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ORIGINAL ARTICLE

Impact of medium-chain triglycerides on gait performance and brain metabolic network in healthy older adults: a double-blind, randomized controlled study

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Abstract Nutritional supplementation with medium-chain triglycerides (MCTs) has the potential to increase memory function in elderly patients with frailty and dementia. Our aim was to investigate the effects of MCT on cognitive and gait functions and their relationships with focal brain metabolism and functional connectivity even in healthy older adults. Participants were blindly randomized and allocated to two groups: 18 g/day of MCT oil and matching placebo formula (control) administered as a jelly stick (6 g/pack, ingested three times a day). Gait analysis during the 6-m walk test, cognition, brain focal glucose metabolism quantified by ^{18}F-fluorodeocyglucose positron emission tomography, and magnetic resonance imaging-based functional connectivity were assessed before and after a 3-month intervention. Sixty-three healthy, normal adults (females and males) were included. Compared with the control group, the MCT group showed better balance ability, as represented by the lower Lissajous index (23.1 ± 14.4 vs. 31.3 ± 18.9; $P < 0.01$), although no time × group interaction was observed in cognitive and other gait parameters. Moreover, MCT led to suppressed glucose metabolism in the right sensorimotor cortex compared with the control ($P < 0.001$), which was related to improved balance ($r = 0.37$; $P = 0.04$) along with increased functional connectivity from the ipsilateral cerebellar hemisphere. In conclusion, a 3-month MCT supplementation improves walking balance by suppressing glucose metabolism, which suggests the involvement of the

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cerebro-cerebellar network. This may reflect, at least in part, the inverse reaction of the ketogenic switch as a beneficial effect of long-term MCT dietary treatment.

Keywords Brain glucose metabolism · Cognition · Gait · Ketone · Medium-chain triglyceride · Elderly

Abbreviations

AAL	Automated Anatomical Labeling
AD	Alzheimer's disease
CDR	Clinical dementia rating
CT	Computed tomography
DARTEL	Diffeomorphic anatomical registration through exponentiated lie algebra
DSST	Digit Symbol Substitution Tests
EPI	Echo-planar imaging
FC	Functional connectivity
FOV	Field-of-view
FDR	False-discovery rate
GDS	Geriatric depression scale
LCT	Long-chain triglycerides
LF	Lissajous figure
LI	Lissajous index
LM	Logical memory
MCI	Mild cognitive impairment
MCT	Medium-chain triglycerides
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
PET	Positron emission tomography
rs-fMRI	Resting-state fMRI
SPECT	Single-photon emission computed tomography
SPM	Statistical Parametric Mapping
SUVR	Standardized uptake value ratio
TE	Echo time
TMT	Trail-Making Test
TR	Repetition time
UMIN-CTR	University Hospital Medical Information Network Clinical Trials Registry
WMS-R	Wechsler Memory Scale-Revised

Introduction

Establishing life expectancy along with good physical and cognitive status is an important global issue, especially in countries with a rapidly aging population like Japan [1]. Increasing evidence suggests that age-related declines in cognition and gait function are serious societal burden among healthy older adults [2]. The incidence of chronic disease or disabilities that shorten life expectancy increases proportionally with age. In the elderly population, Alzheimer's disease (AD) and osteoporosis are both common degenerative diseases [3]. We recently demonstrated that in elderly females with both osteopenia and AD, there is a relationship between hypoperfusion in the posterior cingulate cortex and reduced gray matter volume in the left precuneus with loss of bone mineral density, using brain single-photon emission computed tomography (SPECT) perfusion and voxel-based morphometry MRI [4, 5]. Because these physiologic or pathologic changes accumulate with age and curative medical treatments have not yet been established, efforts at primary prevention by maintaining normal cognitive/physical functioning are particularly important for healthy elderly adults.

It has been proposed that cognitive and walking capacities can be influenced by diet. Among various dietary sources, ketone bodies are an alternative energy substrate to glucose and may be neuroprotective, especially in the elderly brain where glucose utilization deteriorates [6]. Medium-chain triglycerides (MCTs) are mixed fatty acids extracted from natural products like coconut oil and palm kernel oil. They predominantly contain free caprylic (C8) and capric acids (C10), which are ketogenic and can spare brain glucose utilization directly proportional to their blood concentrations [7]. In addition, MCTs appear to have beneficial effects on muscle mass and cognitive behavior: they activate the gastric peptide ghrelin by stimulating hypothalamic hormones (e.g., growth hormone) and/or by modulating neurobiological circuits for synaptic plasticity in the hypothalamic, mesolimbic, and hippocampal pathways [8].

Taken together, dietary supplementation with MCT is thought to be a potential nutritional strategy to improve memory and muscle function in elderly patients. However, most of the studies in this regard are limited to patients with AD and cognitive/physical frailty [9, 10]. Previous randomized controlled trials have shown that 3 months of ingesting MCT jelly (6 g/day) at dinner increases the muscle strength and cognition of frail elderly individuals requiring supportive care [11, 12], and taking a ketogenic MCT drink (125 mL; 15 g MCTs) twice daily for 6 months improves some cognitive outcomes by increasing whole brain energy metabolism in patients with MCI [13, 14].

It is known that the range of substrates available to the brain for energy metabolism becomes restricted with aging, no functional differences can be seen in brain ketone metabolism among older adults, regardless of whether they have neurodegenerative diseases [7, 15]. Therefore, it is plausible that the beneficial ketogenic effects of MCT on improving cognitive and physical functions may also be expected in older adults with healthy aging.

This study was established to determine whether MCT nutritional supplements would improve some functional aspects of cognition (measured by standardized cognitive tests) [16] and gait and balance (measured by a tri-axial trunk accelerometer) [17], and their associations with brain metabolic and neural functions in the healthy elderly.

Methods

Trial design and participants

Between October 2018 and December 2019, we conducted a double-blind, placebo-controlled, parallel-group, 1:1, two-arm, investigator-initiated randomized trial at our institute. It was known as the MCT SMILE project is a double-blind, randomized controlled trial under the MCT SMILE (SuppleMentary for Life in the Elderly) project study. Participants were recruited from advertisements placed on noticeboards at the local health service, the neighborhood clinic, and our research and outpatient departments. Inclusion criteria were as follows: age 65 to 80 years; right-handed; male or female; a global clinical dementia rating (CDR) of 0; a Mini-Mental State Examination (MMSE) score of ≥ 24; and full autonomy for activities of daily living based on full scores in the Barthel index and the Lawton and Brody index [18]. Exclusion criteria were as follows: a diagnosis of a mental disorder according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders; the presence of any acute or chronic disease, including diabetes (fasting plasma glucose > 6 mmol/L or glycated hemoglobin $> 6.0\%$) and hypertension ($> 140/90$ mm Hg); the use of medications and/or nutritional supplements that affect energy metabolism or body composition (e.g., antidepressants, corticosteroids, thyroid disorder medications, creatine and protein supplements); dietary restrictions (e.g., food allergies); and the presence of implanted metal objects or devices contraindicated for MRI. Collaborating physician reviewed the screening tests for all participants before enrolment.

This study adhered to the tenets of the Declaration of Helsinki, and the protocols were approved by the Clinical Research Ethics Committee of the Tohoku University Graduate School of Medicine (approval number: 2018–2-67). The study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) on July 23, 2018 (UMIN000033447).

Intervention

Eligible participants were randomly assigned into two groups: MCT only (MCT group) or matching placebo formula made with canola oil (long-chain triglycerides [LCTs]) as a caloric equivalent non-MCT vegetable oil (control group). Each participant was scheduled for imaging studies, neurocognitive and physical function tests, and blood examination before intervention (for baseline assessment) and at 3 months after intervention (for post-intervention assessment). A yogurt-flavored jelly stick (total weight, 15 g) containing 6 g MCTs (75% C8:0 and 25% C10:0 from total fatty acids) or 6 g LCTs (64% C18:1, 19% C18:2, and 9% C18:3 from total fatty acids) was provided by Nisshin OilliO Group, Ltd. (Kanagawa, Japan). The MCT gel is the same as the commercially available product (Memorion®; https://www.nisshin-oillio.com/wellness/medical/product/memorion/feature.html). Participants were instructed to take either supplement before meals for a total of 3 consecutive months, beginning at one pack per day (6 g/day) and increasing by one pack per week to the final dose of 18 g (3 packs)/day within 3 weeks. Lifestyle, eating habits, and medications were not changed throughout the study period. Each participant maintained a daily logbook to ensure compliance, which was also checked by weekly telephone contact.

Positron emission tomography (PET) image acquisition and preprocessing

Sixty minutes after intravenous injection of 3.7 MBq/mL/kg of ^{18}F-fluorodeoxyglucose (^{18}F-FDG), brain PET/CT images were acquired for 3 min in three-dimensional (3D) mode using a single-bed position.

Each individual's PET image was co-registered to the individual's 3D T1-weighted structural images, and then spatially normalized the T1-weighted structural images to the Montreal Neurological Institute (MNI) space [19, 20] using a new normalization algorithm implemented in Statistical Parametric Mapping (SPM) 12. Partial volume effect correction with the voxel-wise anatomical-region-based non-uniform correction method was described by Arai et al. [21]. We used the mean activity values in the cerebellar cortex of each participant as a reference region (standard uptake value ratio [SUVR]) in the quantitative analysis. Detailed information for the imaging protocol and image processing is provided in the Supplementary material.

Resting-state fMRI (rs-fMRI) and seed-based approach

For resting-state fMRI, echo-planar imaging (EPI) images were obtained while instructing subjects to rest with open eyes in a dark room. The parameters were as follows: 64 × 64 matrix, TR = 3000 ms, TE = 30 ms, 90° flip angle, FOV = 220 × 220 × 218 mm, 34 slices, voxel size = 3.44 × 3.44 × 3.40 mm, and 197 volumes. The rs-fMRI data were preprocessed using the SPM 12. Image preprocessing included study-specific Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) template creation, warping of all realigned and slice-timing-corrected EPI images to the DARTEL template and 8-mm Gaussian kernel smoothing. The CONN functional connectivity (FC) toolbox (www.conn-toolbox.org) was used to extract the BOLD time series from the seed regions and to correlate them with the time series for all other brain voxels (seed-to-voxel analysis). We used the seed-based approach to compute the FC of the subregions where the FC could be altered by MCT intervention based on behavioral data.

Cognitive and psychological assessment

The MMSE and geriatric depression scale (GDS) were used to assess general cognitive function and depression, respectively. Modified versions of the logical memory (LM) subtest of the Wechsler Memory Scale-Revised (WMS-R) [22] were used to assess memory function. In the WMS-R, two short stories (stories A and B) were read aloud to the subjects, who were then instructed to recall details of the stories immediately (LM I, immediate recall) and after 30 min (LM II, delayed recall) [23]. Part B of the Trail-Making Test (TMT-B), the Digit Symbol Substitution Tests (DSST) (coding, copy, and incidental learning [paired associates and free recall]), and the backward digit span from the Wechsler Adult Intelligence Scale provided information on executive functions [24]. TMT-A and forward digit span provided information on attention and processing speed [25].

Physical function assessment

Anthropometric measurements were recorded, including weight, height, BMI, handgrip strength of the dominant hand, and left calf circumference of the smaller side. Gait and balance functions were assessed by two walking trials at a comfortable, self-selected speed along a 6-m level walkway. A tri-axial accelerometer (MG-M1110, LSI Medience, Japan) [17, 26–29] was fixed around the hip, and the resulting motion signals were then recorded at a sampling rate of 100 Hz and used to quantify walking speed (m/min), cadence (step/min), step length (cm), ratio of horizontal (cm) and vertical (cm) displacements, and average acceleration [m/s^2 (G)]. The Lissajous index (LI), as an indicator of the trunk symmetry, was calculated as the product of the maximum value of the X-axis (G) and the maximum value of the Y-axis – 0.98 (downward force) (G) of the frontal plane, as described previously [17].

Blood chemistry and metabolic assessment

Plasma metabolites, including glucose, creatinine, triglycerides, total cholesterol, HDL and LDL cholesterol, acetoacetate, and β-hydroxybutyrate, were analyzed by a commercial clinical laboratory (SRL Inc., Tokyo, Japan) before and after the 3-month intervention. Venous blood samples were taken after a 12-h overnight fast through the intravenous catheter secured for the PET study.

Randomization and blinding

Treatment allocation was conducted using a random number generator by an independent data scientist

who was not a member of this study. Randomization numbers were stored in sequentially numbered, sealed opaque envelopes. Study products were prepared by an unblinded researcher who had no involvement with this project. Participants and researchers could not distinguish between the two supplements based on appearance (created by unlabeled silver sticks), flavor, and texture. All investigators, treating clinicians, and participants were blinded to the treatment allocation. Data analysis was carried out without the knowledge of treatment allocation.

Statistical analysis

Data are presented as the mean ± SD for continuous variables and frequency and proportions for categorical variables. Significance was set at $P < 0.05$. All analyses were performed using IBM SPSS Statistics version 27 (IBM, Armonk, NY, USA). A sample size of 28 participants per group was established, based on a previous work that investigated MCT ingestion for improving the cognitive score of delayed word recall task in elderly patients with mild to moderate AD (a mean treatment difference of 0.6 ± 1.1; equivalent to an effect size of 0.55) [30] and was calculated to detect a clinically relevant effect with a 2-sided α of 0.05 and 90% power. Anticipating a 10% dropout rate during the 3-month intervention, the total sample size for the study was 31 participants per group.

Independent *t*-test was used to compare the mean differences of continuous variables between the 2 groups at baseline. If the continuous variables were nonnormally distributed, Mann–Whitney *U*-test was used. Chi-square test was run to correlate 2 categorical variables and Fisher's exact test was used if the number of each variable was < 5. Possible differences between the groups were explored using a mixed-design ANOVA with within-subject factors (pre versus post) and between-subject factors (MCT versus control). Post hoc analyses were applied to all ANOVA results followed by a Bonferroni correction (α level of 0.025) (equal variances assumed) or Games–Howell (equal variances not assumed), where appropriate. Partial correlation analysis (including age and sex as covariates) was performed to determine the relationships of 3-month changes among statistically significant parameters only in the MCT group (including the main effect of time, treatment, or both). We further conducted a simple linear regression analysis to visualize the differences in the relationships among these parameters in subjects supplemented with MCT or placebo.

For voxel-wise analysis by brain PET, we explored which brain areas showed changes in glucose metabolism specific to the MCT group compared with the control group. We used the mixed ANOVA using the SPM Flexible Factorial module. Results were considered significant at peak-level false-discovery rate (FDR)–corrected $P < 0.05$, with correction for multiple comparisons across the whole brain using random field theory. For analysis of FC using rs-fMRI, regions of interest were identified as seeds for seed-to-voxel analysis based on the brain regions predicted from behavior data before and after intervention by MCT. We extracted the mean time courses of the BOLD signals of each subregion and computed their correlations with the rest of the whole brain voxels. Six motion correction parameters were included as regression variables in the first-level analysis, and age and sex were included in the second-level analysis, using the mixed ANOVA model. The result was thresholded at a primary threshold of voxel-wise $P < 0.001$, and then corrected for FDR at $P < 0.05$, based on cluster extent and Gaussian random field theory.

Results

Baseline and clinical characteristics

Of the 68 potential participants who were screened, 3 (4%) did not meet the eligibility criteria. Sixty-five participants were thus enrolled in the study, among which 2 (3%) dropped out at baseline measurements before starting the intervention (one refused to take supplements due to health claims and the other had a medical illness detected on initial PET/CT scan). Sixty-three participants completed the study (MCT group, $n = 32$; control group, $n = 31$) (Fig. 1). Baseline demographic data of the 63 participants (females/males: MCT, 22/10; control, 21/10) were not different between the two groups (Table 1). Although the plasma acetoacetate and β-hydroxybutyrate levels in the control group were lower at post-intervention

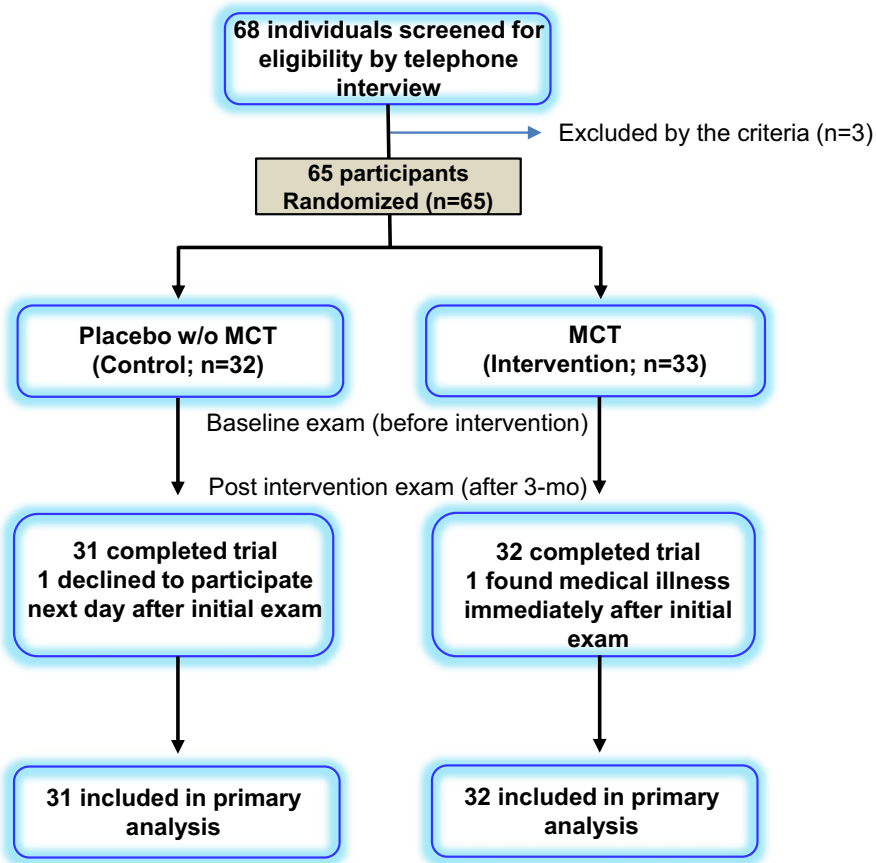

Fig. 1 Subject flow diagram from initial contact until study completion. LCT, 18 g/day of long-chain triglycerides; MCT, 18 g/day of medium-chain triglycerides

Table 1 Participant baseline characteristics[1]

	Control group ($n=31$)	MCT group ($n=32$)
Age (years)	70.3 ± 4.1	69.8 ± 4.0
Education (years)	13.7 ± 2.5	13.4 ± 3.3
Height (cm)	158.6 ± 8.6	157.9 ± 9.0
Weight (kg)	58.2 ± 10.9	56.4 ± 9.0
BMI (kg/m^2)	23.0 ± 3.1	22.5 ± 2.1
Hand grip strength (kg)	28.2 ± 9.4	28.5 ± 8.3
Calf circumference (cm)	34.5 ± 3.7	34.5 ± 2.3
GDS (/15)	1.1 ± 1.1	0.9 ± 1.0
MMSE (/30)	29.4 ± 1.3	29.1 ± 1.3
CDR	0	0
Plasma metabolites		
Triglycerides (mmol/L)	1.0 ± 0.5	1.1 ± 0.6
Total cholesterol (mmol/L)	5.5 ± 1.0	5.5 ± 0.7
Creatinine (μmol/L)	59.9 ± 13.0	62.4 ± 11.5
Glucose (mmol/L)	5.3 ± 0.3	5.4 ± 0.5

[1]Data are expressed as mean ± SD. No statistically significant intergroup differences were detected in baseline variables

CDR Clinical Dementia Rating, *GDS* geriatric depression scale, *MCT* medium-chain triglycerides, *MMSE* Mini-Mental State Examination

than at baseline ($P < 0.05$), no statistically significant intergroup differences were observed for other blood chemistry and metabolic profiles (Table S1; values after a 12-h fast).

Effects of MCT on gait and cognitive functions

Gait and cognitive outcomes (Tables 2 and 3, respectively) are presented as raw scores. The two groups had

Table 2 Raw scores on gait and balance function tests before and after intervention[1]

	Control group			MCT group			Intergroup
	PRE	POST	P^2	PRE	POST	P^2	P^3
Walking speed (m/min)	77.7 ± 10.8	79.3 ± 12.5	0.397	77.6 ± 12.1	78.5 ± 9.6	0.628	0.695
Cadence (step/min)	123 ± 9	125 ± 9	0.359	122 ± 11	123 ± 9	0.367	0.444
Step length (cm)	62.9 ± 6.8	63.7 ± 8.7	0.527	64.0 ± 8.4	64.0 ± 7.5	0.941	0.785
Average acceleration (G)	0.33 ± 0.08	0.34 ± 0.09	0.653	0.33 ± 0.08	0.34 ± 0.08	0.417	0.586
Horizontal displacement (cm)	2.78 ± 0.94	2,79 ± 0.79	0.953	3.02 ± 1.05	2.79 ± 1.03	0.152	0.977
Vertical displacement (cm)	2.73 ± 0.68	2.88 ± 0.79	0.181	2.84 ± 0.92	2.97 ± 0.83	0.230	0.513
Horizontal/vertical displacement	1.06 ± 0.40	1.05 ± 0.46	0.866	1.13 ± 0.42	0.96 ± 0.32	**0.012**	0.207
Lissajous index	34.7 ± 15.6	31.3 ± 18.9	0.410	33.9 ± 19.9	23.1 ± 14.4	**0.011**	**0.009**

[1]Values are expressed as mean ± SD. *P* values (bold font indicates statistical significance) were detected with the use of a mixed ANOVA which refer to differences [2]within-subject factors (PRE and POST) and [3]between subject factors (MCT and control)

G m/s^2, *MCT* medium-chain triglycerides, *POST* after intervention, *PRE* before intervention

Table 3 Raw scores on the neuropsychological tests before and after intervention[1]

	Control group			MCT group			Intergroup
	PRE	POST	P^2	PRE	POST	P^2	P^3
Memory							
LM-IA	13.3 ± 3.5	14.9 ± 3.8	0.003	11.3 ± 4.1	14.1 ± 4.1	< 0.001	0.078
LM-IB	10.4 ± 3.5	12.1 ± 2.9	0.002	9.5 ± 3.1	10.8 ± 3.5	0.013	0.146
LM-IIA	10.0 ± 3.8	12.2 ± 4.1	< 0.001	8.7 ± 4.6	11.2 ± 5.1	< 0.001	0.285
LM-IIB	8.3 ± 3.7	10.2 ± 3.9	< 0.001	7.5 ± 3.4	9.9 ± 3.8	< 0.001	0.552
Executive							
TMT-B	96.3 ± 23.8	88.3 ± 24.2	0.074	96.3 ± 40.3	76.7 ± 27.0	< 0.001	0.073
Digit Span Backwards	5.9 ± 1.6	6.0 ± 1.7	0.690	5.7 ± 2.1	5.8 ± 2.1	0.769	0.631
Digit Symbol-Coding	71.0 ± 14.3	72.0 ± 13.8	0.368	73.3 ± 11.3	75.1 ± 10.7	0.105	0.381
Digit Symbol-Copy	70.8 ± 14.5	71.9 ± 13.8	0.341	72.7 ± 11.6	74.7 ± 10.7	0.080	0.458
Digit Symbol-Pairing	13.0 ± 3.6	13.3 ± 4.2	0.651	12.5 ± 4.3	14.0 ± 4.5	0.018	0.190
Digit Symbol-Free Recall	8.0 ± 1.0	8.1 ± 1.0	0.180	7.9 ± 0.9	8.1 ± 1.1	0.191	0.768
Attention and processing speed							
TMT-A	79.4 ± 19.7	70.9 ± 21.3	0.008	79.9 ± 16.1	75.2 ± 21.4	0.127	0.343
Digit Span Forward	9.0 ± 1.8	8.5 ± 1.6	0.103	9.3 ± 2.0	9.2 ± 2.6	0.746	0.348
Screening tests							
MMSE (/30)	29.4 ± 1.3	29.0 ± 1.2	0.152	29.0 ± 1.3	28.6 ± 1.7	0.073	0.282
GDS (/15)	1.1 ± 1.1	3.0 ± 2.2	0.340	0.9 ± 1.0	2.6 ± 2.1	0.710	0.403

[1]Values are expressed as mean ± SD. *P* values were detected with the use of a mixed ANOVA which refer to differences [2]within-subject factors (PRE and POST) and [3]between subject factors (MCT and control)

GDS geriatric depression scale, *LM* Wechsler Memory Scale-Revised logical memory, *MCT* medium-chain triglycerides, *MMSE* Mini-Mental State Examination, *POST* after intervention, *PRE* before intervention, *TMT* Trail-Making Test

equivalent baseline performance on these functional tests.

General walking parameters, including speed and acceleration, and scores for cognition and depression based on MMSE and GDS did not change after 3 months in either group. However, an improvement in balance was observed in the MCT group compared with the control group ($P<0.01$, time×treatment effects) (Table 2; Fig. 2a), as shown by the decrease in LI (a key indicator of gait symmetry) towards the reference level in older adults [17] (Figure S1).

In the tests for executive function, there were significant differences between the pre- and post-treatment scores of the MCT group for TMT-B ($P<0.001$) and pairing subtest in the DSST ($P<0.05$), but there were no differences for these scores between groups (Table 3; Fig. 2b, c). No significant group differences were detected for the other subdomains of DSST or other cognitive tests, including memory, attention, and processing speed (Table 3).

Effects of MCT on brain glucose metabolism and its relationship with gait balance

As for the whole brain glucose metabolism, there were no obvious differences between the two groups; however, a significantly lower regional brain glucose uptake was found in the right pericentral cortex (postcentral gyrus, 34.1%; right precentral gyrus, 27.3%; cerebral white matter, 5.6%; unknown, 33.0%) in the MCT group (MNI coordinates: $X=30$ mm, $Y=-26$ mm, $Z=70$ mm; peak

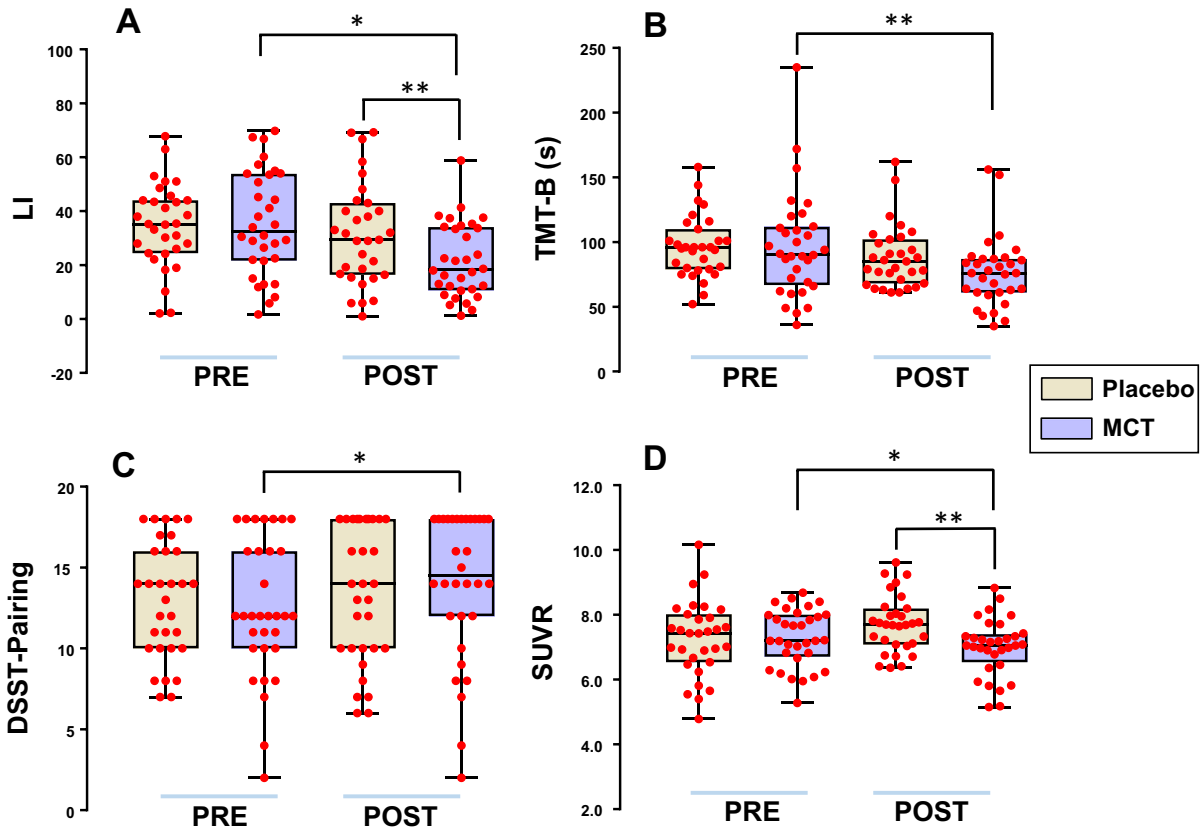

Fig. 2 Box-and-whisker plots of focal brain metabolism, balance, and cognitive parameters before and after 3-month intervention. Within-group differences were observed for LI (**a**), TMT-B scores (**b**), and pairing subtest in the DSST (**c**). Regional brain glucose metabolism in the right pericentral sulcus semi-quantified by SUVR (**d**) decreased by 90% after MCT treatment ($P<0.05$), with no change in the control group. Post-intervention treatment effects were detected for glucose metabolism and LI ($P<0.01$). DSST, Digit Symbol Substitution Test; LI, Lissajous index; MCT, medium-chain triglycerides; POST, after intervention; PRE, before intervention; SUVR, standardized uptake value ratio; TMT-B, Trail-Making Test B

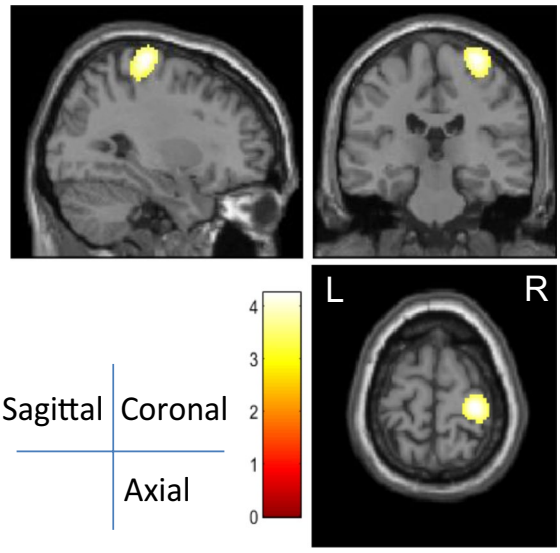

Fig. 3 Regions showing significant group (MCT versus control) differences in brain glucose metabolism measured by ^{18}F-FDG PET before and after 3-month intervention. Highlighted areas indicate regions (right pericentral sulcus; $X=30$ mm, $Y=$-26 mm, $Z=70$ mm; $P=0.047$) with significant decreases in relative glucose metabolism normalized to cerebellar metabolism (SUVR) at a threshold of $P<0.001$. Age and sex were included as covariates. The left side of the image corresponds to the left side of the brain. The color scale indicates *T*-scores. MCT, medium-chain triglycerides; PET, positron emission topography; SUVR, standardized uptake value ratio

level *T*-score = 4.25; cluster size = 649; FDR-corrected $P=0.046$) (Fig. 3). The regional SUVR values of the MCT-treated subjects decreased significantly from the baseline values, while those of the control group remained unchanged (Fig. 2d). No other brain regions showed statistically significant interaction effects between the groups before and after intervention.

Partial correlation analysis focused on statistically significant 3-month changes in the MCT group (including main effect of time, treatment, or both) showed that suppression of glucose uptake (△SUVR) in the right pericentral cortex significantly correlated with an improvement in walking balance (△LI) after adjusting for age and sex ($r=0.371$, $P=0.043$); other parameters had no correlations (TMT-B, $r=-0.084$; $P=0.660$; DSST-pairing, $r=-0.149$; $P=0.432$). In the MCT group, statistically significant relationships between SUVR and LI were also confirmed by scatter plots and simple regression models (Fig. 4).

Given the above results of behavioral data, we hypothesized that the FC associated with the cerebellum—the specific area that participates in balance control and voluntary limb coordination—could be changed after MCT intervention. Therefore, the cerebellar subregions were used as the seeds. The seeds were defined using the AAL

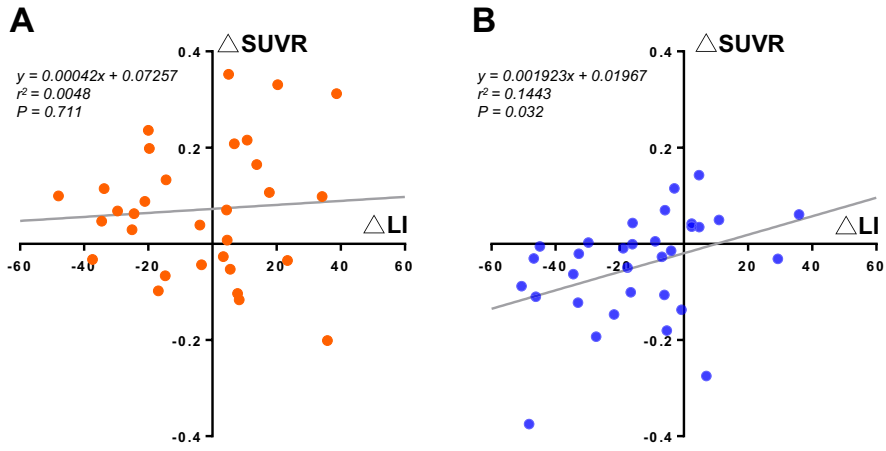

Fig. 4 Scatter plots of the changes in regional brain glucose metabolism in the right pericentral sulcus (△SUVR) and Lissajous index (△LI) in the control (**a**) and MCT (**b**) groups. The plots in the MCT group which survived correction for the multiple comparisons showed a linear trend ($P<0.05$), indicating an association between reduced focal glucose metabolism and walking balance stabilization. LI, Lissajous index; MCT, medium-chain triglycerides; SUVR, standardized uptake value ratio

cerebellar parcellation atlas, which contains 26 cerebellar regions as regions of interest [31]. MCT significantly increased FC from the right cerebellum (lobule X) to the right pericentral cortex (Fig. 5a) compared with the control treatment. In addition, MCT also revealed a significant increase in the connectivity from the left cerebellum (lobule VIII) to the bilateral amygdala and anterior hippocampus (Fig. 5b).

Adverse events

There were no serious or severe adverse events in either group. Six participants (5%) reported at least one symptom (nausea, 2; abdominal discomfort, 1; diarrhea, 1; loose stool, 2; and/or constipation, 1) within 1 week after the supplementation. There were no significant group differences, and most of the symptoms were transitory. There was no change in

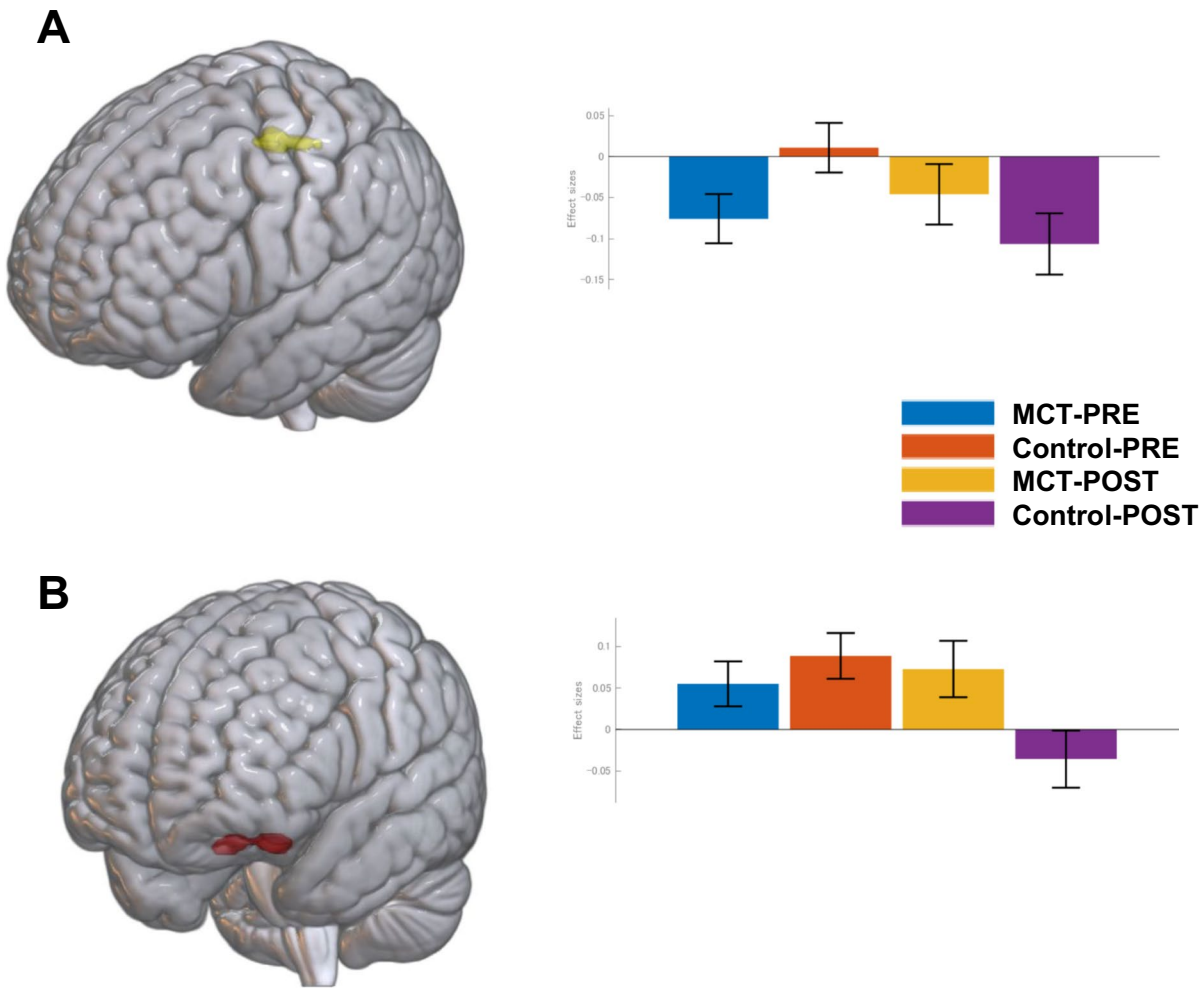

Fig. 5 Regions showing increased functional connectivity from the cerebellum on rs-fMRI after MCT intervention. The red color indicates increased connectivity from the right cerebellum (cerebellum 10 according to AAL atlas) to the right pericentral cortex (MNI coordinates: $X = 36$, $Y = -14$, $Z = 58$; cluster size: 158; FDR-corrected $P = 0.019$) in the MCT group compared with the control group (**a**). The yellow color indicates increased functional connectivity from the left cerebellum (cerebellum VIII according to AAL atlas) to the bilateral amygdala and anterior hippocampus MNI coordinates: $X = 10$, $Y = -4$, $Z = -18$; cluster size: 155; FDR-corrected $P = 0.022$) (**b**) in the MCT group compared with the control group. The box charts in the right column show the effect size in each group for each comparison. AAL, Automated Anatomical Labeling; FDR, false-discovery rate; MCT, medium-chain triglycerides; MNI, Montreal Neurological Institute; rs-fMRI, resting-state fMRI

body weight or any clinically significant changes in either group.

Discussion

Present study

This study involved healthy adults aged 65 to 80 years. The main finding was that a 3-month supplementation of MCT (18 g/day) was associated with an overt improvement in walking balance compared with the control treatment, and it altered the brain metabolism consistent with the connection between the cerebral cortex and the cerebellar hemisphere. To the best of our knowledge, this is the first double-blind, randomized controlled trial focusing on assessing neural and physical functions among healthy elderly individuals using brain imaging.

Efficacy of MCT on gait stability

Dietary MCT supplementation showed a significant improvement in gait balance, represented by LI, although neurobehavioral cognitive changes were expected to be difficult to detect in our healthy elderly participants. Cognitive aging and sarcopenia cause gait to be less automatic, and symmetric coordination requires additional effort to prevent falls among elderly individuals [32, 33]. It has been reported that better prediction of pre-frailty/frailty can be achieved when gait performance parameters are included [34]. In addition to conventional gait parameters, we objectively extracted gait asymmetry and irregularity as a metric that benefits from MCT in older individuals. This may be because balance control is essential for maintaining trunk stability prior to voluntary movement by compensating for destabilizing forces during the walking cycle [35].

MCT-mediated changes in brain glucose metabolism

PET image analysis showed glucose hypometabolism in the right pericentral cortex after a 3-month MCT intervention, indicating alterations in brain metabolic function. ^{18}F-FDG is irreversibly phosphorylated and trapped in cells by glucose transporters; thus, it is utilized in measuring glycolytic rates. In contrast, ketones, which are efficiently synthesized from MCT, increase plasma concentrations early after the ingestion (~90 min) [36], can pass the blood–brain barrier, and induce a so-called metabolic switch from glycolysis to the use of ketone bodies to produce acetyl-CoA for the TCA cycle in mitochondria [37]. Based on the results of a double-tracer PET study, a high-fat ketogenic diet in healthy adults increased the cerebral metabolic rate of ketone bodies (^{11}C-acetoacetate) and suppressed that of glucose (^{18}F-FDG) thus maintaining a net normal metabolic activity [38]. It is unclear whether repeated use of MCT can augment the acute ketogenic response [39]. In this study, however, a 3-month MCT ingestion appears to have a preferable ketogenic response that would rather preserve plasma acetoacetate and β-hydroxybutyrate, while a decline in both markers was observed for subjects receiving LCT as a control without MCT (Table S1). Taken together, our results confirm that our MCT protocol (18 g/day, ingested every meal in a jelly form) could, at least in part, sufficiently correct or bypass this regional brain glucose hypometabolism via ketogenic energetic compensation [7, 40].

Mechanism by which MCT modulates regional brain metabolism

There are some potential explanations for the MCT-induced right-sided focal hypoglycemic metabolism. Given that the primary sensorimotor cortex is related to balance parameters, as demonstrated by the results of partial correlations in the MCT group, it may be linked to dynamic gait stability accompanying voluntary movements, including balance and symmetry, possibly via sensory and cerebellar locomotor controls [41]. Previous studies have shown that impaired proprioception during aging affects gait balance control [42]. In this study, however, substantial variability in lateral displacement was detected after the MCT intervention. Therefore, another explanation may be that bilateral involvement is probable but was not unambiguously demonstrated here due to the small sample size. In the correlation analysis, the SUVR in the right prefrontal cortex was significantly associated with walking balance as represented by LI. This also supports the idea that the same region is responsible for improving physical ability.

Accumulating evidence suggests that there is a functional topography in the cerebellum that divides into several zones, depending on the connectivity with

sensorimotor and multimodal association cortices. This topography reflects the involvement of the cerebro-cerebellar network [43]. Previous fMRI studies have indicated that the connectivity between the cerebellum and precentral cortex works as a compensatory circuit to increase gait stability [9, 11, 44]. Liu et al. (12) also showed that physio-cognitive decline is associated with a disruption of the hippocampus-amygdala-cerebellum connections using diffusion-weighted tractography. Increased FC from the right flocculonodular lobe (lobule X, an area containing a substrate of the vestibular control and emotional processing) to the ipsilateral precentral cortex, and also from the left posterior cerebellum (lobule VIII; a proposed region organizing a sensorimotor-cognitive dichotomy) [43] to the bilateral amygdala, may implicate that some underlying mechanisms of cerebellar contribution to walking balance control can benefit from MCT supplementation.

Study limitations

Our study has several limitations. First, the study design might be underpowered to detect changes in biological functions. Although we calculated the study population according to previous knowledge, the number of participants was not sufficient to detect differences for a 3-month period. The outcome setting, testing walking function without any burdening, may not be the best way to assess change among healthy elderly individuals. Second, we could not target ketone body metabolism in the brain because of the limited availability of the PET tracer. However, combining the prior knowledge that ketone body intake will compensate for glucose demand in the brain and our additional correlation analysis between physiological and imaging outcomes, we believe that the observed difference in glucose metabolism can be a rationale for the favorable effects of MCT.

Conclusion

In conclusion, a 3-month MCT supplementation (18 g/day) in healthy older adults led to an improved walking balance compared with the control group. Possible mechanisms by which MCT contributes to gait stability in the elderly include an altered glucose metabolism in the right sensorimotor cortex, positively increased connectivity from the contralateral cerebellar lobule, and related activation of the bilateral amygdala and anterior hippocampus. While several previous studies have examined the rationale for the effects of MCTs based on biochemical data, our study attempted to add physiological considerations and tested the possibility of improving physical ability through brain function. Furthermore, our results support the novel biological effect of MCTs against senescence through the alteration of organ metabolism, thereby bridging the gap in prior knowledge between cognitive and physiological benefits.

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Author contribution TM and KK co-designed the study. KK, YTat, BT, and IM were responsible for scanning the subjects and supporting the image technology. TM and YTat analyzed the data. TM and KK wrote the first draft of the manuscript. SY was responsible for the characterization and sample collection of the subjects. RK and YTak supervised this study. All authors have contributed to and approved the final manuscript.

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Data availability Supplemental Table S1 and Supplemental Figure S1 are available from the "Supplementary data" link in the online posting of the article. Anonymized data of patients are available from the corresponding author on reasonable request.

Declarations

Ethics approval The study was in accordance with the Helsinki Declaration and national ethical standards. The institutional review board of our center approved the study protocol

(approval number: 2018–2-67). This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) on July 23, 2018 (UMIN000033447).

Consent to participate Written informed consent was obtained from each participant.

Conflict of interest The authors declare no competing interests. The *ICMJE* Form for Disclosure of Potential Conflicts of Interest was completed by the corresponding author on behalf of all co-authors.

References

1. Balachandran A, de Beer J, James KS, van Wissen L, Janssen F. Comparison of population aging in Europe and Asia using a time-consistent and comparative aging measure. J Aging Health. 2020;32(5–6):340–51. https://doi.org/10.1177/0898264318824180.
2. Mahlknecht P, Kiechl S, Bloem BR, Willeit J, Scherfler C, Gasperi A, Rungger G, Poewe W, Seppi K. Prevalence and burden of gait disorders in elderly men and women aged 60–97 years: a population-based study. PLoS ONE. 2013;8(7): e69627. https://doi.org/10.1371/journal.pone.0069627.
3. Woodman I. Osteoporosis: linking osteoporosis with Alzheimer disease. Nat Rev Rheumatol. 2013;9(11):638. https://doi.org/10.1038/nrrheum.2013.152.
4. Takano Y, Tatewaki Y, Mutoh T, Morota N, Matsudaira I, Thyreau B, Nagasaka T, Odagiri H, Yamamoto S, Arai H, et al. Voxel-based morphometry reveals a correlation between bone mineral density loss and reduced cortical gray matter volume in Alzheimer's disease. Front Aging Neurosci. 2020;12:178. https://doi.org/10.3389/fnagi.2020.00178.
5. Takano Y, Mutoh T, Tatewaki Y, Seki T, Yamamoto S, Odagiri H, Arai H, Taki Y. Hypoperfusion in the posterior cingulate cortex is associated with lower bone mass density in elderly women with osteopenia and Alzheimer's disease. Clin Exp Pharmacol Physiol. 2020;47(3):365–71. https://doi.org/10.1111/1440-1681.13217.
6. Kapogiannis D, Avgerinos KI. Brain glucose and ketone utilization in brain aging and neurodegenerative diseases. Int Rev Neurobiol. 2020;154:79–110. https://doi.org/10.1016/bs.irn.2020.03.015.
7. Vandenberghe C, St-Pierre V, Fortier M, Castellano CA, Cuenoud B, Cunnane SC. Medium chain triglycerides modulate the ketogenic effect of a metabolic switch. Front Nutr. 2020;7:3. https://doi.org/10.3389/fnut.2020.00003.
8. Serrenho D, Santos SD, Carvalho AL. The role of ghrelin in regulating synaptic function and plasticity of feeding-associated circuits. Front Cell Neurosci. 2019;13:205. https://doi.org/10.3389/fncel.2019.00205.
9. Abe S, Ezaki O, Suzuki M. Medium-chain triglycerides (8:0 and 10:0) are promising nutrients for sarcopenia: a randomized controlled trial. Am J Clin Nutr. 2019;110(3):652–65. https://doi.org/10.1093/ajcn/nqz138.
10. Takeishi J, Tatewaki Y, Nakase T, Takano Y, Tomita N, Yamamoto S, Mutoh T, Taki Y. Alzheimer's disease and type 2 diabetes mellitus: the use of MCT oil and ketogenic diet. Int J Mol Sci. 2021;22(22):12310. https://doi.org/10.3390/ijms222212310.
11. Abe S, Ezaki O, Suzuki M. Medium-chain triglycerides in combination with leucine and vitamin D benefit cognition in frail elderly adults: a randomized controlled trial. J Nutr Sci Vitaminol (Tokyo). 2017;63(2):133–40. https://doi.org/10.3177/jnsv.63.133.
12. Abe S, Ezaki O, Suzuki M. Medium-chain triglycerides (8:0 and 10:0) increase mini-mental state examination (MMSE) score in frail elderly adults in a randomized controlled trial. J Nutr. 2020;150(9):2383–90. https://doi.org/10.1093/jn/nxaa186.
13. Fortier M, Castellano CA, Croteau E, Langlois F, Bocti C, St-Pierre V, Vandenberghe C, Bernier M, Roy M, Descoteaux M, et al. A ketogenic drink improves brain energy and some measures of cognition in mild cognitive impairment. Alzheimers Dement. 2019;15(5):625–34. https://doi.org/10.1016/j.jalz.2018.12.017.
14. Fortier M, Castellano CA, St-Pierre V, Myette-Côté É, Langlois F, Roy M, Morin MC, Bocti C, Fulop T, Godin JP, et al. A ketogenic drink improves cognition in mild cognitive impairment: results of a 6-month RCT. Alzheimers Dement. 2020. https://doi.org/10.1002/alz.12206.
15. Bentourkia M, Trembblay S, Fortier M, Croteau E, Sarrhini O, Turcotte É, Cunnane S. Regional brain uptake of ketone bodies and glucose in elderly humans: a ^{11}C-acetoacetate and 18F-FDG PET study. IEEE Nuclear Science Symposium Conference Record. 2009;2009:3943–5.
16. Fink HA, Hemmy LS, MacDonald R, Carlyle MH, Olson CM, Dysken MW, McCarten JR, Kane RL, Rutks IR, Ouellette J, et al. AHRQ Technology Assessments. Edtion ed. Cognitive outcomes after cardiovascular procedures in older adults: a systematic review. Rockville (MD): Agency for Healthcare Research and Quality (US), 2014.
17 Takano Y, Mutoh T, Tatewaki Y, Yamamoto S, Shimomura H, Nakagawa M, Arai H, Taki Y. Assessment of gait symmetry in elderly women with low bone mineral density using a portable trunk accelerometer: a pilot study. Med Sci Monit. 2019;25:6669–74. https://doi.org/10.12659/msm.916763.
18. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc. 1983;31(12):721–7. https://doi.org/10.1111/j.1532-5415.1983.tb03391.x.
19. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging. New York: Thieme Medical Publishers Inc; 1988.
20. Ashburner J, Neelin P, Collins DL, Evans A, Friston K. Incorporating prior knowledge into image registration. Neuroimage. 1997;6(4):344–52. https://doi.org/10.1006/nimg.1997.0299.
21. Arai A, Kagaya Y, Takanami K, Takase K. A novel partial volume effect correction method which allows for heterogeneous distribution: the potential advantages in the white matter activity estimation on FDG-PET. J Nucl Med. 2016;57(supplement 2):1924-.

22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98. https://doi.org/10.1016/0022-3956(75)90026-6.
23. Wechsler D. Wechsler Memory Scale-Third Edition. San Antonio: The Psychological Corporation; 1997.
24. Joy S, Kaplan E, Fein D. Speed and memory in the WAIS-III Digit Symbol–coding subtest across the adult lifespan. Arch Clin Neuropsychol. 2004;19(6):759–67. https://doi.org/10.1016/j.acn.2003.09.009.
25. Lipowski M, Walczak-Kozłowska T, Lipowska M, Kortas J, Antosiewicz J, Falcioni G, Ziemann E. Improvement of attention, executive functions, and processing speed in elderly women as a result of involvement in the Nordic walking training program and vitamin D Supplementation. Nutrients. 2019;11(6). https://doi.org/10.3390/nu11061311.
26. Mutoh T, Mutoh T, Takada M, Doumura M, Ihara M, Taki Y, Tsubone H, Ihara M. Application of a tri-axial accelerometry-based portable motion recorder for the quantitative assessment of hippotherapy in children and adolescents with cerebral palsy. J Phys Ther Sci. 2016;28(10):2970–4. https://doi.org/10.1589/jpts.28.2970.
27. Mutoh T, Mutoh T, Tsubone H, Takada M, Doumura M, Ihara M, Shimomura H, Taki Y, Ihara M. Impact of serial gait analyses on long-term outcome of hippotherapy in children and adolescents with cerebral palsy. Complement Ther Clin Pract. 2018;30:19–23. https://doi.org/10.1016/j.ctcp.2017.11.003.
28. Mutoh T, Mutoh T, Tsubone H, Takada M, Doumura M, Ihara M, Shimomura H, Taki Y, Ihara M. Impact of long-term hippotherapy on the walking ability of children with cerebral palsy and quality of life of their caregivers. Front Neurol. 2019;10:834. https://doi.org/10.3389/fneur.2019.00834.
29. Mutoh T, Mutoh T, Tsubone H, Takada M, Doumura M, Ihara M, Shimomura H, Taki Y, Ihara M. Effect of hippotherapy on gait symmetry in children with cerebral palsy: a pilot study. Clin Exp Pharmacol Physiol. 2019;46(5):506–9. https://doi.org/10.1111/1440-1681.13076.
30. Kimoto A, Ohnuma T, Toda A, Takebayashi Y, Higashiyama R, Tagata Y, Ito M, Ota T, Shibata N, Arai H. Medium-chain triglycerides given in the early stage of mild-to-moderate Alzheimer's disease enhance memory function. Psychogeriatrics. 2017;17(6):520–1. https://doi.org/10.1111/psyg.12257.
31. Rolls ET, Huang CC, Lin CP, Feng J, Joliot M. Automated anatomical labelling atlas 3. Neuroimage. 2020;206:116189. https://doi.org/10.1016/j.neuroimage.2019.116189.
32. Yogev G, Plotnik M, Peretz C, Giladi N, Hausdorff JM. Gait asymmetry in patients with Parkinson's disease and elderly fallers: when does the bilateral coordination of gait require attention? Exp Brain Res. 2007;177(3):336–46. https://doi.org/10.1007/s00221-006-0676-3.
33. Maki BE, McIlroy WE. Postural control in the older adult. Clin Geriatr Med. 1996;12(4):635–58.
34. Pradeep Kumar D, Toosizadeh N, Mohler J, Ehsani H, Mannier C, Laksari K. Sensor-based characterization of daily walking: a new paradigm in pre-frailty/frailty assessment. BMC Geriatr. 2020;20(1):164. https://doi.org/10.1186/s12877-020-01572-1.
35. Handelzalts S, Melzer I, Soroker N. Analysis of brain lesion impact on balance and gait following stroke. Front Hum Neurosci. 2019;13:149. https://doi.org/10.3389/fnhum.2019.00149.
36. Yomogida Y, Matsuo J, Ishida I, Ota M, Nakamura K, Ashida K, Kunugi H. An fMRI investigation into the effects of ketogenic medium-chain triglycerides on cognitive function in elderly adults: a pilot study. Nutrients. 2021;13(7). https://doi.org/10.3390/nu13072134.
37. Cunnane SC, Courchesne-Loyer A, St-Pierre V, Vandenberghe C, Pierotti T, Fortier M, Croteau E, Castellano CA. Can ketones compensate for deteriorating brain glucose uptake during aging? Implications for the risk and treatment of Alzheimer's disease. Ann N Y Acad Sci. 2016;1367(1):12–20. https://doi.org/10.1111/nyas.12999.
38. Courchesne-Loyer A, Croteau E, Castellano CA, St-Pierre V, Hennebelle M, Cunnane SC. Inverse relationship between brain glucose and ketone metabolism in adults during short-term moderate dietary ketosis: a dual tracer quantitative positron emission tomography study. J Cereb Blood Flow Metab. 2017;37(7):2485–93. https://doi.org/10.1177/0271678x16669366.
39. Lin TY, Liu HW, Hung TM. The ketogenic effect of medium-chain triacylglycerides. Front Nutr. 2021;8:747284. https://doi.org/10.3389/fnut.2021.747284.
40. Jensen NJ, Wodschow HZ, Nilsson M, Rungby J. Effects of ketone bodies on brain metabolism and function in neurodegenerative diseases. Int J Mol Sci. 2020;21(22). https://doi.org/10.3390/ijms21228767.
41. MacKinnon CD. Sensorimotor anatomy of gait, balance, and falls. Handb Clin Neurol. 2018;159:3–26. https://doi.org/10.1016/b978-0-444-63916-5.00001-x.
42. Lin CH, Faisal AA. Decomposing sensorimotor variability changes in ageing and their connection to falls in older people. Sci Rep. 2018;8(1):14546. https://doi.org/10.1038/s41598-018-32648-z.
43. Stoodley CJ, Valera EM, Schmahmann JD. Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. Neuroimage. 2012;59(2):1560–70. https://doi.org/10.1016/j.neuroimage.2011.08.065.
44. Hyun GJ, Jung TW, Park JH, Kang KD, Kim SM, Son YD, Cheong JH, Kim BN, Han DH. Changes in gait balance and brain connectivity in response to equine-assisted activity and training in children with attention deficit hyperactivity disorder. J Altern Complement Med. 2016;22(4):286–93. https://doi.org/10.1089/acm.2015.0299.