1   **Title:** The effects of medium chain triglyceride (MCT) supplementation using a C_8:C_{10} ratio

2   of 30:70 on cognitive performance in healthy young adults

3

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5

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29

32   **Abstract**

33   ***Purpose:*** The brain can utilise medium chain triglycerides (MCTs) as an alternative fuel than

34   glucose, and research has shown that MCT ingestion improves cognitive function in diseased

35   and/or elderly individuals. The aim of this study is to determine if these improvements can also

36   be observed in young, healthy adults. Furthermore, we aim to establish the ideal dosage and

37   timeframe necessary for an effect.

38

39   ***Methods:*** Participants were divided equally into three groups of 10 (Placebo (0g), 12g and 18g

40   MCT/day) and were supplemented for 4 weeks. The supplement had a $C_8:C_{10}$ ratio of 30:70.

41   Participants visited the laboratory once a week for 5 weeks (baseline, test weeks 1-4) to undergo

42   a battery of cognitive tests; Trail Making, Digit Span, Spatial Span, Covert Shift of Attention,

43   and Rapid Visual Information Processing.

44

45   ***Results:*** After 2-3 weeks of supplementation, MCT ingestion enhanced performance in

46   cognitive tasks, including: Trail Making A/B and Digit Span Forwards/Backwards (ps<0.001)

47   when compared to a placebo group taking a carbohydrate gel. In Spatial Span Backwards, there

48   was a significant main effect of group (p=0.002). Where significance was seen, there were

49   main effects of time after 2-3 weeks (ps<0.05). There was minimal difference between the two

50   MCT intervention groups in most measures (ps>0.05). There were also null results in tasks

51   measuring attention and reaction time (ps>0.05).

52

53   ***Conclusions:*** MCT ingestion improved cognitive performance after 2-3 weeks, with minimal

54   difference between taking 12g and 18g MCT/day groups, suggesting a possible dose-response

55   threshold at 12g MCT/day when supplementing over a short period.

56

57   **Keywords:** MCTs, Processing Speed, Task Switching, Working Memory, Cognition

Introduction

Medium chain triglycerides (MCTs) are mixed fatty acids with a chain length of between 6 and 12 carbon atoms. Naturally occurring sources of MCTs include coconut oil, palm kernel oil and breast milk. For the most part, commercially produced MCTs contain two predominant fatty acids in varying ratios; Caprylic Acid (C_8) and Capric Acid (C_{10}), with only traces of C_6 and C_{12} [1,2]. MCTs are less common in Western diets, with the majority of the fatty acids consumed being long-chain fatty acids (LCFAs), i.e. containing more than 12 carbon atoms [3]. These LCFAs are provided by animals/vegetable oils and fat sources which are vital for essential bodily functions [4]. Despite not normally being present in typical western diets, MCTs are increasingly being incorporated into a growing number of food and nutrition plans due to their potential health benefits [1].

Digestion of MCTs begins in the mouth by the enzyme lingual lipase which is present in saliva. Figure 1 highlights that they are then hydrolysed in the stomach and intestine by pancreatic lipase into medium chain fatty acids (MCFAs) and monoglycerides. This is a faster and more complete process than that of long chain triglycerides (LCTs) [1,5], with MCFAs being absorbed directly into the portal vein, bound to albumin, just minutes after ingestion [3]. Moreover, absorption of MCTs may not require bile and lipase, and therefore, are directly absorbed by the enterocytes [6]. Thus, they are unlike LCFAs, which are firstly incorporated into chylomicrons before being transported into the lymphatic system and taken to the liver [7–9]. The liver oxidises the majority of the MCFAs via β-oxidation [10], leading to the production of ketones, predominantly β-hydroxybutyrate (βHB) [1], as shown in Figure 1. The formation of βHB, as well as acetoacetate and acetone, is normally the result of a greater availability and oxidation of fatty acids in the liver due to an extended low carbohydrate intake, or during prolonged exercise. However, MCTs enable the body to produce these compounds without a change in diet. The acetone formed, arguably, may be used as a gluconeogenic substrate, although it is mainly excreted through urine or exhaled as a waste product. The feasibility of glucose being produced from fatty acids is a very controversial mechanism. It was initially thought that acetone can contribute carbon atoms to glucose formed by the Krebs Cycle [11], however, in the 1980's, new pathways were discovered [12–14]. Recently, Kaleta *et al.* [15] identified 58 possible pathways acetone can take to become glucose. This relatively recent finding contradicts previous assumptions that humans are unable to metabolise acetone, and therefore fatty acids, into glucose. In contrast to LCFAs, MCFAs can transport through the mitochondrial membrane regardless of the presence of carnitine [16,17], allowing oxidation to

92 proceed more rapidly than that of LCFAs [9]. Taken together, the ingestion of MCTs is more
93 ketogenic (i.e. produces ketones more rapidly) in comparison to LCTs, [7,18]. For a thorough
94 comparison of MCTs and LCTs, see Jeukendrup and Aldred [3].

95

96   βHB is exported from the liver into the blood and is converted in the mitochondria in
97 muscle and brain cells into acetoacetate using the enzyme beta-hydroxybutyrate
98 dehydrogenase. Acetoacetate is then converted to acetoacetyl-CoA via the enzyme succinyl-
99 CoA-oxoacid CoA transferase before becoming acetyl-CoA via the enzyme beta-ketoacyl-
100 CoA, which is then oxidised in the Krebs cycle with the subsequent NADH and FADH$_2$
101 production utilised by the mitochondrial electron transport chain to harbour energy [19,20], as
102 illustrated in Figure 1. The brain can utilise βHB as an alternate energy source to glucose, which
103 is otherwise the main fuel source [10,21]. Additionally, the MCFAs that bypass metabolism in
104 the liver can directly cross the blood-brain-barrier due to their relatively shorter carbon chain
105 length and are oxidised in astrocytes: LCFAs are unable to do so [22,23]. Therefore, MCTs
106 provide both direct and indirect (via βHB) additional fuel sources for the brain [21].

107

108   **[Insert Figure 1 Around Here]**

109

110   Since MCTs provide several routes of energy supply for brain metabolism [21], and in
111 light of the potential for cerebral insulin resistance in elderly/diseased individuals [24–26], it
112 has been suggested that ingestion of MCT supplements alongside a regular diet can offset
113 cognitive decline in these populations [21,25–29]. For example, Page *et al.* [29] found that, in
114 diabetic individuals, acute MCT ingestion increased performance in digit symbol coding and
115 total map searching, while preventing declines in tests requiring verbal working memory and
116 attention when experiencing hypoglycaemia. Memory performance was also improved in
117 participants with Alzheimer's disease [25–28] and mild cognitive impairment [30] following
118 both acute and chronic MCT loading protocols. In healthy elderly participants, Ota *et al.* [21]
119 demonstrated cognitive improvements in digit span and trail making tasks following a single
120 20g serving of MCTs, although no such effects were indicated by O'Neill *et al.* [31] after 14
121 successive days of MCT ingestion, possibly due to the very high rates of diarrhoea experienced
122 by participants impacting on treatment efficacy.

123

124   Diseased and/or elderly individuals are more likely to have a reduced baseline cognitive
125 function, possibly due to cerebral insulin resistance, such that it has been proven that ketogenic

126   interventions lead to βHB becoming a primary energy source for the brain, alleviating cognitive

127   dysfunction [24–26]. However, even in young healthy individuals, the range of substrates

128   available to the brain for energy metabolism remains restricted as compared to skeletal muscle,

129   for example. Specifically, the brain relies on glucose, ketones and MCTs for energy, whilst

130   being unable to utilise LCTs. Moreover, there are no significant differences in brain ketone

131   metabolism between older adults, individuals with cognitive impairment/Alzheimer's Disease

132   and healthy young adults [32–34]. Therefore, it remains plausible that the improvements in

133   cognitive function following MCT supplementation demonstrated in diseased/elderly

134   populations may also be seen in healthy subjects.

135

136   Typically, commercially available MCT products contain varying ratios of C_8 and C_{10}

137   [2]. C_8 has been shown to be more ketogenic than C_{10} [7,18], and preferentially metabolised by

138   neuronal cells, whereas C_{10} is metabolised at a slower rate, leading it to accumulate [35].

139   However, C_{10} is easier to digest than C_8 due to its longer carbon chain length, reducing the risk

140   of gastronomical distress [1,36]. Hence, adherence to MCT supplementation may be impacted

141   by the C_8-C_{10} ratio. Vandenberghe *et al*. [18] demonstrated that only a modest amount of C_8 is

142   required (within a C_8-C_{10} mixture) to retain a peak plasma ketone response no different to that

143   of C_8 alone. Moreover, C_{10}, rather than C_8, has the potential to increase the number of

144   mitochondria over time in neuronal cells, although of a smaller size than untreated cells [37].

145   Hughes *et al.* [37] observed that C_{10}, but not C_8, increased citrate synthase activity after 6 days

146   of MCT supplementation, indicative of enhanced mitochondrial biogenesis. This effect may be

147   due, at least in part, to the peroxisome proliferator activator receptor γ (PPARγ), a promotor of

148   mitochondrial biogenesis [38], which is activated by C_{10}, but not C_8. [39]. Hughes *et al.* found

149   that in the presence of a PPARγ antagonist, the increase in citrate synthase activity due to C_{10}

150   was prevented. Taken together, these data are supportive of the notion of mitochondrial

151   biogenesis being induced in neuronal cells following C_{10} MCT supplementation.

152

153   The present study utilised a C_8-C_{10} ratio of 30:70 in the MCT supplement. This

154   incorporates the benefits of both C_8 and C_{10}, while also limiting the risk of gastronomical

155   distress previously seen when using a supplement with a higher ratio of C_8 [27,40]. The primary

156   aim was of this study is to determine whether the improvements in cognitive function due to

157   MCT ingestion seen in diseased/elderly individuals will also be demonstrated in a young and

158   healthy population. We hypothesised that chronic MCT ingestion would improve some aspects

159   of cognitive function, as measured by a standardised battery of laboratory-based cognitive tests

160 including trial making, digit and working memory span, covert shift of attention, and rapid
161 visual information processing (sustained attention). Following previous findings that used
162 similar measures [21,25–30], we predicted there to be improvements within at least some of
163 the tasks, most likely in the trail making and memory span tasks, as demonstrated by Ota *et al.*
164 [21,26]. This study has the secondary aim of establishing the minimum effective dose of this
165 unique MCT composition during a 4-week period of supplementation.

166

167 **Methods**

168

169 *Participants*

170 30 university students (19.7 ± 1.5 years, 16 males and 14 females) volunteered for the present
171 study. Participants were all clear of any neurological and health impairments and had not
172 partaken in any cognitively demanding tasks for at least 12 hours prior to each testing session.
173 The study was approved by the local research ethics committee (approval number: S 22-11-19
174 PA 053) and designed and conducted in accordance with the Declaration of Helsinki (2013).

175

176

177 *Experimental Procedure*

178 The study followed a repeated-measures, single-blind design involving a single weekly visit to
179 the laboratory at the exact same time for 5 consecutive weeks. After a 12h overnight fast,
180 participants undertook a single battery of cognitive tests at each visit, which lasted < 30 mins.
181 Baseline measurements were taken before the participants had started their supplementation
182 period due to the fact that it takes a number of days before C_{10} has a significant effect upon
183 mitochondrial function [37], and up to 72h for ketones to be metabolised in the brain of
184 nondiabetic individuals [41]. Each successive round of testing took place after 7 successive
185 days of supplementation, with the participants taking an MCT/placebo gel immediately prior
186 to their laboratory visits. Participants took the gels every day for a total of 4 weeks to ensure
187 sufficient time for an increase in blood plasma ketone bodies (acetoacetate and β-
188 hydroxybutyrate) [28].

189

190　　　Participants were randomly allocated into one of 3 groups using a random number
191 generator using computer software, and the groups were matched for age and gender: Placebo
192 (0g MCT/day), 12g MCT/day and 18g MCT/day. The MCT was provided to participants using
193 a commercially available MCT gel (Nuroco, London, UK) that contains 59 kcal and 6g of MCT

194   with a 30:70 ratio of C_8:C_{10}. In order to offset possible unpleasant gastronomical issues that

195   arise from taking MCTs [40], the number of MCT gels (6g) given to the 12g and 18g groups

196   were increased incrementally over the course of the 4-week period (Figure 2). To match the

197   number of overall gels taken by all participants, a carbohydrate gel (Energel+, Nutrition X,

198   Gloucester, UK) was provided with similar calorific intake (94 kcal, difference 35 kcal vs.

199   MCT gel) and flavouring to that of the MCT gel. All gels were wrapped in black tape to blind

200   them from the participants. Participants were instructed to take their first, second and third gels

201   30 mins prior to breakfast, lunch and dinner, respectively. When visiting the lab, participants

202   were instructed to take their gel immediately prior to entering the laboratory to and have

203   breakfast as soon as possible after completion of the tests in order to abide by the instructed

204   30-minute interval between gels and meals as closely as possible.

205

206   **[Insert Figure 2 Around Here]**

207

208   *Cognitive Assessments*

209

210   *Trail Making*

211   Trail Making (TM) broadly assesses processing speed, sequencing and visual-motor skills [42].

212   There are two parts; A and B. In part A, participants are required to draw lines as quickly as

213   possible between the numbers 1 and 25 in ascending order. In part B, participants are required

214   to draw lines as quickly as possible between the ascending orders of both numbers (1-13) and

215   letters (A-L). Due to the need to switch attention between letters and numbers in part B (1-A,

216   2-B, etc.), it is comparably much more difficult than part A. If any errors were made, it was

217   immediately pointed out by the experimenter and the participant had to correct for it.

218   Participants initially practiced for each part, which comprised of only 8 circles.

219

220   *Memory Span*

221   Two aspects of working memory were assessed: verbal and visuo-spatial. Verbal working

222   memory was assessed using the digit span test (DS) and visuo-spatial working memory was

223   assessed using the spatial span test (SS). The experimenter either read out a series of numbers

224   (DS) or tapped blocks in a certain predetermined order (SS). The participants had to either

225   repeat the numbers back (DS) or tap the blocks (SS) in the corresponding order (forwards test

226   phase) or in reverse order (backwards test phase). The backwards test phase is comparably

227   more difficult than the forwards test phase due to the requirement of the executive function to

228 re-order items before responding [43]. There were two trials in each item, with the number of
229 numbers/blocks increasing by one item every trial. The test was terminated when participants
230 incorrectly recalled a sequence on both trials of any one item or recalled all items correctly.
231 Each test phase had a maximum score of 16, with the exception being DS backwards, which
232 had a maximum score of 14. There was no practise necessary due to the first trials only being
233 2 numbers/blocks long, which was sufficiently easy to gain a full understanding of the task.
234

235 *Covert Shift of Attention (CSoA)*
236 Exogenous (involuntary) and endogenous (voluntary) attention were assessed via a covert
237 attention paradigm [44]. Each test involved rapidly responding to a cue that was presented on
238 an LCD monitor using Matlab (MathWorks, Natick, MA, USA) running Psychtoolbox (version
239 3.0.11). Stimuli featured a background with a white crosshair at screen-centre, and two unfilled
240 white squares at a 5-degree horizontal eccentricity. Participants were instructed to fixate on the
241 crosshair while they used their left or right index fingers to press the 'f' or 'j' keys on a
242 keyboard in response to the left or right white squares becoming filled, respectively.
243

244　　　The exogenous and endogenous tests were differentiated by the unique characteristics
245 of a pre-cue. For exogenous cuing, the pre-cue initially involved a white unfilled square
246 surrounding one of the other two squares for 50ms. Therein, one of the two squares became
247 filled for 1500ms or until the participants responded. Trials could be discriminated by the
248 relation between the side of space of the initial pre-cue and the location of the response cue.
249 That is, a compatible relation between the side of space of the pre-cue and location of the
250 response cue was regarded as a cued trial, while an incompatible relation was regarded as an
251 uncued trial. The time difference between the pre-cue and response cue was set to 100ms and
252 800ms in order to exercise processes of cue facilitation and inhibition, respectively. That is, a
253 100ms asynchrony typically generates a quicker response for cued compared to uncued trials
254 (facilitation), while a 800ms asynchrony typically generates the inverse effect (inhibition)
255 [45,46]. There was an equal distribution of 20 trials for each type of trial (cued, uncued), side
256 of space (left, right) and stimulus-onset asynchrony (100ms, 800ms). In addition, there were
257 16 catch trials where a response cue would not appear following the initial pre-cue, and thus
258 required no response. Thus, there were total of 96 trials for the experiment and 20 trials for
259 initial practice.
260

261   For endogenous cuing, the pre-cue initially involved a set of white arrowheads (<< /

262 >>) appearing at screen-centre for 50ms. Following a further delay of 450ms, one of the two

263 squares was filled in white for 1500ms or until the participants responded. In a similar vein to

264 exogenous cuing, trials could be discriminated by the nature of the initial pre-cue and the

265 location of the response cue. That is, a compatible relation between the direction of pre-cue

266 and location of the response cue was regarded as a valid trial, while an incompatible relation

267 was regarded as an invalid trial. Importantly, the frequency of valid trials was noticeably greater

268 than invalid trials, which typically cues attention toward the same direction as the pre-cue.

269 Consequently, the ability to inhibit and reorient attention can be found when reducing the extent

270 of the typically quicker responses for valid compared invalid trials [45,46]. There were 32

271 valid, 8 invalid and 8 catch trials–comprising a total of 48 trials–for the experiment and 10

272 trials for initial practice.

273

274   Reaction times were recorded as the time difference between stimulus and response

275 onset. Trials where there was a false (<100ms) or delayed (>1000ms) reaction, or responses

276 were made to the incorrect side of space were removed from any subsequent calculations. The

277 dependent measure involved the cuing effect, which was calculated as the mean participant

278 reaction time to the cued/valid trials minus the uncued/invalid trials. Thus, a more negative

279 score indicated a quicker response to the cued/valid trials than the uncued/invalid trials.

280

281 *Rapid Visual Information Processing (RVIP)*

282 RVIP assesses the ability to sustain attention to visual stimuli [47–49]. Stimuli featured single

283 digits (1-10) being sequentially presented at the centre of an LCD monitor. Participants were

284 instructed to press the spacebar key of a keyboard as soon as a digit was presented that

285 completed a unique three-digit sequence: 2-4-6, 4-6-8, 3-5-7. Each digit was presented for

286 600ms with no inter-stimulus interval. However, the digits were alternatively presented for

287 1500ms whenever they completed a target sequence. There were 8 target sequences per min,

288 and the test lasted continuously for 5mins (100 digits per min). Prior practice on the test was

289 completed over 1min. The dependent measures involved reaction times to target sequences,

290 proportion of false (<100ms) or delayed (>1000ms) reactions, and proportion of missed targets.

291

292 *Statistical Analysis*

293 The data were analysed through linear mixed modelling (LMM) using the statistical package

294 IBM SPSS Statistics (Version 25, Chicago, IL, USA). An LMM was utilised due to its ability

295 to provide unbiased data in the presence of missing data (there was 57 missing data points from

296 a total of 1800) [50]. Baseline measurements were entered as a covariate and the treatment

297 effect from baseline (i.e. difference from baseline) were analysed in each measure. All models

298 began as a null and were progressed to more complex parsimonious hierarchical models. The

299 4 time points (weeks 1, 2, 3 and 4) and the three experimental groups (Placebo, 12g and 18g)

300 were treated as categorical fixed effects. Random effects were associated with the individual

301 participants. Significant effects were decomposed using the Fisher LSD post hoc procedure.

302

303   A basic variance components model was executed to calculate the intraclass correlation

304 (ICC) of the random factors for participant number to determine if any contributed significance

305 variance to the dependent variable, as seen in Table 1. Model fit was assessed using Akaike's

306 information criterion (AIC). For the dependent variable (treatment effect), AIC revealed the

307 models that best fit the data utilised either the AR-1 or AR-1: Heterogenous repeated

308 covariance structure for the repeated measures. Significance was set at $P < .05$. Where

309 appropriate, post hoc analyses (LSD) and the inclusion of 95% confidence intervals (CI) of the

310 differences is reported. All data is represented as mean difference from baseline ± standard

311 error.

312

313

314 **Results**

315 *Variance Calculations*

316 Table 1 shows the ICC's (%) of the random factors accounted for in the linear model. The

317 individuals contributed significant variance to the dependent variable in all measures. Hence,

318 they were included in all of the larger hierarchical models.

319   **[Insert Table 1 Around Here]**

320 *Trail Making*

321 For TM A, there was no significant main effect of group (p=0.149), although there was a

322 significant main effect of time (p<0.001). This effect was superseded by a significant group x

323 time interaction (p<0.001) (Figure **3**A). Post hoc analysis revealed that the 12g group

324 performed significantly better than the Placebo group in week 4 (p=0.045). The 18g group

325 performed significantly better than the Placebo group in weeks 3 (p=0.001) and 4 (p<0.001),

326 and the 12g group in weeks 3 (p=0.014) and 4 (p=0.001). There were no further significant

327 differences in any of the weeks (*ps* > .05).

328 For TM B, there was no significant main effect of group (p=0.065), although there was

329 a significant main effect of time (p<0.001). This effect was superseded by a significant group

330 x time interaction (p<0.001) (Figure **3**B). Post hoc analysis revealed that the 12g and 18g

331 groups performed significantly better than the Placebo group in weeks 2 (p=0.018; p=0.023),

332 3 (p=0.018; p=0.001) and 4 (p=0.016; p=0.001), respectively. There was no significant

333 difference between the 12g and 18g groups in any of the weeks (ps > .05).

334 *Memory Span*

335 For DS Forwards, there were significant main effects of both group and time (ps<0.001). These

336 effects were superseded by a significant group x time interaction (p<0.001) (Figure **3**C). Post

337 hoc analysis revealed that the 12g and 18g groups significantly outperformed the Placebo group

338 in weeks 2 (p<0.001; p=0.007), 3 (ps<0.001) and 4 (ps<0.001), respectively. There was no

339 significant difference between the 12g and 18g groups in any of the weeks (ps > .05).

340 For DS Backwards, there were significant main effects of both group (p=0.001) and

341 time (p<0.001). These effects were superseded by a significant group x time interaction

342 (p<0.001) (Figure **3**D). Post hoc analysis revealed that the 12g and 18g groups significantly

343 outperformed the Placebo group in Weeks 2 (p=0.009; p<0.001), 3 (ps=0.002; p<0.001) and 4

344 (ps<0.001), respectively. There was no significant difference between the 12g and 18g groups

345 in any of the weeks (ps > .05).

346 In SS Forwards, there were no significant main effects of group (p=0.591) and time

347 (p=0.883), nor a significant group x time interaction (p=0.435) (Figure **3**E). In SS Backwards,

348 there was a significant main effect of group (p=0.002), which indicated that the Placebo group

349 was outperformed overall by the 12g (mean=1.3 ± .38; 95% CI=52 to 2.1) and 18g (mean=1.3

350 ± .38; 95% CI=.50 to 2.1) groups, although, there was no significant difference between the

351 12g and 18g groups. There was also a significant main effect of time (p=0.001), which indicated

352 that when compared to week 1, performance was significantly better in weeks 2 (mean=0.77 ±

353 .19; 95% CI=.40 to 1.1), 3 (mean=0.77 ± .23; 95% CI=.31 to 1.2), and 4 (mean=0.77 ± .25;

354 95% CI=.25 to 1.3) (Figure **3**F). However, there was no significant group x time interaction

355 (p=0.801).

356 **[Insert Figure 3 Around Here]**

357 *Covert Shift of Attention (CSoA)*

358 For the exogenous test, there were 1122 out of 14400 trials (7.79%) that were in error, and thus
359 removed prior to analysis. In the endogenous test, 469 out of 7200 trials (6.51%) were removed
360 prior to analysis due to being in error.

361   In the exogenous test, there appeared to be general cue facilitation and inhibition effects
362 courtesy of the negative (cued < uncued) and positive (cued > uncued) scores for the 100ms
363 and 800ms asynchronies, respectively (Table 2). For the 100ms asynchrony, there were no
364 significant main effects of group (p=0.672) and time (p=0.461), nor a significant group x time
365 interaction (p=0.665). Likewise, for the 800-ms asynchrony, there were no significant main
366 effects of group (p=0.201) and time (p=0.111), nor a significant group x time interaction
367 (p=0.873).

368   For the endogenous test, there appeared a general cuing effect courtesy of the negative
369 scores (valid < invalid) (Table 2). However, there were no significant main effects of group
370 (p=0.91) and time (p=0.619), nor a significant group x time interaction (p=0.222).

371 **[Insert Table 2 Around Here]**

372 *Rapid Visual Information Processing (RVIP)*

373 For RT, there were no significant main effects of group (p=0.407) and time (p=0.858), nor a
374 significant group x time interaction (p=0.132) (Table 3). Likewise, for errors due to responding
375 to a non-target, there were no significant main effects of group (p=0.529) and time (p=0.251),
376 nor a significant group x time interaction (p=0.134).

377   For errors due to missing targets, there was no significant main effect of group
378 (p=0.753), although there was a significant main effect of time (p<0.001) (Table 3). Post hoc
379 analysis revealed that compared to week 1, there were less errors in weeks 3 (mean=-9.9 ± 2.1;
380 95% CI = -14.1 to -5.8) and 4 (mean=-9.1 ± 2.1; 95% CI = -13.4 to -4.8). Furthermore, when
381 compared to week 2, less errors in weeks 3 (mean=-6.6 ± 1.9; 95% CI = -10.4 to -2.9) and 4
382 (mean=-5.8 ± 2.1; 95% CI = -10.0 to -1.6). There was no significant difference between weeks
383 1 and 2 (p=0.073), nor between Weeks 3 and 4 (p=0.671). Meanwhile, there was no significant
384 group x time interaction (p=0.197).

385 **[Insert Table 3 Around Here]**

386 *Participant Feedback*

387 After week 4 of supplementation, the participants filled out a feedback form. The most pressing

388 issues were those of side effects. If introduced too quickly, MCTs are known to potentially

389 cause gastrointestinal issues [1,36] due to their relatively short carbon chain. In order to reduce

390 this risk, the MCTs dosages used were relatively low. Our study used a maximum total dose of

391 18g of MCT/day. This amount was also used by Xu *et al.* [28], and their participants

392 experienced little to no side effects. Furthermore, the dosage was gradually increased week by

393 week and the supplement contained a higher ratio of C_{10}, which causes fewer stomach issues

394 than C_8. Despite this, some minor side effects were experienced by 50% of the 18g group and

395 by 40% of the 12g group.

396 **Discussion**

397 The present study aimed to determine if chronic MCT ingestion improved performance in

398 cognitive tasks for healthy individuals, and if so, quantify the ideal dose and time frame to elicit

399 these improvements. Our data suggests that MCT supplementation improves cognitive

400 performance in healthy individuals after a minimum of 2-3 weeks, following ingestion of 12 -

401 18g of MCTs per day. This dose was similar to the 17.3g MCT/day used by Xu *et al*. [28], who

402 demonstrated improvements in cognition after 30 days of supplementation. As the participants

403 in the present study supplemented MCTs alongside their habitual diet, the findings suggest that

404 MCT ingestion improves cognition independent of overall macronutrient composition [19,51].

405 Hence, MCT supplementation can be incorporated much more easily into people's diets rather

406 than needing to have a fully ketogenic diet.

407　　　The increased cognitive performance by the 12g and 18g groups in both test phases of

408 TM compared to the placebo group provides a firm basis for accepting the hypothesis that

409 MCTs would increase cognitive performance in this regard; specifically processing speed,

410 sequencing and/or visual-motor skills. In the A test phase, the 18g group's performance

411 increased after three weeks whereas it took four weeks for the 12g group to outperform the

412 placebo group. However, the 18g group still outperformed the 12g group in week 4. In the B

413 test phase of the TM task, both the experimental groups performed significantly better than the

414 placebo group in weeks 2, 3 and 4. This suggests that the higher MCT dose accelerated and

415 increased the improvement in performance in A, whereas dosage did not matter in B. The fact

416   that the MCTs improved performance in this task follows on from Ota *et al.* [21], where they
417   saw a similar improvement in TM following their administration of MCT within healthy elderly
418   patients. However, the present study featured healthy, young participants with naturally
419   comparatively higher cognitive function at baseline, meaning these results are perhaps easier
420   to generalise to the wider population. It is of interest for future investigations to perhaps
421   decompose this influence of MCT on TM, including the separate contributions of cognitive and
422   visual-motor components.

423   There were positive findings regarding the working memory tests, supporting previous
424   findings that MCTs can improve performance in memory tests [21,25–28]. In weeks 2-4, the
425   experimental groups performed significantly better than the placebo group in digit working
426   memory tasks with no difference between the two groups. However, in the SS task, the
427   forwards test phase showed no significant difference between the groups at any time point,
428   whereas the 12g and 18g group outperformed the placebo group overall in the backwards test
429   phase. This is possibly because the backwards test phase is more demanding than the forwards
430   phase, meaning there is greater scope for improvement. These results support Ota *et al.* [21],
431   showing that the effects of the MCTs were more abundant in DS performance than for SS. The
432   present study therefore builds on previous data that MCTs can improve different aspects of
433   memory span, both in cognitively impaired and healthy populations.

434   The CSoA measure indicated that there were no differences between the MCT and
435   Placebo groups throughout the study weeks. Specifically, there was no change within the
436   exogenous cuing task, where responses are usually quicker at a short asynchrony (100ms)
437   (facilitation), but inversely slower at a long asynchrony (800ms) (inhibition), following the
438   presentation of cued compared uncued stimuli [44]. Likewise, there was no change within the
439   endogenous cuing task, where responses are usually biased toward the same side of space as a
440   disproportionately presented pre-cue. These cuing tasks have been known to be heavily
441   influenced by related factors such as vestibular inputs [52], testosterone levels [53], and age
442   [54]. Moreover, the visual selective attention processes that are associated with these cuing
443   tasks can be attributed to a broad neural network that comprises the parietal, frontal and
444   premotor cortices [55]. While it is premature at best to suggest that these neural regions remain
445   unaffected by MCTs-especially considering the previously stated influences on TM and
446   memory span both in the present study and in previous work [21,25–28]–it is possible that any

447 influence of MCTs within cognitive performance does not extend specifically to visual
448 selective attention.

449 In the RVIP task, MCTs did not influence RT and the amount of responses to non-
450 targets, in spite of previous evidence indicating that different types of fatty acids (e.g., Omega-
451 3 polyunsaturated [56]) can improve sustained attention. There was, however, an overall
452 continual decrease in the amount of errors from not responding to the targets that was
453 independent of any the groups. The fact that there was no difference between the groups in this
454 regard suggests that this improvement was due to a mere learning effect. It may be that the
455 RVIP task for sustained attention is not sensitive enough to detect small changes between trials
456 due to the relatively small doses of MCTs used in this study [49]. Future investigations should
457 adapt the task to overcome this. One suggestion is to increase the task time-[57] and/or increase
458 the number of stimuli in order to increase mental fatigue. However, from the evidence that is
459 currently available, it would suggest that the influence of MCTs on cognitive performance also
460 does not comprise of the ability to sustain attention.

461 MCTs have repeatedly been shown to benefit cognitive performance in diseased and
462 healthy populations [21,25–29]. The present study has shown this intervention to be similarly
463 beneficial in some regards in healthy, young individuals. The mechanisms underpinning this
464 effect is considered to be via an augmentation of energy supply to the brain in the form of βHB
465 and MCFA, both of which are rapidly available to the brain in excess following ingestion of
466 MCTs [21]. However, due to the relatively low doses of MCTs used in the present study, the
467 increases in cognitive performance are likely due to an increased rate of mitochondrial
468 biogenesis. This is possibly due to the increased activation of PPARγ, owing to the high
469 proportion of C_{10} ingested by the participants [37]. Nevertheless, the majority of studies,
470 including the present data, show that the benefits to cognitive function are only revealed after
471 either a number of weeks of daily supplementation, or a very high acute dose, the latter of
472 which increases the risk of side effects [21,25–29]. The former may be an artefact of improved
473 tolerance to MCT ingestion with time, resulting in improved absorption and thus entry into the
474 circulation. In the present study, MCT ingestion was increased on a weekly basis in each group
475 as a means to avoid acute intolerance of the supplementation regimen; hence the improvements
476 to cognitive function may be as a result of reaching some critical threshold of acute MCT
477 consumption.

478   An alternative mechanism whereby chronic MCT ingestion enhances cognitive
479 performance is via metabolic adaptations within the participant's brain cells; namely increasing
480 mitochondria number; improving mitochondrial function and reducing mitochondrial oxidative
481 damage [27,37]. C_{10} (which was favoured in the present study), but not C_8, has been shown to
482 result in increased citrate synthase and complex I activity in isolated neuronal cells [37], with
483 concomitant evidence of mitochondrial biogenesis. The fact it took several weeks for the effects
484 on cognitive performance to display, suggests that the positive results herein were due to one
485 or more of the chronic adaptations outlined above.

486   Irrespective of the specific mechanisms underpinning the augmentation of cognitive
487 performance, most previous studies have favoured C_8 in the supplementation regimen
488 [21,25,27] since this has been shown to be more ketogenic than C_{10} [18]. However,
489 gastrointestinal distress is more common and severe with C_8 as compared to C_{10} [36], thus
490 impacting on participant compliance. Therefore, we utilised a 30:70 ratio of C_8:C_{10} in the
491 present study to off-set these issues. Whilst the data of Vandenberghe *et al.* [18] suggest this
492 may have blunted the ketogenic response to each gel, their data also demonstrates that only a
493 modest amount of C_8 is required (within a C_8-C_{10} mixture) to retain a peak plasma ketone
494 response no different to that of C_8 alone. Moreover, the single-day design of [18] does not
495 replicate the chronic ingestion regimen adopted in the present study.

496   Whilst we were unable to undertake blood sampling to determine plasma ketone
497 concentrations in the present study, it seems possible that the chronic nature of the MCT
498 ingestion regimen and the mixture of C_8-C_{10} utilised resulted in augmentation of ketone and
499 MCFA supply for the purposes of brain metabolism. This, alongside the metabolic adaptations
500 C_{10} elicits, explains the positive effects seen in the cognitive task performances. Specifically,
501 there were improvements in Trail Making A and B, Digit Span forwards and backwards, and
502 Spatial Span backwards after 2-3 weeks of daily consumption of 12g or more of MCTs. These
503 findings expand upon previous evidence regarding the positive impact of MCT ingestion on
504 cognitive performance, specifically within young, healthy individuals. Despite this, the fact
505 that blood ketones were not measured is a limitation of the study. Furthermore, future research
506 should also adopt a double-blinded procedure, unlike the single-blinded design of the present
507 study.

508

Conclusion

In conclusion, the present study expanded on previous literature regarding the positive impact of MCTs on cognitive performance, specifically in young, healthy individuals. Our data suggests a minimum of 2-3 weeks of MCT gel supplementation is required for participants to display cognitive improvements, with use of a 30:70 ratio of C_8:C_{10} to eliminate possible participant withdrawal due to issues of gastrointestinal distress. There also appears to be minimal differences between 12g and 18g MCT/day for the majority of measures collected. Therefore, it would be recommended that two MCT gels (2 x 6g) per day are taken to augment cognitive improvements whilst limiting gastric distress. Future research should establish whether such improvements are also observed during cognitive demanding tasks, such as those commonly experienced within sport.

Author Declaration

Table Captions:

Table 1. The ICC's (%) of each random factor considering the dependent variables.

Table 2. Adjusted means ± SE values for each of the CSoA measures (negative scores indicate quicker responses to the cued/valid trials than the uncued/invalid).

Table 3. Adjusted mean difference from baseline ± SE values for each of the RVIP measures.

Figure Captions:

Figure 1. Schematic illustrating MCT metabolism in the body. Firstly, MCTs are hydrolysed in the stomach by pancreatic lipase into medium chain fatty acids (MCFA) which are absorbed directly into the portal vein [3]. The liver firstly converts MCFA into Acetyl-CoA via β-oxidation. This is then converted into Acetoacetyl-CoA, before becoming β-Hydroxy β-methylglutaryl-CoA (HMG-CoA). This is then metabolised into the ketone Acetoacetate. This can then further breakdown into βHB and Acetone [1,10]. Acetone is mainly excreted as a waste product through urine or CO_2, but can also enter gluconeogenesis to produce glucose [10]. Acetoacetate and βHB travel through the blood stream and enter the mitochondria of brain and muscle cells. Here, more Acetoacetate is generated from βHB via the enzyme 3-β-hydroxybutyrate dehydrogenase (BDH). This is then transformed into Acetoacetyl-CoA via succinyl-CoA-oxoacid CoA transferase (SCOT). Finally, beta-ketoscyl-CoA metabolises this into Acetyl-CoA which enters the Krebs Cycle, producing NADH and $FADH_2$ for the Electron Transport Chain (ETC) [19,20]. The ETC generates 23 molecules of ATP for each Acetoacetate molecule and 26 molecules of ATP per βHB [58].

Figure 2. Schematic view of participant flow.

Figure 3. Adjusted mean differences from baseline ± SE values for A) Trail Making A; B) Trail Making B; C) Digit Span Forwards; D) Digit Span Backwards; E) Spatial Span Forwards; F) Spatial Span Backwards. * denotes a significant difference between the 12g/18g group and the Placebo Group; # denotes a significant difference between the 18g group and both the 12g and Placebo Groups.

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Table 1. The ICC's (%) of each random factor considering the dependent variables.

Dependent Variable	ICC (%)
TM A (score)	46.78*
TM B (score)	56.45*
DS Forwards (score)	50.28*
DS Backwards (score)	49.29*
SS Forwards (score)	49.87*
SS Backwards (score)	54.27*
Exo 100ms mean difference	72.45*
Exo 800ms mean difference	40.71*
Endo mean difference	46.46*
RVIP RT (ms)	68.68*
RVIP Response to non-target (%)	66.30*
RVIP Missed Targets (%)	62.49*

* Represents significant determinant of variance within the linear mixed model ($P<0.05$).
ICC = Intraclass Correlation; TM = Trail Making; DS = Digit Span; SS = Spatial Span; Exo = Exogenous; Endo = Endogenous; RVIP = Rapid Visual Information Processing; RT = Reaction Time.

Table 2. Adjusted mean ± SE values for each of the CSoA measures (negative scores indicate quicker responses to the cued/valid trials than the uncued/invalid).

Week	Measure	Placebo				12g MCT/day				18g MCT/day			
		1	2	3	4	1	2	3	4	1	2	3	4
	Exo 100 RT Difference (ms)	-19.5 ± 19.9	-2.41 ± 40.1	-22.9 ± 33.4	-19.9 ± 52.3	-26.9 ± 22.9	-28.4 ± 44.2	-31.4 ± 62.2	-10.8 ± 15.0	-16.3 ± 15.0	-13.2 ± 30.9	-22.6 ± 24.5	-24.4 ± 27.5
	Exo 800 RT Difference (ms)	12.2 ± 7.43	22.1 ± 9.07	5.66 ± 12.0	-5.41 ± 16.3	8.88 ± 15.2	12.8 ± 14.0	8.76 ± 7.58	-9.73 ± 15.3	24.4 ± 26.5	22.7 ± 7.45	10.6 ± 12.9	16.2 ± 10.2
	Endo 800 RT Difference (ms)	-16.1 ± 9.53	23.2 ± 26.0	-6.86 ± 17.4	-15.9 ± 14.9	-38.2 ± 47.3	-72.2 ± 24.7	-34.2 ± 22.3	-51.4 ± 14.0	-27.1 ± 12.8	5.06 ± 30.2	-51.7 ± 17.8	-46.6 ± 18.3

CSoA = Covert Shift of Attention; Exo = Exogenous; Endo = Endogenous.

Table 3. Adjusted mean difference from baseline ± SE values for each of the RVIP measures.

Week	Measure	Placebo				12g MCT/day				18g MCT/day			
		1	2	3	4	1	2	3	4	1	2	3	4
	RT (ms)	-58.0 ± 23.0	-69.8 ± 23.2	-57.0 ± 23.8	-38.0 ± 26.1	-45.0 ± 23.0	-23.7 ± 23.2	-16.5 ± 22.9	-19.7 ± 26.1	-57.9 ± 23.0	-42.3 ± 23.7	-75.0 ± 22.9	-87.5 ± 25.5
	Errors (responded to non-target)	-3.0 ± 5.0	-0.8 ± 4.4	-1.5 ± 3.9	2.2 ± 4.3	6.5 ± 5.0	1.2 ± 4.4	-2.3 ± 3.8	-1.8 ± 4.3	-0.27 ± 5.0	-4.7 ± 4.5	-5.4 ± 3.8	-9.9 ± 4.2
	Errors (missed targets)	-16.7 ± 4.5	-17.0 ± 4.8	-21.3 ± 4.6*	-19.2 ± 4.4*	-13.5 ± 3.5	-21.0 ± 4.8	-24.6 ± 4.5*	-24.9 ± 4.4*	-9.3 ± 4.5	-11.4± 4.9	-23.3 ± 4.5*	-22.7 ± 4.3*

RVIP = Rapid Visual Information Processing; RT = Reaction Time. * denotes significant effect of time from weeks 1 & 2.