unrelated to cannabis

use. The remaining tasks from the neuropsychological study included only one assessment of individual cognitive processes and thus intra-study specificity cannot be examined any further. In summary there appears to be moderate to high levels of specificity consistency dependent on the cognitive domain.

The eye-tracking study reported in Chapter Five included two tasks in which every dependent variable was replicated across both tasks. Although a number of the dependent variables from the Switching Search Task (SST) contained additional set switching processes, as demonstrated by a switch cost, every dependent variable on the SST would recruit comparable processes to the Visual Search Task (VST). For all of the variables on the VST which cannabis users displayed deficits, there were near identical impairments on the SST. In particular, the number of revisits to stimuli on the VST was replicated on the SST, although the type of stimuli revisited differed. This suggests high specificity of cannabis-related impairments in the eye-tracking study.

6.3.4. Temporality

The studies conducted in the current research programme were not longitudinal and thus it could not be determined if the deficits on the various indicators of cognitive performance by the cannabis users relative to controls preceded or followed the use of cannabis. Therefore this criterion is not met nor is it violated.

Previous epidemiological research has provided some evidence that cannabis use precedes cognitive impairment. Meier et al (2012) conducted a longitudinal study with over 1000 participants and tested IQ and cognitive function at various follow up sessions. The authors found that individuals who never used cannabis showed increases in IQ scores over the follow up sessions while those who used cannabis after the initial testing point showed decreases in IQ commensurate with the number of cannabis dependence diagnoses over the different follow-ups. This was the first large scale study of its kind to be conducted and future research will need to confirm the findings before a conclusion can be reached.

6.3.5. Biological Gradient

The neuropsychological and eye-tracking studies assessed whether a dose-related response led to increased levels of cognitive impairments. The current research

programme utilised two separate measures of cannabis quantity: total lifetime cannabis use and years of cannabis use. Of the seven dependent variables which were found to be impaired in cannabis users in the neuropsychological study, four of these variables were significantly correlated with either lifetime cannabis use or years of cannabis use which therefore meets the biological gradient criterion. Surprisingly, none of the dependent variables which were impaired by the cannabis users in the eye-tracking study were significantly related to these two measures of cannabis use. This could be due to the smaller sample size as one of the variables had a moderate correlation coefficient with lifetime cannabis use and three of the variables had a moderate correlation coefficient with years of cannabis use. Moderate is interpreted as 0.3-0.5 for Pearson's *r* or Spearman's Rho. While interpretation of *p*-values would suggest the biological gradient criterion was violated for the second study, interpretation of the correlation coefficients would suggest the criterion was met for at least three of these variables.

6.3.6. Plausibility

Plausibility refers to whether or not a plausible mechanism can link the cause (chronic cannabis use) with the effect (cognitive impairments). The current research has not contributed to the literature regarding the plausibility of a mechanism as this is beyond the scope of this research. However, two possible causal mechanisms linking chronic cannabis and cognition have been suggested which are neurotoxicity (e.g. Lorenzetti et al., 2010) and neuro-dysfunction (e.g. Kanayama et al., 2004; Bloomfield et al., 2014). A further short-term causal mechanism of withdrawal symptoms (e.g. Budney et al, 2003) has been proposed to explain why there is a trend for impairments to be much greater in individual with past month cannabis use (Schreiner & Dunn, 2012). This has also received a certain degree of support within longitudinal data (Hanson et al., 2010) however these authors demonstrated that not all impairments returned to normal after three weeks of abstinence.

The eye-tracking study attempted to address the short term mechanism by correlating the dependent variables with the length of abstinence however there were no significant relationships. This suggested that the impaired performance in cannabis users was not mediated by the length of abstinence, which supports a long term damage explanation such as neurotoxicity induced by cannabis use.

In conclusion, the current thesis does not add much new evidence to the plausibility criterion however other research discussed in Section 1.1.5 highlights the potential for neurotoxicity or dopaminergic dysregulation to explain the pattern of impaired cognitive processes which the current research programme detected in cannabis users and early onset cannabis users.

6.3.7. Coherence

As a majority of this discussion has already been made in the Chapter One, this will not all be covered to avoid redundancy. Firstly, the current results described in the two quasi-experimental studies in Chapters Three and Four can be summarised as impairments on a certain proportion of the cognitive dependent variables, but not all. There were no tasks on which the cannabis users outperformed controls or tobacco users. Furthermore, the early onset users displayed the greatest degree of impairments while there was only one dependent variable in which the late onset users displayed greater deficits than the early users. The vast majority of the previous literature is in coherence with these results for the cannabis data as determined by reviews and meta-analyses (Crean et al., 2011; Schreiner & Dunn, 2012) and the majority of the previous literature on early onset cannabis use is in coherence with the current early-onset data (Ehrenreich et al., 1999; Gruber et al., 2011; Fontes et al., 2011) while one study found that cognitive impairments disappeared after controlling for IQ (Pope et al., 2003).

Secondly, data from other fields lends coherence to the cognitive impairments discovered here. This is demonstrated by cannabis users performing worse than controls in educational outcomes (Horwood et al., 2010; Lynskey & Hall, 2000; Verwiej et al., 2013). While other associations are noted with cannabis use (e.g. mental health), only educational deficits are noted in cannabis users which could be explained via cannabis induced cognitive deficits. This does not imply that cognitive impairments are the leading explanation of these education deficits, but rather that these educational deficits are coherent with the cognitive deficits.

6.3.8. Experiment

Due to ethical considerations it is not possible to conduct experimental research on the cognitive consequences of long-term cannabis use. It is likely that this criterion, perhaps the strongest indicator of causation, will never be explored in this area. The inability to

meet this criterion does not imply that causation is impossible to infer as if all other criteria are met and replicated, then a causal interpretation could be the best explanation for the data. The limitations of the quasi-experimental approach can be found in the Methodology chapter (Section 2.1.1).

6.3.9. Analogy

This last criterion is that when a comparable cause (X_2) to the one which is being examined (X_1) has a certain effect (Y_1), the evidence required for a causal interpretation of X_1 on Y_1 can be reduced. This has been critiqued as being too open for interpretation (Höfler, 2005) and thus any imagined analogy could potentially and erroneously lower the required level of evidence for a causal interpretation. While numerous recreational drugs other than cannabis have been shown to have a negative effect on cognitive functioning such as ecstasy (Hadjiefthyvoulou et al., 2011), ketamine (Morgan et al., 2014), and cocaine (Vonmoos et al., 2013) and while there is a possibility of a shared indirect mechanism via neurotoxicity or dopaminergic dysfunction (Klogpanichapak, Govitrapong, Sharma & Ebadi, 2006; Morton, 2005; Zou et al., 2009), causation cannot be shown for ecstasy, ketamine, cocaine, or any other illegal drugs due to lack of true experimental designs. Therefore this last criterion cannot be used to infer causation as an appropriate analogy of cannabis' effects on cognition is not available.

6.3.10. Other Causal Variables

During the two quasi-experimental studies described within this thesis the use of covariates was implemented to parcel out the effects of possible confounds. While cannabis use was the primary candidate for explaining the deficits reported there remained some possibility that non-cannabis variables were influencing performance. The final results were reported after controlling for all salient covariates which met ANCOVA assumptions however there were several cases in which covariates could not be controlled for and these variables differed significantly between groups. In the neuropsychology study alcohol use, tobacco use, and other drug use all differed between controls, tobacco users, and cannabis users (total or divided). While in the eye-tracking study anxiety, tobacco use, and other drug use differed between controls and cannabis users.

In both studies the levels of other drug use were negligible, averaging less than *two* lifetime uses for each participant in contrast to the much higher levels of cannabis averaging around 1000 and 500 lifetime uses across the two studies. This suggests that other drug use is not a causal factor explaining the cognitive deficits. Tobacco use also differed between groups and was correlated with several of the dependent variables in the neuropsychological study. However cannabis users showed impairments relative to tobacco users while tobacco users did not differ from controls on these variables suggesting that tobacco was not a causal factor in these deficits. Weekly alcohol use was significantly higher in the cannabis group relative to the controls in the neuropsychological study yet was unrelated to any of the dependent variables which were impaired in cannabis users suggesting that alcohol use was not explaining the deficits. In the eye-tracking study cannabis users displayed impairments on one variable in which anxiety was identified as a confound. As anxiety could not be controlled for on this variable it is possible that cannabis users displayed these impairments due to the greater levels of anxiety. While the vast majority of the impaired variables over the two quasi-experimental studies are unlikely to be due to one of the tested confounding variables, this suggests anxiety is a valid candidate for explaining the number of revisits to distractor stimuli in the eye-tracking study. It cannot be determined in the current study if anxiety led to cannabis use and also caused the impairments or if cannabis increased anxiety which led to the impairments. Both of these interpretations are possibilities as the directional nature of the relationship between cannabis and anxiety has not been determined (Crippa et al., 2009) while anxiety has been clearly show to impair tasks which recruit attentional processes (Eysenck et al., 2007).

Despite anxiety possibly mediating the cannabis-related deficits on one variable, the majority of impaired performances by cannabis users over the neuropsychological and eye-tracking studies appeared to be unrelated to the potential confounds which were examined.

6.3.11. Summary

Considering nine of Hill's criteria for inferring causation and when disregarding the two criteria which are not possible within this domain; experiment and analogy, there is strong evidence to suggest that the cognitive deficits described in the current thesis are causally related to cannabis use.

The remaining criteria were largely met by the current studies: strength of the association, consistency; specificity; biological gradient; and coherence. The current studies did not address temporality or plausibility however these have been met by other research (e.g. Meier et al., 2012; Lorenzetti et al., 2010). It is worth noting that the biological gradient criterion, i.e. a dose-response effect, was not found for all impaired cognitive processes. It could be that some of the tasks in which cannabis users displayed impairments were not due to cannabis but rather some other confounding variable which was not taken into consideration. As true– as opposed to quasi–experimentation cannot be done, a causal effect cannot be proven. However, based on the current research, a causal interpretation for a proportion of the cognitive deficits discovered in cannabis users appears to be the best explanation. In contrast, while there is strong evidence meeting some of the criteria for an early onset causal theory (e.g. plausibility; Downer et al., 2007; Wilson et al., 2000), there is little consistency amongst the research due to the relatively new focus on the age of onset of cannabis use. More research on the age of onset of cannabis use will help determine if it has a causal, negative impact on cognition.

6.4. Severity of Impairments

The primary method used in quantitative, inferential analyses is the process of testing the null hypothesis. Null hypothesis testing involves determining whether an effect is notably different from the norm, such that the effects did not arise by chance. There are many problems with this approach, not least that any statistically significant finding may not actually be *substantively significant* (Fife-Schaw, 2006). A substantive significance is one which has psychological or theoretical importance. Given the ubiquity of the former term (statistical significance) and the rarity of the latter, it becomes necessary to clarify whether a significant effect discovered can be classified as substantive or merely statistical. It is worth noting that it is possible for a substantive significance to not be statistically significant.

When a statistically significant group difference is discovered in any field relating to cognition or executive function, it is referred to as a deficit (or impairment etc.) if performance is lower than the control group, or an improvement (or enhancement etc.) if performance is higher than the control group. These terms are common throughout multiple fields including, but not limited to, schizophrenia (e.g. Kopald, Mirra, Egan,

Weinberger & Goldberg, 2012), dementia (e.g. Stopford, Thompson, Neary, Richardson & Snowden, 2012) and autism (e.g. Rosenthal et al., 2013). If such terminology is shared across these various fields without explicit clarification it has the potential for readers to infer that the deficits associated with cannabis use are comparable with those associated with schizophrenia or any other diagnosis.

This leads to the question, are the deficits in executive function associated with cannabis use substantively significant? A direct method of addressing the scale of the impairments would be to add a group of other drug users to a study already comprised of cannabis users and controls, to compare the between group differences in executive function. This would help determine which drugs cause the most damage. Further methods of addressing the scale of the damage would be to compare either effect sizes or the mean scores from standardised tests.

6.4.1. The Direct Method

Several studies have recruited cannabis users in addition to another drug using group, which helps determine the severity of the impairments. This allows the comparison of different drugs on the outcome variable of cognition. This approach has been tested among different illegal drugs including MDMA and cocaine (Verdejo-Garcia, López-Torrecillas, Aguilar de Arcos & Perez-Garcia, 2005; Verdejo-Garcia et al., 2007) and has been able to determine the differential level of impairments and the specificity of these impairments across different executive function and other cognitive constructs.

The current thesis did not use this approach but instead opted to recruit cannabis users with little-to-no use of other recreational drugs. There were two exceptions to this; alcohol use and tobacco use are so prevalent among cannabis users that it is difficult to avoid recruiting participants with use of these two drugs. To determine if cannabis use caused impairments substantively greater than tobacco use the neuropsychological study reported in this thesis compared a control group with a tobacco using group and with cannabis users. While the cannabis using group displayed many cognitive deficits relative to controls there were no variables in which tobacco users showed deficits relative to controls. Alcohol, by contrast, was used as a covariate and the effects on cognition could be not determined as a non-alcohol using group was not recruited. Therefore this direct method of assessing the severity of cannabis related cognitive

impairments only suggests that cannabis is significantly more severe than tobacco use and therefore other methods will have to be used to determine severity.

6.4.2. Effect Size Comparisons

The use of effect sizes could represent a useful tool for assessing the severity of cannabis related impairments in cognition. As previously mentioned, the use of statistical significance testing is ubiquitous however the reporting of effect sizes is much less prevalent. The use of a significance test (p-value) does not indicate the size of an effect, however the aptly named effect size does accomplish this goal (Fife-Schaw, 2006). There are multiple versions of the effect size statistic, however one of the most common used version - Cohen's d - is a measurement of how two groups differ based on a pooled standard deviation (Cohen, 1988). Comparing the severity of impairments based on effect sizes is an improvement on merely reporting test statistics and p-values, however it is vulnerable to criticism that different samples present with difference variances which therefore means that an effect size of $d = 0.5$ in one study will not be identical in terms of the raw data to the same value in another.

The neuropsychological study reported in Chapter Three of the current thesis compared controls, tobacco users and cannabis users on a range of cognitive tests. The tests which reached statistical significance will be the primary discussion point here. Cannabis users presented with deficits on three tests compared to controls (d=-.74 to -.88) and three tests compared to tobacco users (d=-.60 to -.94). Based on a basic interpretation from Cohen (1988) who suggested guidelines for small ($d\approx.3$), moderate ($d\approx.5$) and large ($d\approx.8$) effect sizes, it can be seen here that the size of the cannabis related impairments in cognition were large when compared to controls and moderate/large when compared to tobacco users. Comparing the effect sizes reported here to similar research it appears that the scale of the impairments are comparable (d=-.69 to -.80; Gruber et al., 2011).

Schreiner and Dunn (2012) conducted the most recent meta-analysis of cannabis use and cognition and found that among the significant results, effect sizes ranged from small to moderate (Hedge's g=0.21-0.36). These effect sizes could be smaller for several reasons. Firstly, Hedge's g is a more conservative effect size than Cohen's d and this could be explaining the discrepancy (Schreiner & Dunn, 2012). The current study included a focus on the early onset cannabis users and thus any meta-analysis which

specifically looked at early onset cannabis users (e.g. age of cannabis onset ≤16) could find larger effect sizes just as data from the current thesis did. At a more basic level, it is possible that chance characteristics of the sample recruited and described in Chapter Three happened to have cognitive deficits at the tail end of the distribution. It is likely that all three of these variables were explaining the differences in effect sizes.

When comparing cannabis use impairments to other drugs it would appear that ecstasy/MDMA use (*d*=.40-.73; Kalechstein, de la Garza II, Mahoney, Fantegrossi & Newton, 2007), methamphetamine use (*d*=.34-.66; Scott et al., 2007), and addicition to alcohol (recent use: *d*=.33-.70; one month abstinence: *d*=.27-77; one year abstinence: *d*=.13-.30; Stavro, Pelletier & Potvin, 2012) results in greater levels of impairments across similar domains of cognition as determined by meta-analyses. With the exception of long term abstinence and recovery from alcoholism, these impairments are demonstrably larger than the data reported in the recent cannabis meta-analysis (Schreiner & Dunn, 2012). While the majority of the studies analysed within each meta-analysis attempted to control for other drug use this was not always possible, in particular ecstasy and methamphetamine use is typically accompanied by other recreational drug use which could be explaining or contributing towards the observed cognitive deficits. Despite this limitation, it is notable that the cognitive deficits discovered in cannabis users appear to be approximately half the magnitude of those discovered in ecstasy users, methamphetamine users, and in alcoholics who are still going through treatment.

6.4.3. Standard Test Comparisons

There are numerous standardised measures available for assessing executive function, and although a number of studies design their own measures for use with specialist equipment (e.g. fMRI; eye-trackers), the neuropsychological batteries remain a popular choice in chronic cannabis use research. These standardised tests allow for the comparison of scores across multiple studies and are often norm referenced.

Within the neuropsychological study, the D-KEFS, WAIS, and WASI are all norm referenced across a wide age range. For the D-KEFS and the WAIS subtest, the Symbol Search Task (SST) the raw scores are converted into age scaled score in which 10±2 is the mean ± standard deviation from the normative data. The WASI Full-Scale IQ

(FSQI), verbal IQ (VIQ), and Performance IQ (PIQ) are all age scaled in which 90-109 is considered average. For the three cannabis using groups: the total group, the early onset users, and the late onset users; the scores on the D-KEFS and the SST were no more than one standard deviation away from the normative mean across all tests in which the cannabis using groups were impaired. Interestingly, the mean score of the early onset group scored below this cut-off of "8" on one variable in which they were not significantly impaired: the Switching subtest of the Verbal Fluency test.

All of the groups' mean scores on the WASI estimates of FSIQ, VIQ, and PIQ were within the average range of 90-109 and therefore this suggests that on average the groups had normal IQ levels. Considering the cannabis users' performance with regards to the normative data suggests that despite significant and large deficits in cognitive performance relative to controls or tobacco users, the cannabis users still maintained a "normal" level of cognitive functioning. It is possible that these minor deficits could slightly impact quality of life, as has been suggested for educational performance (Lynskey et al., 2003), however actually determining the contribution of long-term cannabis-induced cognitive deficits into real world consequences has not been investigated.

6.4.4. Heterogeneity of the Cannabis Use Group

The cannabis groups reported in the neuropsychological and eye-tracking studies had a wide range of cannabis use. Some individuals had been using regularly for a short period of time (months), some had been using regularly for a long period of time (years), and some had been using intermittently for a long period of time (years). There were also some individuals who "binged" at the weekend with cannabis, while others smoked a small amount daily. As there were multiple associations between cognitive performance and different cannabis use behaviours such as lifetime spliffs smoked, years of use, desired level of intoxication when using, and the age of onset of use, it is clear that the deficits were not evenly spread over the group. As all outliers in the analyses were winsorised it suggests that the effects were not being influenced too greatly by a few cases however there still is a possibility that not every individual suffers from cognitive impairments as a result of cannabis use, especially when considering that there is evidence for individuals with lower IQ to be more vulnerable to the cognitive effects of cannabis (Pope & Yugellun-Todd, 1996).

6.4.5. Summary of the Severity

Three different methods were adopted to try and determine the scale of the impairments detected in the current groups of cannabis users. The direct method suggested that cannabis use confers much greater risk to cognitive impairments than tobacco use. The effect size approach suggested that cannabis induced impairments reported in the meta-analyses (Schreiner & Dunn, 2012) were half the magnitude of those reported in other drug use behaviours such as methamphetamine use, ecstasy use, and alcoholism. In contrast, the deficits found in the current studies were comparable to these other drug use behaviours.

The standardised test approach suggested that for all the neuropsychological variables tested, in addition to the IQ variables used for covariate purposes, cannabis users almost completely scored within the normal range as determined by the normative data of the respective tests. It is likely the large effect sizes were due to a control group which over-performed relative to the average level which would be expected from a random sampling method. Overall, it appears that the cannabis-related deficits were large in statistical terms however the cannabis users still performed at a "normal" cognitive level.

6.5. Wider Implications

6.5.1. Harm Reduction

A request from the UK government to review the at-the-time current classification of cannabis as a Class C drug was sent to the Advisory Council on the Misuse of Drugs (ACMD) in 2007. The ACMD subsequently responded with a report highlighting that cannabis should remain a Class C drug (advice to which the government did not adhere), however the report also highlighted that the principle aim should be to reduce the harm associated with the drug (ACMD, 2008).

The present studies described in Chapter Four and Chapter Five highlight that cannabis use at an early age is associated with greater and more numerous executive function deficits than later onset users and non-smoking controls. This adds to a growing body of research finding similar early onset risks relating to cognition (Pope et al., 2003; Fontes et al., 2011; Gruber et al., 2011), psychiatric conditions such as depression (Fergussen

& Horwood, 1997; Lynskey et al., 2004), or schizophrenia (Di Forti et al., 2015), and educational problems such as lower grades and less time in education (Horwood et al., 2010).

Given the widespread risk associated with early onset cannabis use it appears the first step in reducing harm would be to minimise the number of individuals who start using cannabis early in life. Determining the success of different harm reduction strategies (e.g. prohibition; legalisation; education of the consequences; etc.) is beyond the scope of the current thesis however the current research programme does provide useful information about the potential dangers of long term cannabis use at an early age.

6.5.2. Education

The current thesis (Chapter Five) found that early onset cannabis use was associated with poorer educational achievement as indicated by the number of GCSE grades. While a causal interpretation is not possible here it is viable that cannabis use had a causal influence on education. One possible mechanism for this causal influence is by the impairment of executive function as several researchers have identified that executive function predicts school grades (Grimley & Banner, 2008; Riding et al, 2003). Given the finding within the current thesis that executive function is impaired in cannabis users, and such impairments typically last for at least a month (Schreiner & Dunn, 2012), it is possible that regular long term cannabis use could consistently impair executive function to a point where education achievement is affected. This role of impaired cognition is likely just one very small part of the complex relationship between cannabis use and education with acute cannabis, covarying mental health problems, familial influences, and peer influences also contributing to the relationship (Horwood et al., 2010; Lynskey et al., 2003; Mensch & Kandel, 1988; Verwiej et al., 2013).

While the current study could not contribute to understanding if alterations in cognitive faculties such as executive function are contributing to the reduced educational achievement in cannabis users this is discussed below as an avenue for future research. Regardless of the cognitive role, the use of cannabis could be a marker to highlight that a school student requires extra support to ensure they do not fall behind in school.

6.6. Limitations

While several limitations specific to the individual studies are discussed in their respective chapters there were several overarching limitations within the current research which will be discussed here. Furthermore, limitations which were predicted and discussed in the methodology chapter will not be repeated here.

6.6.1. Methodological Critique

A problem with the CannaForm which arose was the responses on three items. Certain responses indicated that a large number of individuals misunderstood the question and therefore the responses were not counted as valid. An example of this was the question:

1. Where did you first try cannabis?

   ☐ School ☐ College ☐ University ☐ Other (please specify).....

The majority of participants understood the wording of the question however a number took the literal interpretation, a consqeuence which was not foreseen when constructing the questionnaire, and typically responded with "at a festival", "in amsterdam" or "at a party".

This problem also arose on several questions including estimating the amount of alcohol used per week and the the number of A-levels obtained. As a result varying degrees of data was not usable for these three questions. This process allowed the develpment of the CannaForm to a point where it is now clear and understandable and future testing will be able to determine whether the improvements have been succesful.

The implication of these errors are mostly that there were missing data and assuming the pattern of missing data across participants was random there could be no bias as a result. While the large sample size of the survey (Chapter Five) meant that the loss in data was not problematic, the sample sizes in the quasi-experimental chapters were affected by this. The eye-tracking study involved the loss of data to a point were a different measure of alcohol use was chosen; the number of days a week when drinking was used to estimate alcohol use.

6.6.2. Sample Size Critique

One of the main limitations within the current research programme was the sample size for the quasi-experimental studies. While the overall sample size was not small for the neuropsychological study the individual group sizes of the early and late onset cannabis groups were small (n=16; n=16). This was also true for the eye-tracking study (n=12; n=10) for the early and late onset groups, respectively. While cannabis using samples of this size are frequently reported during neuropsychological studies (e.g. Grant et al., 2012; Gruber et al., 2011; Whitlow et al., 2004) and imaging studies (e.g. Gruber et al., 2012; Hester et al., 2009; Tapert et al., 2007) there are still statistical implications of using samples of this size.

The major limitation of such sample sizes are that the results cannot be generalised to other cannabis users from such samples (Sturgis, 2006). Despite this limitation studies including small samples are necessary when dealing with specific populations in which few individuals meet the necessary criteria. The benefits of these studies include highlighting areas of future research, contributing to meta-analyses, and systematic reviews (Sturgis, 2006).

6.7. Future Research

6.7.1. Determining Causation

This chapter has discussed the dilemma of causation in detail and suggested how the current research contributes to determining the causal relationship. Future research should focus on several areas to help determine causation. There is substantial evidence for a causal link between cannabis use and cognitive deficits however the area which needs a greater focus is the temporality criterion. More research similar to that conducted by Meier et al (2012) needs to be done by looking at what comes first; cannabis use or cognitive deficits. The focus should be on how quantity of cannabis leads to cannabis deficits rather than diagnoses of dependence as done by Meier et al (2012) as this will allow the findings to be extrapolated out to those who use cannabis yet are not dependent on the drug.

In contrast to general cannabis use, a causal link between early onset cannabis use and cognitive deficits is not as clear. More research examining the relationship between

these two variables will aid in meeting many of Hill's criteria (Hill, 1965). A specific research focus is not necessarily recommended here as the main goal is to replicate previous findings in order to determine the consistency criterion of Hill's criteria.

6.7.2. Cannabis Initiation and Cognitive Development

A possible mechanism proposed for explaining why early onset cannabis use is more damaging to cognition is that the exogenous chemicals in cannabis interfere with normal cognitive development. As discussed in section 1.3.4, different executive function components develop at different rates and therefore, if cannabis use does affect the developmental trajectory of cognition, then different executive function components should be differentially affected by cannabis.

Although the research on cognitive development is also in its infancy, there are some clear findings which can generate testable hypotheses. Due to the margin of error associated with determining when an individual cognitive construct, such as inhibition, reaches adult levels the easiest way to start would be to look at the earliest component to mature and the latest component to mature. Longitudinal and cross-sectional data suggests that working memory and the cognitive processes which underlie perseverative errors on the WCST mature earliest, while strategic planning matures latest (see Section 1.3.4.) If interrupted cognitive development is the mechanism behind such deficits then early onset cannabis users should display lower performance on strategic planning measures in contrast to perseveration/working memory. Perseveration has been found to be impaired in early onset cannabis users (Gruber et al., 2011; Fontes et al., 2011) although Pope et al (2003) found that late onset users were more likely to display deficits on this variable. No age of onset studies have examined strategic planning to determine if this variable would be more at risk for impairment. The main problem with this line of evidence is that different tasks have different levels of sensitivity and therefore may be more likely to detect deficits contaminating the primary hypothesis. This would only be problematic if the bias in task sensitivity was not random. For example if the tasks of processes which mature later happen to be greater in sensitivity than tasks of processes which mature early then this would erroneously support the hypothesis and thus be a type I error, while the opposite is also true which would lead to a type II error. There is no easy solution to this problem and it would seem prudent to still test this hypothesis while considering the limitations of this approach.

6.7.3. Binge Smoking Cannabis

The current research has focussed on the age of onset of cannabis use for explaining the pattern of deficits recorded in cannabis users however several other variables are suggested. One variable may be bingeing on cannabis which was measured by asking participants to describe the level of intoxication they like to reach when using cannabis, on a scale from 0-10. In the neuropsychological study this variable was found to explain a proportion of the deficits discovered on the TMT Visual Scanning test by cannabis users. However, lifetime spliffs smoked was also related to this variable and therefore it could be that increased level of intoxication was only an indicator for increased cannabis use. A similar finding was reported by Montgomery et al (2012) who found that spliffs used per session and lifetime cannabis use were both related to impaired prospective memory in cannabis users. The eye-tracking study did not replicate this finding and therefore the role of bingeing is not clear. If a study was designed to match cannabis users for total cannabis use while dividing them into two groups of "bingers" and another group of frequent but low dose cannabis use, this would help determine if the pattern of cannabis use behaviours has any relevance for cognitive integrity.

6.7.4. Cannabis strains

Police seizures show that skunk has much greater levels of Δ^9-THC and much lower levels of CBD than other strains such as hash (Potter et al., 2008). Evidence appears to suggest that skunk mediates a large number of the harms associated with cannabis use such as increased risk for schizophrenia (Di Forti et al., 2015); and that CBD appears to ameliorate the anxiety inducing (Niesink & van Laar, 2013) and memory impairing (Morgan et al., 2012) properties of Δ^9-THC. Using a method reported by Morgan et al (2012) in which hair samples are used to detect levels of Δ^9-THC and CBD, groups could be compared in other domains of cognition. While the strains of cannabis may differ over time, the length of the individuals hair will be the primary limitation to this method as longer hair will allow a much more detailed look into the individual's long-term consumption of these two cannabinoids.

6.7.5. Abstinence Induced Recovery of Function

Given the evidence for a causal interpretation of the cannabis-cognition relationship, determining the mechanism for how this occurs is of importance. While several

possibilities have been suggested such as a neurotoxic theory of cannabis-induced impairments an alternative and temporary explanation has recently gained support. Schreiner and Dunn (2012) found compelling evidence for short term impairments most likely explainable via a withdrawal mechanism. The authors compared a number of studies with the only abstinence criterion being that the subjects were not acutely intoxicated at the time of testing. They re-analysed all the studies after only including those with at least (approximately) one month of abstinence from cannabis. These analyses showed that impairments in cannabis users were present in the first meta-analysis but not when the abstinence criteria was longer than one month. The limitations of this study are discussed in the literature review of this thesis (Section 1.4.9) however the implications are important. If the cognitive deficits which have been widely discovered in cannabis users are just due to a withdrawal effect then one of the major side effects of using cannabis would only be temporary as opposed to neurotoxicity in which damage could last much longer or even permanently.

Studies have tested this explanation with different cohorts (e.g. McHale & Hunt, 2008; Thames et al., 2014) however a longitudinal approach (e.g. Hanson et al., 2010) which includes cognitive testing after one or two days abstinence, followed by a repeated testing after one month of abstinence would help determine if there was a recovery of function as opposed to just cohort effects.

6.7.6. Ecological Validity

The range of impaired cognitive constructs within cannabis users is varied and well replicated (Schreiner & Dunn, 2012) however these theoretical constructs are inferred by performance on tasks which are lacking ecological validity. One category of research among cannabis users which is yet to receive sufficient attention is how these cognitive deficits manifest in real world activities.

One candidate topic as a real world indicator of cannabis induced cognitive impairments is educational performance. The relationship between cannabis use and educational variables is well researched (Horwood et al., 2010; Lynskey et al., 2003; Mensch & Kandel, 1988; Novins & Mitchell, 1998) and several mechanisms have been proposed to explain the association. Lynskey et al (2003) suggested a role of cannabis induced cognitive impairments to mediate the relationship between cannabis use and education

however at the time there was little evidence to suggest that cannabis use had a substantive effect on cognition. Currently there is more evidence supporting this possibility and therefore the role of cannabis impacting cognition which damages educational achievement needs to be explored. This complex interaction is laden with confounding variables and determining that cannabis-induced cognitive impairments has a role in diminished educational performance will be problematic. An epidemiological approach would best answer this question, determining baseline levels of cognitive and educational performance in a large sample of children or teenagers before monitoring how these levels vary over time and change following the onset of cannabis use. This would need to take into account the effects of mental health, familial educational and drug use factors, motivation, and acute cannabis use.

Another possible avenue of future research within the ecologically valid domain is that of driving performance. The eye-tracking study discussed within the current thesis found evidence that cannabis users take longer to scan for target stimuli and take longer to confirm that target stimuli are not there. Furthermore, cannabis users made more revisits to stimuli could be due to participants moving on from an area of interest before fully processing the stimulus contents. The speculative implications of this within a driving framework is that cannabis users may take longer to identify hazards, take longer to determine that there is not a hazard present, and may move on from a particular fixation before determining for sure if there was or was not a hazard present. There is no direct evidence for this suggestion as the pattern of eye movements and visual processing may be altered in more salient circumstances such as when driving as opposed to in a laboratory visual search test. The first approach to determining whether the visual search deficits reported within the two studies of the current thesis (Chapter Three and Four) and in previous research (Ehrenriech et al., 1999; Hanson et al., 2010; Huestegge et al., 2002), have any driving implications is to test whether abstinent cannabis users perform worse on a standardised hazard perception test such as that used by the DVLA in the UK. This could be tested with an eye-tracker to determine if the results replicate work done in this thesis and by Huestegge et al (2002). Another driving concern is that cannabis users in the current study were found to be impaired relative to tobacco users on the GPT, a measure previously found to predict the number of driving errors in older adults (Dawson et al., 2010). The use of a driving simulator (e.g. Richer

& Bergeron, 2009) or a road test (e.g. Dawson et al., 2010) could be used to test whether abstinent cannabis users make more driving mistakes than controls.

6.8. Summary

The thesis has aimed to elucidate the relationship between early onset cannabis use and executive function. Through two quasi-experimental studies reported here there is substantial evidence for cognitive impairments associated with cannabis use within the domains of visual scanning, set switching and visuo-motor coordination. While the neuropsychological study provided strong evidence for an age of onset effect, the eye-tracking study only provided partial support this hypothesis. These data suggest that there may be a developmental vulnerability to cannabis use prior to the age of 16. It also appears that other drug use and educational achievement predict an early age of onset of cannabis, highlighting the need to account for these variables when examining the age of onset effect on cognition.

While legalisation and prohibition policies are consistently changing throughout the world, these findings contribute to a growing body of evidence which highlights the risk of using cannabis during the teenage years. Whether individual political states choose to legalise, decriminalise, or prohibit the use and distribution of cannabis; evidence driven guidelines for the use of cannabis need to be made available as long as harm reduction is the priority.

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