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Title: The effects of medium chain triglyceride (MCT) supplementation using a C_8:C_{10} ratio of 30:70 on cognitive performance in healthy young adults

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Abstract

Purpose: The brain can utilise medium chain triglycerides (MCTs) as an alternative fuel than glucose, and research has shown that MCT ingestion improves cognitive function in diseased and/or elderly individuals. The aim of this study is to determine if these improvements can also be observed in young, healthy adults. Furthermore, we aim to establish the ideal dosage and timeframe necessary for an effect.

Methods: Participants were divided equally into three groups of 10 (Placebo (0g), 12g and 18g MCT/day) and were supplemented for 4 weeks. The supplement had a C_8:C_{10} ratio of 30:70. Participants visited the laboratory once a week for 5 weeks (baseline, test weeks 1-4) to undergo a battery of cognitive tests; Trail Making, Digit Span, Spatial Span, Covert Shift of Attention, and Rapid Visual Information Processing.

Results: After 2-3 weeks of supplementation, MCT ingestion enhanced performance in cognitive tasks, including: Trail Making A/B and Digit Span Forwards/Backwards ($ps<0.001$) when compared to a placebo group taking a carbohydrate gel. In Spatial Span Backwards, there was a significant main effect of group ($p=0.002$). Where significance was seen, there were main effects of time after 2-3 weeks ($ps<0.05$). There was minimal difference between the two MCT intervention groups in most measures ($ps>0.05$). There were also null results in tasks measuring attention and reaction time ($ps>0.05$).

Conclusions: MCT ingestion improved cognitive performance after 2-3 weeks, with minimal difference between taking 12g and 18g MCT/day groups, suggesting a possible dose-response threshold at 12g MCT/day when supplementing over a short period.

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

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

βHB is exported from the liver into the blood and is converted in the mitochondria in muscle and brain cells into acetoacetate using the enzyme beta-hydroxybutyrate dehydrogenase. Acetoacetate is then converted to acetoacetyl-CoA via the enzyme succinyl-CoA-oxoacid CoA transferase before becoming acetyl-CoA via the enzyme beta-ketoacyl-CoA, which is then oxidised in the Krebs cycle with the subsequent NADH and $FADH_2$ production utilised by the mitochondrial electron transport chain to harbour energy [19,20], as illustrated in Figure 1. The brain can utilise βHB as an alternate energy source to glucose, which is otherwise the main fuel source [10,21]. Additionally, the MCFAs that bypass metabolism in the liver can directly cross the blood-brain-barrier due to their relatively shorter carbon chain length and are oxidised in astrocytes: LCFAs are unable to do so [22,23]. Therefore, MCTs provide both direct and indirect (via βHB) additional fuel sources for the brain [21].

[Insert Figure 1 Around Here]

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

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

interventions lead to βHB becoming a primary energy source for the brain, alleviating cognitive dysfunction [24–26]. However, even in young healthy individuals, the range of substrates available to the brain for energy metabolism remains restricted as compared to skeletal muscle, for example. Specifically, the brain relies on glucose, ketones and MCTs for energy, whilst being unable to utilise LCTs. Moreover, there are no significant differences in brain ketone metabolism between older adults, individuals with cognitive impairment/Alzheimer's Disease and healthy young adults [32–34]. Therefore, it remains plausible that the improvements in cognitive function following MCT supplementation demonstrated in diseased/elderly populations may also be seen in healthy subjects.

Typically, commercially available MCT products contain varying ratios of C_8 and C_{10} [2]. C_8 has been shown to be more ketogenic than C_{10} [7,18], and preferentially metabolised by neuronal cells, whereas C_{10} is metabolised at a slower rate, leading it to accumulate [35]. However, C_{10} is easier to digest than C_8 due to its longer carbon chain length, reducing the risk of gastronomical distress [1,36]. Hence, adherence to MCT supplementation may be impacted by the C_8-C_{10} ratio. Vandenberghe *et al*. [18] demonstrated that only a modest amount of C_8 is required (within a C_8-C_{10} mixture) to retain a peak plasma ketone response no different to that of C_8 alone. Moreover, C_{10}, rather than C_8, has the potential to increase the number of mitochondria over time in neuronal cells, although of a smaller size than untreated cells [37]. Hughes *et al.* [37] observed that C_{10}, but not C_8, increased citrate synthase activity after 6 days of MCT supplementation, indicative of enhanced mitochondrial biogenesis. This effect may be due, at least in part, to the peroxisome proliferator activator receptor γ (PPARγ), a promotor of mitochondrial biogenesis [38], which is activated by C_{10}, but not C_8. [39]. Hughes *et al.* found that in the presence of a PPARγ antagonist, the increase in citrate synthase activity due to C_{10} was prevented. Taken together, these data are supportive of the notion of mitochondrial biogenesis being induced in neuronal cells following C_{10} MCT supplementation.

The present study utilised a C_8-C_{10} ratio of 30:70 in the MCT supplement. This incorporates the benefits of both C_8 and C_{10}, while also limiting the risk of gastronomical distress previously seen when using a supplement with a higher ratio of C_8 [27,40]. The primary aim was of this study is to determine whether the improvements in cognitive function due to MCT ingestion seen in diseased/elderly individuals will also be demonstrated in a young and healthy population. We hypothesised that chronic MCT ingestion would improve some aspects of cognitive function, as measured by a standardised battery of laboratory-based cognitive tests

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

Methods

Participants

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

Experimental Procedure

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

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

with a 30:70 ratio of C_8:C_{10}. In order to offset possible unpleasant gastronomical issues that arise from taking MCTs [40], the number of MCT gels (6g) given to the 12g and 18g groups were increased incrementally over the course of the 4-week period (Figure 2). To match the number of overall gels taken by all participants, a carbohydrate gel (Energel+, Nutrition X, Gloucester, UK) was provided with similar calorific intake (94 kcal, difference 35 kcal vs. MCT gel) and flavouring to that of the MCT gel. All gels were wrapped in black tape to blind them from the participants. Participants were instructed to take their first, second and third gels 30 mins prior to breakfast, lunch and dinner, respectively. When visiting the lab, participants were instructed to take their gel immediately prior to entering the laboratory to and have breakfast as soon as possible after completion of the tests in order to abide by the instructed 30-minute interval between gels and meals as closely as possible.

[Insert Figure 2 Around Here]

Cognitive Assessments

Trail Making

Trail Making (TM) broadly assesses processing speed, sequencing and visual-motor skills [42]. There are two parts; A and B. In part A, participants are required to draw lines as quickly as possible between the numbers 1 and 25 in ascending order. In part B, participants are required to draw lines as quickly as possible between the ascending orders of both numbers (1-13) and letters (A-L). Due to the need to switch attention between letters and numbers in part B (1-A, 2-B, etc.), it is comparably much more difficult than part A. If any errors were made, it was immediately pointed out by the experimenter and the participant had to correct for it. Participants initially practiced for each part, which comprised of only 8 circles.

Memory Span

Two aspects of working memory were assessed: verbal and visuo-spatial. Verbal working memory was assessed using the digit span test (DS) and visuo-spatial working memory was assessed using the spatial span test (SS). The experimenter either read out a series of numbers (DS) or tapped blocks in a certain predetermined order (SS). The participants had to either repeat the numbers back (DS) or tap the blocks (SS) in the corresponding order (forwards test phase) or in reverse order (backwards test phase). The backwards test phase is comparably more difficult than the forwards test phase due to the requirement of the executive function to

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

Covert Shift of Attention (CSoA)

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

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

For endogenous cuing, the pre-cue initially involved a set of white arrowheads (<< / >>) appearing at screen-centre for 50ms. Following a further delay of 450ms, one of the two squares was filled in white for 1500ms or until the participants responded. In a similar vein to exogenous cuing, trials could be discriminated by the nature of the initial pre-cue and the location of the response cue. That is, a compatible relation between the direction of pre-cue and location of the response cue was regarded as a valid trial, while an incompatible relation was regarded as an invalid trial. Importantly, the frequency of valid trials was noticeably greater than invalid trials, which typically cues attention toward the same direction as the pre-cue. Consequently, the ability to inhibit and reorient attention can be found when reducing the extent of the typically quicker responses for valid compared invalid trials [45,46]. There were 32 valid, 8 invalid and 8 catch trials–comprising a total of 48 trials–for the experiment and 10 trials for initial practice.

Reaction times were recorded as the time difference between stimulus and response onset. Trials where there was a false (<100ms) or delayed (>1000ms) reaction, or responses were made to the incorrect side of space were removed from any subsequent calculations. The dependent measure involved the cuing effect, which was calculated as the mean participant reaction time to the cued/valid trials minus the uncued/invalid trials. Thus, a more negative score indicated a quicker response to the cued/valid trials than the uncued/invalid trials.

Rapid Visual Information Processing (RVIP)

RVIP assesses the ability to sustain attention to visual stimuli [47–49]. Stimuli featured single digits (1-10) being sequentially presented at the centre of an LCD monitor. Participants were instructed to press the spacebar key of a keyboard as soon as a digit was presented that completed a unique three-digit sequence: 2-4-6, 4-6-8, 3-5-7. Each digit was presented for 600ms with no inter-stimulus interval. However, the digits were alternatively presented for 1500ms whenever they completed a target sequence. There were 8 target sequences per min, and the test lasted continuously for 5mins (100 digits per min). Prior practice on the test was completed over 1min. The dependent measures involved reaction times to target sequences, proportion of false (<100ms) or delayed (>1000ms) reactions, and proportion of missed targets.

Statistical Analysis

The data were analysed through linear mixed modelling (LMM) using the statistical package IBM SPSS Statistics (Version 25, Chicago, IL, USA). An LMM was utilised due to its ability

to provide unbiased data in the presence of missing data (there was 57 missing data points from a total of 1800) [50]. Baseline measurements were entered as a covariate and the treatment effect from baseline (i.e. difference from baseline) were analysed in each measure. All models began as a null and were progressed to more complex parsimonious hierarchical models. The 4 time points (weeks 1, 2, 3 and 4) and the three experimental groups (Placebo, 12g and 18g) were treated as categorical fixed effects. Random effects were associated with the individual participants. Significant effects were decomposed using the Fisher LSD post hoc procedure.

A basic variance components model was executed to calculate the intraclass correlation (ICC) of the random factors for participant number to determine if any contributed significance variance to the dependent variable, as seen in Table 1. Model fit was assessed using Akaike's information criterion (AIC). For the dependent variable (treatment effect), AIC revealed the models that best fit the data utilised either the AR-1 or AR-1: Heterogenous repeated covariance structure for the repeated measures. Significance was set at $P<.05$. Where appropriate, post hoc analyses (LSD) and the inclusion of 95% confidence intervals (CI) of the differences is reported. All data is represented as mean difference from baseline ± standard error.

Results

Variance Calculations

Table 1 shows the ICC's (%) of the random factors accounted for in the linear model. The individuals contributed significant variance to the dependent variable in all measures. Hence, they were included in all of the larger hierarchical models.

[Insert Table 1 Around Here]

Trail Making

For TM A, there was no significant main effect of group ($p=0.149$), although there was a significant main effect of time ($p<0.001$). This effect was superseded by a significant group x time interaction ($p<0.001$) (Figure **3**A). Post hoc analysis revealed that the 12g group performed significantly better than the Placebo group in week 4 ($p=0.045$). The 18g group

performed significantly better than the Placebo group in weeks 3 (p=0.001) and 4 (p<0.001), and the 12g group in weeks 3 (p=0.014) and 4 (p=0.001). There were no further significant differences in any of the weeks (*ps* > .05).

For TM B, there was no significant main effect of group (p=0.065), although there was a significant main effect of time (p<0.001). This effect was superseded by a significant group x time interaction (p<0.001) (Figure **3**B). Post hoc analysis revealed that the 12g and 18g groups performed significantly better than the Placebo group in weeks 2 (p=0.018; p=0.023), 3 (p=0.018; p=0.001) and 4 (p=0.016; p=0.001), respectively. There was no significant difference between the 12g and 18g groups in any of the weeks (ps > .05).

Memory Span

For DS Forwards, there were significant main effects of both group and time (ps<0.001). These effects were superseded by a significant group x time interaction (p<0.001) (Figure **3**C). Post hoc analysis revealed that the 12g and 18g groups significantly outperformed the Placebo group in weeks 2 (p<0.001; p=0.007), 3 (ps<0.001) and 4 (ps<0.001), respectively. There was no significant difference between the 12g and 18g groups in any of the weeks (ps > .05).

For DS Backwards, there were significant main effects of both group (p=0.001) and time (p<0.001). These effects were superseded by a significant group x time interaction (p<0.001) (Figure **3**D). Post hoc analysis revealed that the 12g and 18g groups significantly outperformed the Placebo group in Weeks 2 (p=0.009; p<0.001), 3 (ps=0.002; p<0.001) and 4 (ps<0.001), respectively. There was no significant difference between the 12g and 18g groups in any of the weeks (ps > .05).

In SS Forwards, there were no significant main effects of group (p=0.591) and time (p=0.883), nor a significant group x time interaction (p=0.435) (Figure **3**E). In SS Backwards, there was a significant main effect of group (p=0.002), which indicated that the Placebo group was outperformed overall by the 12g (mean=1.3 ± .38; 95% CI=52 to 2.1) and 18g (mean=1.3 ± .38; 95% CI=.50 to 2.1) groups, although, there was no significant difference between the 12g and 18g groups. There was also a significant main effect of time (p=0.001), which indicated that when compared to week 1, performance was significantly better in weeks 2 (mean=0.77 ± .19; 95% CI=.40 to 1.1), 3 (mean=0.77 ± .23; 95% CI=.31 to 1.2), and 4 (mean=0.77 ± .25; 95% CI=.25 to 1.3) (Figure **3**F). However, there was no significant group x time interaction (p=0.801).

[Insert Figure 3 Around Here]

Covert Shift of Attention (CSoA)

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

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

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

[Insert Table 2 Around Here]

Rapid Visual Information Processing (RVIP)

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

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

[Insert Table 3 Around Here]

Participant Feedback

After week 4 of supplementation, the participants filled out a feedback form. The most pressing issues were those of side effects. If introduced too quickly, MCTs are known to potentially cause gastrointestinal issues [1,36] due to their relatively short carbon chain. In order to reduce this risk, the MCTs dosages used were relatively low. Our study used a maximum total dose of 18g of MCT/day. This amount was also used by Xu *et al.* [28], and their participants experienced little to no side effects. Furthermore, the dosage was gradually increased week by week and the supplement contained a higher ratio of C_{10}, which causes fewer stomach issues than C_8. Despite this, some minor side effects were experienced by 50% of the 18g group and by 40% of the 12g group.

Discussion

The present study aimed to determine if chronic MCT ingestion improved performance in cognitive tasks for healthy individuals, and if so, quantify the ideal dose and time frame to elicit these improvements. Our data suggests that MCT supplementation improves cognitive performance in healthy individuals after a minimum of 2-3 weeks, following ingestion of 12 - 18g of MCTs per day. This dose was similar to the 17.3g MCT/day used by Xu *et al*. [28], who demonstrated improvements in cognition after 30 days of supplementation. As the participants in the present study supplemented MCTs alongside their habitual diet, the findings suggest that MCT ingestion improves cognition independent of overall macronutrient composition [19,51]. Hence, MCT supplementation can be incorporated much more easily into people's diets rather than needing to have a fully ketogenic diet.

The increased cognitive performance by the 12g and 18g groups in both test phases of TM compared to the placebo group provides a firm basis for accepting the hypothesis that MCTs would increase cognitive performance in this regard; specifically processing speed, sequencing and/or visual-motor skills. In the A test phase, the 18g group's performance increased after three weeks whereas it took four weeks for the 12g group to outperform the placebo group. However, the 18g group still outperformed the 12g group in week 4. In the B test phase of the TM task, both the experimental groups performed significantly better than the placebo group in weeks 2, 3 and 4. This suggests that the higher MCT dose accelerated and increased the improvement in performance in A, whereas dosage did not matter in B. The fact

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

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

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

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

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

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

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

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

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

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

The authors declare funding for this project was provided from an external source (Nuroco, London, UK). However, the study was carried out independently at the university. The authors would also like to thank Nutrition X for the provision of the carbohydrate gels as part of the study.

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).

		Placebo				12g MCT/day				18g MCT/day			
Week		1	2	3	4	1	2	3	4	1	2	3	4
	Measure												
	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.

		Placebo				12g MCT/day				18g MCT/day			
Week		1	2	3	4	1	2	3	4	1	2	3	4
	Measure												
	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.