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Reductions in body weight and insulin resistance are not associated with changes in grey matter volume or cortical thickness during the PREVIEW study

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ABSTRACT

Introduction: The effect of changes in body weight or insulin resistance on grey matter volume and cortical thickness change are unclear. The present observational study assessed effects of an 8-week weight loss period (≥8% of body weight), and a subsequent 22-month weight maintenance period on grey matter volume and cortical thickness.

Methods: A total of 24 participants (12f/12 m; age 52.8 ± 10.6 years) with overweight/obesity and pre-diabetes were recruited. T1-weighted magnetic resonance imaging was used to determine grey matter volume and cortical thickness at baseline, after the weight loss period and after a medium to high dietary protein weight maintenance period.

Results: At baseline, global grey matter volume was inversely associated with HOMA-IR, adjusted for sex and age ($r = -0.42$; $p = .049$). During the weight loss period participants decreased their BMI (32.1 ± 3.3 to 28.1 ± 2.8 kg/m^2, $p < .01$), body-fat (41.6 ± 6.4 to 35.0 ± 8.0%, $p < .01$) and insulin resistance (HOMA-IR: 4.0 ± 2.0 to 1.8 ± 0.9, $p < .01$). During the 22-month weight maintenance period, these parameters gradually increased again (BMI: 29.3 ± 3.8 kg/m^2; body-fat: 37.8 ± 9.3%; HOMA-IR: 2.9 ± 1.4, $p < .01$). Global grey matter volume and cortical thickness did not change significantly during the weight loss or weight maintenance period. Changes in body weight, body-fat percentage or insulin sensitivity were not associated with changes in global grey matter volume.

Conclusion: In conclusion, we confirmed that global grey brain matter volume was inversely associated with insulin resistance at baseline, yet an intervention yielding a decrease in insulin resistance did not lead to changes in global grey brain matter volume or cortical thickness.

Trial registration: The trial is registered with ClinicalTrials.gov, NCT01777893.

1. Introduction

Overweight and obesity and its related metabolic dysfunctions have been previously linked to altered grey matter volume and cortical thickness [1–5]. While grey matter volume is a function of cortical surface area and cortical thickness, the latter has been posed as a more relevant marker of brain functioning than grey matter volume [6]. Multiple studies have shown a relationship between grey matter volume and cortical thickness with body weight and insulin sensitivity, but findings have been inconsistent [2,4,7–16]. Grey matter volume was negatively associated with BMI and waist circumference [11,12], and was shown to be reduced in obese participants compared to overweight participants [13,14]. However, other results show both, negative and positive relations between BMI and regional grey matter volume in a large cohort with healthy individuals [7]. While there have been reports on an inverse association between cortical thickness and BMI [2,8], other studies found no differences in cortical thickness [10] or increased cortical thickness [9] in individuals with overweight/obesity

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compared to lean individuals. With regard to insulin resistance, cortical thickness was shown to be inversely associated with insulin resistance in different brain regions [4] and average cortical thickness and grey matter volume was reduced in people with T2D compared to participants without T2D [15,16].

This reduction may be induced by hyperglycemia [17] or brain insulin resistance [18] which have been associated with neuronal dysfunction and cell death.

The results suggest that cortical thickness and grey matter volume are dynamic variables affected by different physiological parameters. Studies have reported longitudinal changes in cortical thickness and grey matter volume related to aging [19,20], but it remains unclear if and how cortical thickness or grey matter volume change with changes in body weight or insulin resistance. Previously a higher BMI was shown to be a predictor of decline in temporal and occipital grey matter over the time period of 5 years [21] and other studies reported increases in cortical thickness after weight loss induced by bariatric surgery [22] and sleeve gastrectomy [23]. In the current observational study, we investigated the effects of the PREVIEW intervention on cortical thickness and grey matter volume over the time period of two years, while the participants followed a weight loss and weight maintenance intervention program. We hypothesized that these participants would have increased grey matter volume and cortical thickness along with decreased BMI and/or insulin resistance.

2. Design and methods

2.1. Participants

In total, twenty-four participants were assessed in this study. Participants were all part of the PREVIEW study (Prevention of Diabetes through lifestyle intervention and population studies in Europe and around the World, EU 7th Framework Programme, grant agreement no. 312057, ClinicalTrials.gov NCT01777893), which has been initiated to find the most effective lifestyle (diet and physical activity) for the prevention of type 2 diabetes in overweight and obese participants with increased risk for type 2 diabetes (www.previewstudy.com) [24]. Inclusion criteria were: age 25–70 years, BMI $\geq 25\ kg/m^2$, fasting plasma glucose of 5.6–6.9 mmol/l and/or plasma glucose concentration of 7.8–11.0 mmol/l at 2 h after an oral glucose tolerance test (OGTT), and willingness to undergo MRI procedures. Exclusion criteria included T2D, left-handedness, claustrophobia and history of neurological disorders in addition to the general PREVIEW exclusion criteria (ClinicalTrials.gov NCT01777893). Forty participants of the PREVIEW study were recruited at Maastricht University to investigate to effects of the PREVIEW study on brain responsiveness to food cues, as was described previously [25]. Of these participants, twenty-four participants completed magnetic resonance imaging (MRI) scans with sufficient quality of the anatomical images to be used in the current study. The study was approved by the Medical Research Ethics Committee of Maastricht University Medical Center and in accordance with guidelines of the Declaration of Helsinki. All participants provided written informed consent for participation.

2.2. Study design

All participants started with an 8-week weight loss period on a LED with the aim to lose at least 8% of their body weight. The LED provided 3.4 MJ (35–40 E% protein, 45–50 E% carbohydrate, 15–20 E% fat) per day with four sachets of the Cambridge Weight Plan®, 3 of which were dissolved in 250 mL low fat milk and one in 250 mL water. Additionally, energy-free drinks and < 400 g per day of non-starchy, low-CHO vegetables were allowed. The weight loss period was followed by a weight maintenance period with instructions to follow dietary guidelines with the instruction to maintain the achieved body weight. Additional weight loss was allowed. Dietary guidelines were provided in two groups, a moderate protein moderate glycaemic index group (MPMGI) and a high protein low glycaemic index (HPLGI) group. The MPMGI group received instructions to ingest 15/55/30 percentage of total energy intake from protein/carbohydrate/fat and focus on products/meals with a glycaemic index ≥56. The HPLGI group received instructions to ingest 25/45/30 percentage of total energy intake from protein/carbohydrate/fat and focus on products/meals with a glycaemic index ≤50. Participants were randomized at the start of the study and were notified of their group allocation after the LED period. More detailed information on the dietary guidelines and of the intervention groups has been reported before [24]. See supplementary Fig. 1 for an overview of the general PREVIEW study design. At baseline, after weight loss and after 2 years, measurements were performed after an overnight > 10 h fasting period. Measurements included MRI, air displacement plethysmography to determine body composition and blood sampling to determine fasting glucose and fasting insulin.

2.3. MRI acquisition

Scanning was performed on a 3 Tesla scanner (Magnetom, Siemens, Erlangen, Germany). High-resolution T1-weighted structural volume was acquired with a MPRAGE sequence using the following parameters: matrix 256 × 256 mm, voxel resolution 1.0 × 1.0 × 1.0 mm, 1 mm slice thickness, no gap, flip angle = 9, TE = 2.98 ms, TR = 2300 ms. All scans were conducted on the same scanner and operating system.

2.4. Image processing

Preprocessing and analysis of the MRI data was performed with a combination of the "volBrain" online analysis pipeline (http://volbrain.upv.es) [26] and BrainVoyager version 20.6 (Brain Innovation B·V, Maastricht, The Netherlands). First, the data was processed within the volBrain pipeline, which included the following procedures: inhomogeneity correction, brain normalizations to MNI152 space, a second fine inhomogeneity correction, intensity standardization, intracranial cavity segmentation, tissue classification, hemisphere segmentation, cerebellum and subcortical structures segmentation. More details can be found in Manjon and Coupé [26]. Using this pipeline, grey matter volume as percentage of intracranial cavity was obtained for the total brain and the left and right cerebrum. After running the volBrain pipeline, preprocessed and normalized anatomical images were imported into BrainVoyager for further data processing and analysis steps.

2.5. Preparation for cortical thickness measurement

First, an automatic brain peeling based on the voxel intensities within the data was applied. The peeled anatomy was converted from the original 1 mm data resolution into a 0.5 mm isovoxel representation. In a third step, the ventricles and subcortical regions were filled using a partially mask-based approach. Fourth, the cerebellum was removed automatically from the data. Following that, a tissue contrast enhancement procedure based on a sigma filter with a range of 5 was applied. The final preparation steps included an adaptive segmentation of the border between grey and white matter as well as a dilation to the CSF / pial surface. The resulting document included only two intensity levels for grey and white matter/subcortical regions. Cortical thickness was measured on the basis of this highly simplified representation of the data using LaPlace equations [27].

2.6. Surface-based analysis

In a second analysis path, the boundary between grey and white matter created for the calculation of cortical thickness values was used to create a highly detailed surface mesh representation for each hemisphere of each subject at each time point. The surface meshes were then

normalized and aligned using the cortex-based alignment approach described in Fischl et al. [28]. Intra and Inter-subject alignment was performed using the specific curvature information available for each cortical hemisphere.

2.7. Combination of volumetric thickness value and surface information

Volumetric cortical thickness data was sampled into the corresponding surface meshes to create a cortical thickness surface map for each subject, hemisphere and time point. All these cortical thickness surface maps were aligned on the surface using the output of the aforementioned cortex-based alignment results, which allows a direct and fair comparison of cortical thickness at specific macroanatomical landmarks. All results were depicted on an average surface mesh representation created with the usage of the cortex-based alignment information. More information on the variability of cortical landmarks and its improvement via cortex-based alignment can be found in Frost and Goebel [29].

2.8. Body weight and composition

Body weight was measured using a calibrated scale (Life Measurement Corporation, Inc., Concord, CA, USA) and body composition was determined using the BodPod System (Life Measurement Corporation, Inc., Concord, CA, USA) [30]. Height was measured using a wall-mounted stadiometer to the nearest 0.1 cm (Seca, model 222, Seca, Hamburg, Germany).

2.9. Blood samples and insulin resistance

Blood samples to determine glucose and insulin concentrations were taken in a fasted condition. Blood samples were analysed at the National Institution for Health and Welfare in Helsinki, Finland. The homeostatic model assessment for insulin resistance (HOMA-IR) was used to assess insulin resistance and was calculated as follows: fasting glucose x fasting insulin / 22.5 [31]. Plasma glucose was measured by enzymatic hexokinase method and insulin was measured using chemiluminescent microparticle immunoassay.

2.10. Statistical analysis

Data are expressed as mean ± SD SPSS 23 (IBM corp., Armonk NY, USA). Analyses were performed using BrainVoyager 20.6 (Brain Innovation B.V., Maastricht, The Netherlands) and the Statistical Package for the Social Sciences (SPSS, IBM Corp., IBM SPSS Statistics, V23, Armonk, NY, USA). Pearson's correlation analysis was used to determine the relation between average cortical thickness or grey matter volume and anthropometric parameters. Whole brain correlation analyses were used to determine the relation between regional cortical thickness and anthropometric variables. Repeated measures ANOVA and whole brain repeated measures ANOVA were used to assess differences in grey matter volume and average/regional cortical thickness during the intervention. Mixed model regression analysis was used to determine relationships of anthropometric variables and insulin resistance with GM or CT. For the whole brain analyses, Monte Carlo simulations were performed in BrainVoyager to identify cluster-extent thresholds with a cluster alpha of 0.05. Simulations were performed with 1000 iterations and an independent voxel threshold of $p < .001$. Anatomical labels were obtained for the centre-of-gravity coordinates in MNI space of significant clusters using the automated anatomical labeling atlas.

Since the participants were allocated to two different dietary intervention groups in the PREVIEW study, group effects were tested. There were no differences at baseline or different changes between the groups in any of the variables.

3. Results

3.1. Baseline relations with grey matter volume

We found a negative association between age and grey matter volume ($r = -0.55$; $p = .005$) with grey matter volume being lower in men compared to women (45.2 ± 2.2% vs 48.2 ± 2.0%; $p = .002$). The age was not different between genders. After adjusting for age and gender, grey matter volume was inversely associated with HOMA-IR ($r = -0.42$; $p = .049$). There were no significant associations between grey matter volume and BMI or body-fat percentage.

3.2. Baseline relations with cortical thickness

There were no associations between average cortical thickness and age, BMI or HOMA-IR. Cortical thickness was not different between men and women. A positive association between average cortical thickness and body-fat percentage was found ($r = 0.51$; $p = .01$), which changed into a trend after adjustment for age and gender ($r = 0.40$; $p = .065$). Average cortical thickness was positively associated with average grey matter volume ($r = 0.58$; $p = .003$). Regional cortical thickness, assessed with whole brain correlation analysis, was positively related to body-fat percentage in the right anterior cingulate ($r = 0.72$, $p < .05$ whole brain corrected) (Fig. 1).

3.3. Changes during the intervention

BMI, body-fat percentage and HOMA-IR were reduced after weight loss and 2 years compared to baseline and increased at 2 years compared to after weight loss (Table 1). There were no significant changes in grey matter volume or in average cortical thickness during the intervention. There were no different changes in grey matter volume or average cortical thickness between men and women. Regional cortical thickness assessed with whole brain repeated measures ANOVA,

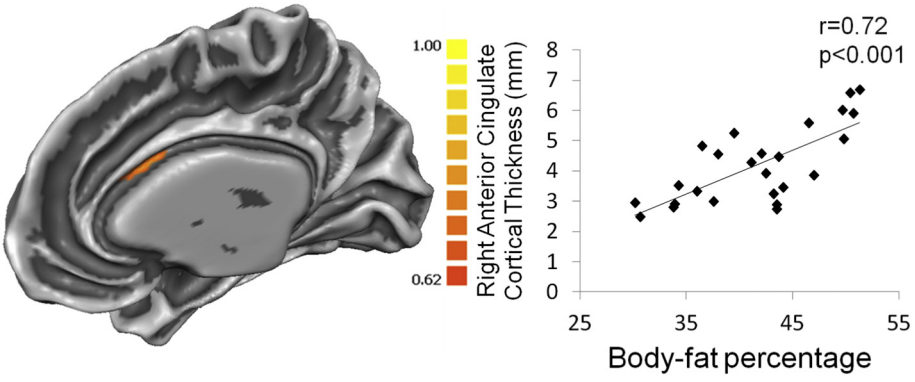

Fig. 1. Association between cortical thickness and body-fat percentage in the right anterior cingulate. Monte Carlo simulations were used to determine minimal cluster size using an independent voxel threshold of $p < .001$ and cluster alpha of $p < .05$. Scatter plot of extracted average cortical thickness and body-fat percentage is shown on the right.

Table 1
Participant characteristics at baseline, after weight loss and after 2 years.

N (f/m)	Baseline			After weight loss			2 years		
	24 (12/12)								
Age (year)	52.8	±	10.6						
Body-fat (%)	41.2	±	6.2	34.6	±	7.8*	37.3	±	9.1*#
BMI (m/kg^2)	32.0	±	3.3	28.1	±	2.8*	29.2	±	3.9*#
Fasting insulin (mU/l)	13.9	±	6.7	7.4	±	2.7*	10.6	±	4.5*#
Fasting glucose (mmol/l)	6.3	±	0.6	5.8	±	0.5*	5.9	±	0.5*
HOMA-IR	4.0	±	2.0	1.9	±	0.8*	2.8	±	1.5*#
GM (cm^3)	670.2	±	55.8	671.3	±	55.4	668.6	±	53.2
GM (% intracranial volume)	46.7	±	2.6	46.7	±	2.5	46.6	±	2.6
Cortical thickness (mm)	2.86	±	0.20	2.88	±	0.16	2.89	±	0.15

Data are presented as mean ± standard deviation. Changes over time were determined using repeated-measures ANOVA, * $P < .05$ significantly different from baseline, #P < .05, significantly different from after weight loss. BMI = body mass index; HOMA-IR = homeostatic model assessment for insulin resistance; GM = grey matter volume.

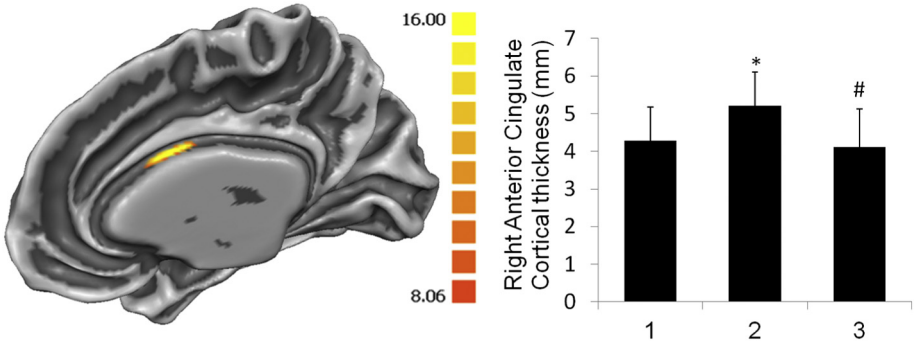

Fig. 2. Effects on cortical thickness in the right anterior cingulate gyrus during the intervention.
Effects were assessed with whole brain repeated measures ANOVA. Monte Carlo simulations were used to determine minimal cluster size using an independent voxel threshold of $p < .001$ and cluster alpha of $p < .05$. Bar graph of extracted average cortical thickness at baseline [1], after weight loss [2] and after 2 years [3] is shown on the right. Repeated measures ANOVA were used to assess differences between time points. * $P < .05$ significantly different from baseline #P < .05, significantly different from after weight loss.

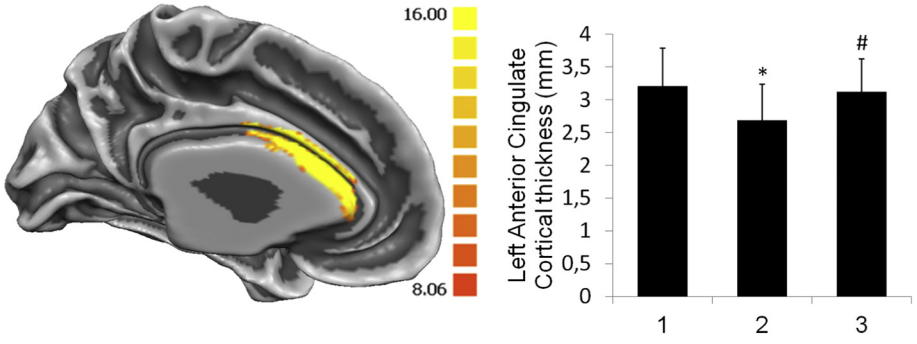

Fig. 3. Effects on cortical thickness in the left anterior cingulate gyrus during the intervention.
Effects were assessed with whole brain repeated measures ANOVA. Monte Carlo simulations were used to determine minimal cluster size using an independent voxel threshold of $p < .001$ and cluster alpha of p < .05. Bar graph of extracted average cortical thickness at baseline [1], after weight loss [2] and after 2 years [3] is shown on the right. Repeated measures ANOVA were used to assess differences between time points. * $P < .05$ significantly different from baseline #P < .05, significantly different from after weight loss.

showed an effect in the right and left anterior cingulate. Cortical thickness in the right anterior cingulate was increased after weight loss compared to baseline and 2 years (Fig. 2) ($p < .001$). Cortical thickness in the left anterior cingulate was reduced after weight loss compared to baseline and 2 years (Fig. 3) (p < .001). Changes in cortical thickness of the right and left anterior cingulate were not associated. Changes in cortical thickness in the anterior cingulate of the left or right hemisphere were not associated to changes in BMI, body-fat percentage or HOMA-IR.

4. Discussion

In this study, we investigated whether changes in body weight, body composition and insulin resistance were associated with structural brain changes, especially grey matter volume and cortical thickness. We found grey matter volume and cortical thickness unchanged, while body weight, body-fat percentage and insulin resistance were significantly reduced during a 2 year weight loss and weight maintenance period, we did see changes in cortical thickness in the right and left anterior cingulate gyrus after the weight loss period. These changes were in opposing directions and were not related to any of the anthropometric or blood parameters.

Multiple cross-sectional studies reported associations between grey matter or cortical thickness and adiposity, insulin resistance or T2D [2,4,7,8,11,12,15]. Therefore, the intuitive next step seems to assess if grey matter or cortical thickness change along with weight loss and related metabolic parameters. The participants in the current study significantly reduced their body weight, body-fat percentage and insulin resistance using a LED and showed slight regain in these parameters after 2 years in the PREVIEW intervention. However, these changes were not mirrored by changes in grey matter volume or cortical thickness. We also did not find baseline associations with grey matter or cortical thickness and body weight.

Multiple suggestions may be put forward to explain the lack of association between changes in grey matter volume or cortical thickness with changes in weight status, adiposity or insulin resistance. Due to too short a study period or too large inter individual variation in relation to intra-individual changes we may have not been able to pick up on changes in grey matter volume or cortical thickness. The latter may also explain why we did not find baseline associations between grey

matter volume or cortical thickness and BMI. Studies with larger participant numbers and maybe even longer study periods are needed to assess the question in more detail. Another possibility may be that structural brain changes are unilaterally affected by increased body weight. It is thought that obesity-associated systemic inflammation leads to permanent neurodegeneration via increased brain oxidative stress and neuroinflammation [32–34]. This may explain why BMI functions as a predictor for reduced grey matter volume [21]. Contrarily, multiple studies suggested that cortical thinning can be reversed. Weight restoration led to increases in cortical thickness in patients with anorexia nervosa [35]. This observation together with the demonstrated increase in cortical thickness after bariatric surgery [22,23], suggests that there is an inverted u-shaped relationship between bodyweight and cortical thickness. Moreover, smoking cessation was able to reverse cortical thinning [36] and an exercise intervention increased cortical thickness and brain volume in brain tumor survivors [37]. Whether cortical thinning and reductions in grey matter volume can be reversed by a lifestyle intervention to induce weight loss, still needs to be investigated.

While changes in body-fat percentage or HOMA-IR were not related to changes in grey matter volume or cortical thickness, they were associated at baseline. Similar to other studies, HOMA-IR was inversely associated with grey matter volume [38,39], potentially playing a putative role for cognitive dysfunction and neurodegenerative diseases [40,41]. The importance of insulin and insulin sensitivity for physiological as well as pathophysiological brain function has gained attention with the discovery of regionally distributed brain insulin receptors in areas subserving cognition and emotion, including the anterior cingulate cortex [42]. It has been suggested earlier that insulin homeostasis may directly affect brain volume through different mechanisms. The detrimental effects of chronic central hyperinsulinemia include consequences for prosurvival as well as a proapoptotic signal transduction processes through the suppression of tau protein phosphorylation on the one hand, and a accumulation of amyloid beta due to desensitization of antiapoptotic pathways on the other hand [43].

Body-fat percentage was positively associated to cortical thickness at baseline. This is in line with other studies [9,44] and may be associated with increased adiponectin and leptin levels, which are suggested to be neuroprotective and anti-inflammatory [45,46].

Opposing effects were found for changes in cortical thickness in the left and right anterior cingulate during the intervention. While the cortical thickness in the right anterior cingulate was increased after weight loss, but normalized after 2 years, it was reduced and normalized in the left anterior cingulate. These changes were not related to changes in body weight, body-fat percentage or insulin resistance. The anterior cingulate is an important relay station and plays a role in response inhibition. Inhibitory responses may be increased especially after a period of dieting, which may be why we found changes after the LED period. Several parameters have been proposed in the past to be associated with changes in cortical thickness, including intracortical myelination or pruning. However, our results regarding the specific and lateralized ACC related changes cannot be explained conclusively.

We did not relate structural measures to functional measures and hence cannot state whether changes in cortical thickness reflect changes in functionality.

In conclusion, we observed no relationship between grey matter volume or cortical thickness with weight loss, long-term weight maintenance, improvements in insulin resistance, and body-fat percentage. At baseline, insulin resistance was inversely related to grey matter volume while body-fat percentage was positively related to cortical thickness. Furthermore, we found an inverse association between age and grey matter volume and the latter was lower in men compared to women in accordance with previous studies [47–50]. This difference between men and women may be attributed to different effects of the sex hormones, since estrogen has been shown to be neuroprotective while testosterone has been associated with myolinogenesis which can lead to reduced grey matter volume [51].

The changes in insulin resistance or body-fat percentage induced by the PREVIEW intervention were not related to changes in grey matter volume or cortical thickness. It remains unclear, whether it is possible to reverse a loss of grey matter volume and cortical thickness by means of a weight loss intervention.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.06.017.

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Author contributions

The author's responsibilities were as follows: Mathijs Drummen conducted the study, analysed the data and wrote the manuscript; Armin Heinecke performed processing and analyses of the brain data and reviewed the manuscript; Elke Dorenbos assisted with the study and reviewed the manuscript; Anita Vreugdenhil assisted with setup of the study and medical assistance and reviewed the manuscript; Anne Raben initiated and coordinated the PREVIEW study and reviewed the manuscript; Margriet Westerterp-Plantenga designed and supervised the study and reviewed the manuscript; Tanja Adam designed and supervised the study, supervised data analysis and reviewed the manuscript.

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Disclosure

Dr. M. Drummen reports no disclosures.
Dr. A. Heinecke reports no disclosures.
Dr. E. Dorenbos reports no disclosures.
Dr. A.C.E. Vreugdenhil reports no disclosures.
Dr. A. Raben reports no disclosures.
Dr. M.S. Westerterp-Plantenga reports no disclosures.
Dr. T.C. Adam reports no disclosures.

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