

Tyrosine negatively affects flexible-like behaviour under cognitively demanding conditions

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Citation:

ROBSON, Anna, LIM, Lee Wei and AQUILI, Luca (2019). Tyrosine negatively affects flexible-like behaviour under cognitively demanding conditions. *Journal of Affective Disorders*, 260, 329-333. [Article]

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1 Tyrosine negatively affects flexible-like behaviour under
2 cognitively demanding conditions

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26 **Background:** The catecholaminergic precursor to dopamine, tyrosine, is an important
27 modulator of cognitive performance. A number of studies have demonstrated that the
28 beneficial effects of tyrosine on cognitive performance are most pronounced when
29 individuals are exposed to stressful situations, such as hypothermia. However, little is
30 known about whether manipulation of stress using non-aversive stimuli, such as
31 cognitive demand, can also bring about similar improvements.

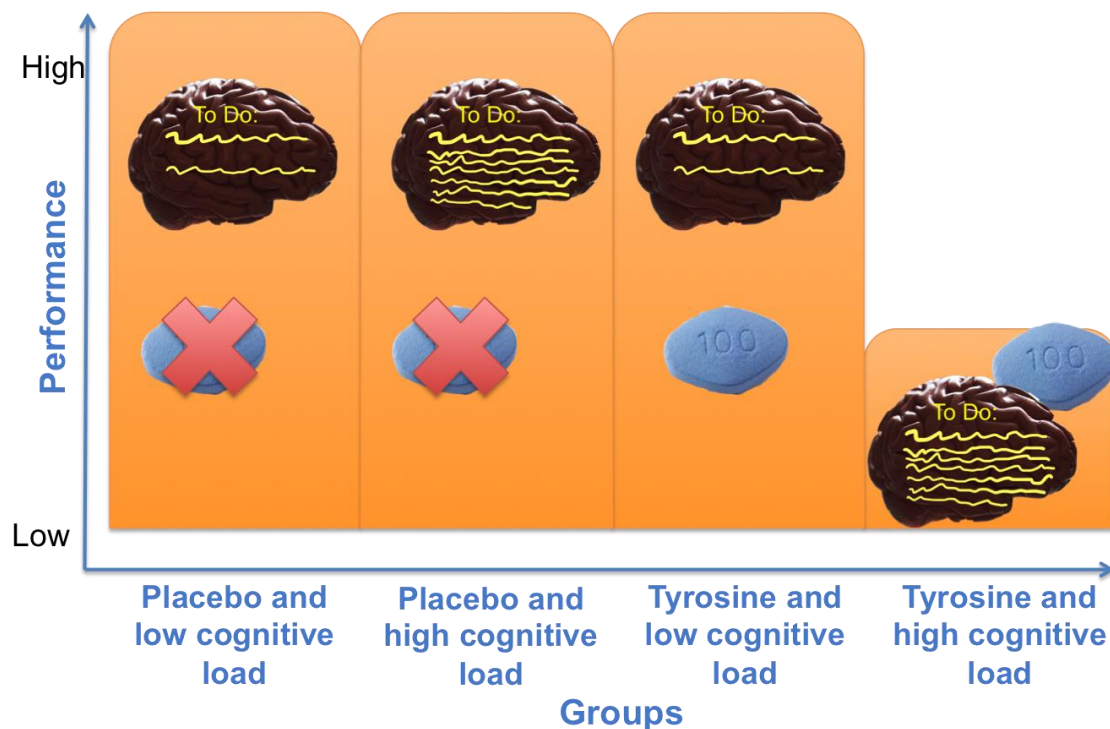
32 **Methods:** We conducted a randomized, double-blind, placebo-controlled experiment to
33 test the effects of tyrosine administration and cognitive load (low or high) on cognitive
34 flexibility, a measure known to be influenced by catecholaminergic function. A total of
35 70 healthy volunteers completed a baseline cognitive flexibility test (Wisconsin Card
36 Sorting Test: WCST). Participants were given a dose of either tyrosine (2.0 g) or
37 placebo (cellulose) and subject to either low cognitive load (simple reaction time task)
38 or high cognitive load (digit memory span task), immediately followed by a WCST for
39 a second time.

40 **Results:** Contrary to expectations, we found that instead of ameliorating performance
41 under the high cognitive load condition, tyrosine worsened cognitive flexibility.

42 **Limitations:** Physiological marker of stress was not measured.

43 **Conclusions:** Our results suggest that aversive stressors and cognitive demand
44 modulate the effects of tyrosine on cognitive performance in a differential manner.

45 **Keywords:** Tyrosine, Dopamine; Cognitive flexibility



46

47 The effect of Tyrosine and cognitive load on cognitive flexibility shown in a graphical
 48 abstract.

49

50 **Introduction**

51 Cognitive flexibility is the brain's ability to think about multiple concepts at the same
 52 time and quickly switch between concepts (Majdic et al., 2017), which can be tested
 53 using various paradigms including reversal learning and set shifting. The neuronal
 54 circuitry underpinning cognitive flexibility encompasses parts of the prefrontal cortex
 55 and the striatum, and the catecholaminergic neurotransmitter dopamine acts as an
 56 important modulator of fronto-striatal activity (Klanker, Feenstra & Denys, 2013).

57 Studies involving the pharmacological manipulation of the dopaminergic system have
 58 revealed that increased dopaminergic transmission through D₂ receptors was beneficial
 59 to set shifting performance (Van Holstein et al., 2011) but not to reversal learning

60 (Cools et al., 2009). A similar finding was reported when the dopamine precursor L-
61 Dopa was administered to patients with Parkinson's disease, which improved set
62 shifting but impaired reversal learning performance (Cools, 2006). Studies on
63 amphetamine as a psychostimulant have reinforced the idea that dopaminergic activity
64 and cognitive performance have an inverted U-shaped relationship (Cools and
65 D'Esposito, 2011), with low or high doses impairing reversal learning (Idris, Repeto &
66 Neill, 2005) but intermediate doses leaving performance intact (Soto et al., 2012).

67 More recently, a number of studies have investigated the potential effect of the
68 dopaminergic precursor tyrosine on cognitive flexibility, which theoretically might offer
69 a number of advantages over L-Dopa. Unlike L-Dopa, the conversion of tyrosine to
70 dopamine is restricted by competition from other endogenous amino acids and by the
71 rate-limiting tyrosine-hydroxylase enzyme (Jongkees, Hommel, Kühn & Colzato, 2015).
72 These restrictions comparatively limit the overall enhancement of dopamine levels by
73 tyrosine, and reduce the likelihood of shifting participants to the far end of the inverted
74 U-shaped curve.

75 Tyrosine administration has been shown to improve task switching (Steenbergen,
76 Sellaro, Hommel & Colzato, 2015). Our group found tyrosine had beneficial effects on
77 set shifting, which was dependent on dorsolateral prefrontal cortex activity (Dennison,
78 Gao, Lim, Stagg & Aquili, 2019). However, reports on the effectiveness of tyrosine on
79 cognition are rather more inconsistent (Jongkees et al., 2015). Some of this
80 heterogeneity is related to the clinical population tested (e.g. depression vs ADHD)
81 (Gelenberg et al., 1990; Posner et al., 2009), and due to inter-individual differences of
82 dopaminergic gene expression in the striatum (Colzato et al., 2016). Moreover, it has

83 been suggested that the positive cognitive effects of tyrosine may be most prominent
84 when individuals are exposed to stressful situations (Jongkees et al., 2015).

85 Aversive stimuli such as stress increase catecholamine activity and use up resources,
86 resulting in the depletion of neurotransmitter levels and behavioural depression
87 (Kvetnansky, Sabban & Palkovits, 2009). Under these circumstances, tyrosine can act to
88 replenish this depletion. In studies on hypothermia as the stressor, tyrosine
89 administration reversed the impairments on attention and memory (Mahoney, Castellani,
90 Kramer, Young & Lieberman, 2007). Additional stressors in which tyrosine has been
91 shown to have beneficial effects include sleep deprivation and an auditory stressor
92 (Deijen and Orlebeck, 1994; Magill et al., 2003). Non-aversive stimuli such as high
93 cognitive demand have also been hypothesized to lead to similar catecholaminergic
94 depletion (Jongkees et al., 2015), but this has been hardly investigated. Thomas,
95 Lockwood, Singh & Deuster (1999) were the first to show that tyrosine improved
96 working memory performance only when performing multiple tasks simultaneously.
97 Finding out whether tyrosine has enhancing effects only under particularly challenging
98 conditions such as high cognitive load would be important as it would confirm that
99 catecholaminergic depletion can be reversed both when individuals are exposed to overt
100 and non-overt stressors.

101 **Method**

102 We conducted a randomized, double-blind, placebo-controlled study to test whether
103 tyrosine beneficial effects on cognition during aversive stressful conditions (e.g.,
104 hypothermia) could be recreated using a non-aversive stressful stimuli (e.g., high
105 cognitive load). In addition, we wanted to test the effect on a different domain,

106 cognitive flexibility, as tyrosine administration was shown to ameliorate cognitive
107 flexibility performance under normal conditions (Steenbergen et al., 2015; Dennison et
108 al., 2019).

109 This study was approved by the ethics committee of Sheffield Hallam University and
110 was conducted in compliance with the Declaration of Helsinki (World Medical
111 Association, 1964). Participants consisted of 70 university students (M=19.9 years,
112 SD=1.6) including 59 females and 11 males). Written informed consent was obtained
113 from all participants in the study. Exclusion criteria included individuals with cardiac,
114 hepatic, renal and neurological disorders, history of alcohol or drug addiction, and
115 psychiatric illness, as well as those with a history of taking tyrosine supplements.

116 Participants were randomly assigned to the tyrosine or placebo groups. Participants
117 received either 2.0 g of tyrosine (BulkPowders Ltd, UK.) or 2.0 g of microcrystalline
118 cellulose (Redwells Creative Limited, UK) dissolved in 400 mL of orange juice as in
119 previously published protocols (Dennison et al., 2019). All participants were tested in
120 the morning (9am-11am) and were asked to refrain from eating or drinking for at least
121 three hours. This is to prevent tyrosine competition with other amino acids which may
122 prevent its effectiveness. Participants waited 60 min before testing, as a previous
123 study on tyrosine modulation of cognitive flexibility found that the peak plasma
124 concentration level occurred at 60 min following oral administration (Steenbergen et al.,
125 2015)[10].

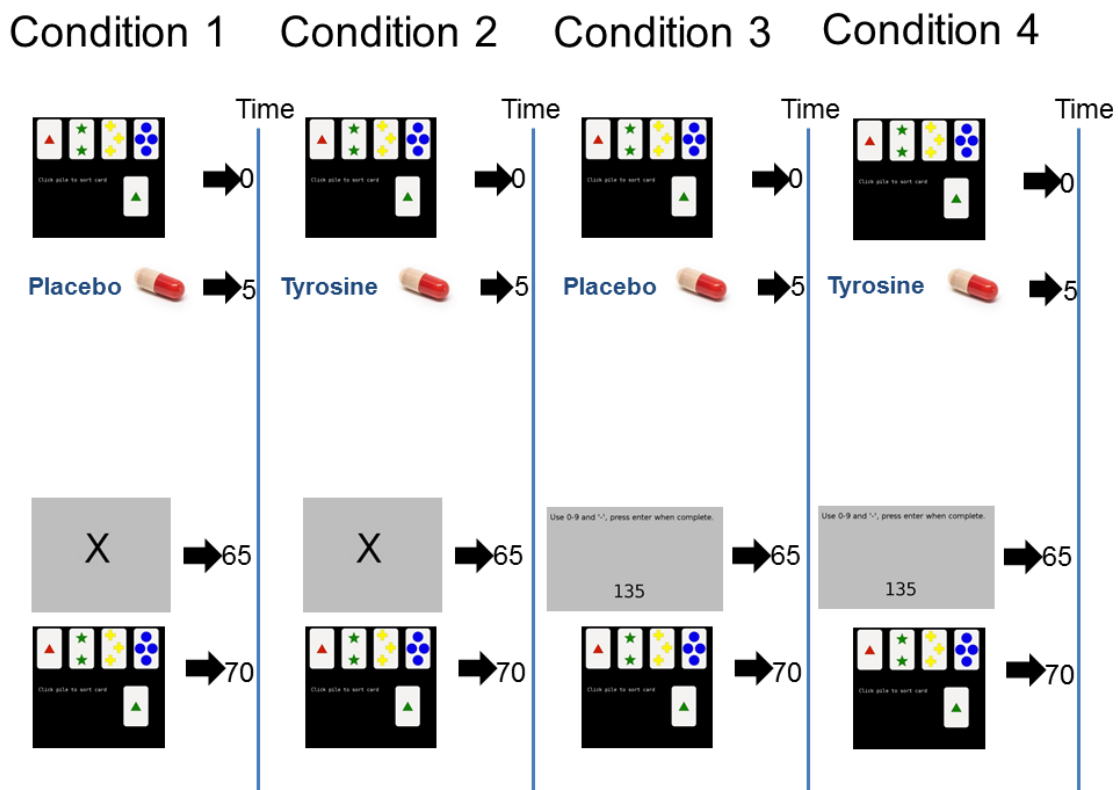
126 To assess cognitive flexibility, we used an adapted Wisconsin Card Sorting Test
127 (WCST) implemented in PEBL software (Mueller and Piper, 2014). The WCST
128 provides a measure of task switching behaviour, in which subjects are required to match

129 a sample card to a set of four reference cards based on one of the following three rules:
130 colour, shape, and number. Following a series of correct matches, the classification
131 rules are changed unexpectedly and the subject must learn to switch responses (Monchi,
132 Petrides, Petre, Worsley & Dagher, 2001). We measured reaction times and
133 perseverative errors. Reaction times reflect the time taken to make a choice following
134 the presentation of the sample and reference cards. Perseverative errors are counted as
135 choosing the same incorrect response following a rule shift (e.g., classification rule
136 shift: shape-colour; perseverative error: shape-shape; non-perseverative error: shape-
137 number). The task lasted between 5 and 7 minutes.

138 For the cognitive load, participants were asked to complete either a simple reaction time
139 task (low cognitive load) or a forward digit span memory task (high cognitive load)
140 implemented in PEBL software. In the simple reaction time task, participants pressed
141 the space bar as soon as possible following the presentation of a stimulus (the letter "x")
142 in the middle of the screen. The dependent measure of interest was the time taken
143 (reaction time in milliseconds) to respond to the stimulus. In the forward digit span
144 memory task, participants were shown a sequence of digits on the screen, one at a time,
145 starting with a list of three items. Participants were then asked to recall (by typing) the
146 sequence in the exact order as it appeared. Participants had to recall correctly two out of
147 three lists with the same number of items before moving to a list containing additional
148 digits. The dependent measure of interest was the length of the longest list.

149 After screening for eligibility, participants were instructed to refrain from
150 eating/drinking for a minimum of 3 h to reduce competition from other amino acids that
151 share the same transporter (Fernstrom, 1990). Participants were then required to attend a

152 session lasting approximately 75 min. They first signed a consent form and then
 153 completed a WCST (time 1). They then received either tyrosine or placebo according to
 154 the group allocation. After 60 min following tyrosine or placebo intake, half the
 155 participants completed a simple reaction time task (low cognitive load), and the other
 156 half completed a forward digit span memory task (high cognitive load). As soon as they
 157 finished the tasks (approximately 5 min), a WCST was administered for the second time
 158 (time 2). Finally, participants were asked to fill out a tyrosine/placebo double-blind
 159 questionnaire before being debriefed. An outline of the experimental procedure is
 160 shown in Figure 1.



161

162

163 Fig. 1. Graphical illustration of the experimental procedure.

164 At time 0, all participants completed a WCST as a baseline measure of cognitive
165 flexibility. Approximately 5 min later after completing the WCST, participants were
166 administered either a placebo or tyrosine. After 65 min, which is the time for tyrosine to
167 reach peak concentration in plasma, participants completed either the simple reaction
168 time task (low cognitive load: condition 1 and 2) or the forward digit span memory task
169 (condition 3 and 4). Finally, all participants completed a WCST for the second time.

170 **Results**

171 Statistical analyses were performed using SPSS version 24 (SPSS Inc). The sample size
172 was calculated to achieve a power at 0.8, an alpha level set at 0.05, and a large effect
173 size (η^2) of 0.14 (G*Power 3.1.9.2, Germany). For the two dependent measures of the
174 WCST (reaction time and perseverative errors), we ran a 2x2 factorial ANOVA with
175 drug as one factor (placebo, tyrosine) and cognitive load as the second factor (low and
176 high). Performance of the low and high cognitive load tasks was analysed using an
177 independent samples t-test comparing placebo to tyrosine participants.

178 The double-blind efficacy of tyrosine/placebo was analysed using a percent correct
179 measure. A score of 100 was given if a participant correctly identified the condition,
180 else a score of 0 was given. A Chi-Square test was used to assess the blinding efficacy.

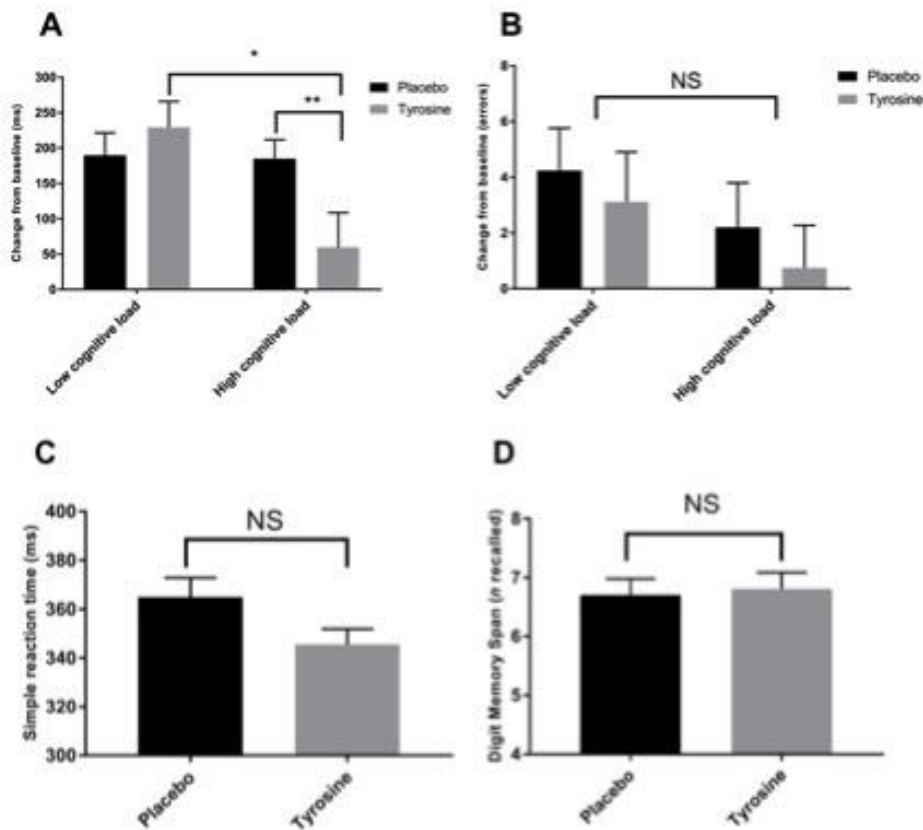
181 We first analysed changes in reaction times (RT) across conditions. We calculated the
182 change in performance from baseline (Time 1: T1) to post-drug (Time 2: T2) (i.e. [T1] -
183 [T2]), as in a recently published paper (Dennison et al., 2019). A 2x2 factorial between-
184 subjects ANOVA with drug as one factor (Placebo, Tyrosine) and cognitive load as the
185 other factor (Low, High) demonstrated there was no main effect of drug [$F(1, 66) = 1.41$,
186 $p = 0.239$, $\eta^2 = .02$]. However, there was a significant main effect of cognitive load [$F(1,$

187 66) =5.84, $p=0.018$, $\eta^2=.08$], with the high cognitive load condition reducing the
188 improvements in reaction times from baseline ($M=129.3$, $SD=168.1$) compared to the
189 low cognitive load condition ($M=209.5$, $SD=140.8$), which showed greater
190 improvements. Importantly, there was a significant interaction effect between drug and
191 cognitive load [$F(1, 66) =5.22$, $p=0.026$, $\eta^2=.07$]. To break down this interaction,
192 follow-up simple main effect analyses were performed. For low cognitive load, there
193 was no significant reaction time difference between placebo and tyrosine [$F(1, 66)$
194 =0.58, $p=0.446$, $\eta^2=.00$], whereas for high cognitive load, tyrosine reduced the
195 improvement in reaction times from baseline compared to placebo [$F(1, 66) =6.71$,
196 $p=0.016$, $\eta^2=.08$]. Comparing within cognitive loads, there was no significant difference
197 between low and high cognitive loads in placebo participants [$F(1, 66) =.00$, $p=0.924$,
198 $\eta^2=.00$]. Interestingly, there was a significant difference between low and high
199 cognitive loads in tyrosine participants [$F(1, 66) =10.48$, $p=0.002$, $\eta^2=.13$], with high
200 cognitive load slowing down reaction times compared to the low condition (Fig 1A).

201 We next investigated the second measure of cognitive flexibility using the perseverative
202 error, analysed as above. There was no main effect of drug [$F(1, 66) =.78$, $p=0.433$,
203 $\eta^2=.00$], or main effect of cognitive load [$F(1, 66) =1.83$, $p=0.180$, $\eta^2=.02$], or
204 significant drug x cognitive load interaction [$F(1, 66) =.01$, $p=0.919$, $\eta^2=.00$] (Fig 1B).

205 To ensure the effects of tyrosine on cognitive flexibility were not influenced by changes
206 in simple reaction times (i.e., low cognitive load task) or memory (i.e., high cognitive
207 load task), we ran two independent sample t-tests. There were no significant differences
208 in the performance between placebo and tyrosine participants on the simple reaction
209 time task ($t(32) = 1.92$, $p=0.065$) or on the digit span memory task ($t(32) = -.28$,

210 $p=0.781$). These results confirmed the specificity of the tyrosine effects on cognitive
211 flexibility as modulated by cognitive load (See Fig 2C and 2D).



212

213 Fig. 2. A. Effect of drug (Placebo, Tyrosine) and cognitive load (Low, High) on
214 cognitive flexibility as measured by a change in reaction times from baseline (pre-drug).
215 B. Effect of drug (Placebo, Tyrosine) and cognitive load (Low, High) on cognitive
216 flexibility as measured by a change in perseverative errors from baseline (pre-drug). C.
217 Differences in performance between placebo and tyrosine participants on the low
218 cognitive load task (simple reaction time). D. Differences in performance between
219 placebo and tyrosine participants on the high cognitive load task (digit memory span

220 task). Indication: Error bars represent SEM. * indicates significance at $p < .05$; ** at p
221 $< .01$. NS= not significant when $p > .05$.

222 The double-blind efficacy of placebo/tyrosine administration was analysed using a Chi-
223 Square test. There was no significant association between the condition (i.e., placebo or
224 tyrosine) and the participant correctly identified it [$\chi^2(1) = 1.22, p = 0.269$].

225 **Conclusion**

226 This study aimed to test whether the beneficial effects of tyrosine on cognitive
227 performance under aversive stressful conditions (e.g., hypothermia) as reported in the
228 literature could be replicated under non-aversive but potentially stressful conditions (i.e.,
229 cognitive demand). We were particularly interested in measuring cognitive flexibility
230 performance, as this has been shown to have a dopaminergic component (Klanker,
231 Feenstra & Denys, 2013). Contrary to expected results, high cognitive load reduced
232 tyrosine improvements in baseline reaction times when compared to placebo controls.
233 Moreover, the high cognitive load did not produce a performance deficit (compared to
234 the low cognitive load) in the placebo participants, but the opposite was true for those
235 given tyrosine. Significantly, the detrimental effects of tyrosine on cognitive flexibility
236 driven by the high cognitive load manipulation was specific, as tyrosine did not alter
237 performance of the simple reaction time task (low cognitive load) or the forward digit
238 span memory task (high cognitive load).

239 Previous research using cognitive demand as a non-aversive stressor showed tyrosine
240 had a beneficial effect on memory performance (Thomas et al., 1999). However,
241 tyrosine improved working memory only when multitasking (i.e., high cognitive
242 demand) and not during a simple task battery (i.e., low cognitive demand), which

243 suggests cognitive demand could induce a stress-like state similar to that elicited by an
244 overt stressor such as hypothermia, and that tyrosine could act to replenish the
245 catecholaminergic depletion (Jongkees et al., 2015). Interestingly, cold exposure as a
246 stressor changed cortisol levels (Mahoney et al., 2007), but the high cognitive demand
247 task did not alter cortisol, indicating cognitive demand may not trigger a physiological
248 stress response. Future studies employing cognitive demand as a proxy for a stressful
249 stimulus would need to further clarify the impact on catecholamine secretion and
250 cortisol.

251 There are a number of important differences between the current study and that of
252 Thomas et al. (1999), which need to be noted when making comparisons. First, in the
253 study by Thomas et al., they measured working memory, whereas we assessed cognitive
254 flexibility. Although both working memory and cognitive flexibility performance are
255 modulated by the dopaminergic system, several lines of evidence suggest that working
256 memory is primarily mediated by D1 receptors, whilst cognitive flexibility by D2 (Ott
257 and Nieder, 2019). Second, the cognitive load manipulation in the previous study
258 included the simultaneous performance of a number of tasks, whereas we administered
259 either a forward digit memory span or a simple reaction time task. Nevertheless, the
260 high cognitive load task used in this study produced the intended overall (i.e., main
261 effect) detrimental effect on performance. Third, the majority of our participants were
262 females (59/70), and there have been reports of gender differences in response to stress
263 (Allen, Bocek & Burch, 2011) and cognitive flexibility (Kalia et al., 2018).

264 Previous studies have shown that tyrosine can improve cognitive flexibility under
265 normal, non-stressful conditions (Steenbergen et al, 2015; Dennison et al., 2019).

266 Although the different types of cognitive flexibility tasks used in these studies and in
267 the present study may provide a partial explanation for the contrasting results, it is still
268 plausible that the beneficial effects of tyrosine on cognitive flexibility could be nullified
269 by the simple attention task and worsened by the more demanding memory test, as
270 demonstrated in our study. Regardless, the precise biological mechanism by which this
271 behavioural effect is mediated needs to be further explored. Furthermore, the finding by
272 Hensel et al. (2019) that showed tyrosine intake caused brain connectivity alterations
273 between the prefrontal cortex and the striatum also needs further investigation.

274 *Limitations:* One of the limitations of the study was that we cannot confirm that the high
275 cognitive load task resulted in a physiological stress response as reported in studies
276 using hypothermia as a stressor. The second limitation relates to the gender imbalance
277 in our sample (more females) which only provides partial generalizability of our results.

278 In conclusion, we provide evidence that high cognitive demand and aversive stressful
279 stimuli (e.g., cold exposure) may have contrasting bidirectional influence on tyrosine
280 administration on cognitive performance.

281 AR performed the statistical analysis of the data and wrote the manuscript. LWL wrote
282 the manuscript. LA designed the experiments, collected the data, performed the
283 statistical analysis of the data, and wrote the manuscript.

284 Conflicts of interest: none.

285 This research did not receive any specific grants from funding agencies in public,
286 commercial, or non-profit sectors.

287

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