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Authors

Hendrik Hartmann[a,b,c], Lieneke K. Janssen[a,d], Nadine Herzog[b], Filip Morys[e], Daniel Fängström[c], Sean J. Fallon[f], Annette Horstmann[a,b,c]

Affiliations

a: Collaborative Research Centre 1052, University of Leipzig, Leipzig, Germany

b: Department of Neurology, Max Planck Institute for Human Cognitive & Brain Sciences, Leipzig, Germany

c: Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Helsinki, Finland

d: Institute of Psychology, Otto-von-Guericke University Magdeburg, Magdeburg, Germany

e: Montreal Neurological Institute, Montreal, QC, Canada

f: University of Plymouth, Plymouth, United Kingdom

Corresponding author

Hendrik Hartmann, Haartmaninkatu 3, 00290 Helsinki, Finland,

hendrik.hartmann@helsinki.fi

Abbreviations

fMRI: functional magnetic resonance imaging

HFS: high-fat/high-sugar

LFS: low-fat/low-sugar

pDAP: peripheral dopamine precursor

SNP: single nucleotide polymorphism

Key words

high fat diet, high sugar diet, dopamine, working memory, humans, cognition

1 Introduction

Obesity has been associated with alterations in the central system of the neurotransmitter dopamine and associated cognition and decision-making (Coppin et al., 2014; Janssen & Horstmann, 2022; Mathar et al., 2017; Small, 2017). Recent animal work suggests that obesity-related findings might actually be driven by a high fat and/or high sugar diet (HFS). For example, a high-fat diet decreased dopamine signaling in the striatum and prefrontal cortex of mice and rats (Adams et al., 2015; Barry et al., 2018; Cone et al., 2013; Estes et al., 2021; Fordahl & Jones, 2017; Meireles et al., 2016; Nguyen et al., 2017; van de Giessen et al., 2012). More specifically, a diet high in saturated fat, in contrast to unsaturated fats, reduced dopamine signaling in the striatum, though both types of diet increased body weight (Barnes et al., 2020; Hryhorczuk et al., 2016). Diets with high sugar content were shown to have opposite effects and enhance dopamine signaling in the striatum of rats (Adams et al., 2015; Rospond et al., 2019). Because of these opposing effects, several studies combined both macronutrients in a high-fat and high-sugar (HFS) diet; using this combined approach, HFS diets have consistently been reported to decrease dopamine signaling in the striatum (Fritz et al., 2018; Jones et al., 2017; Patel et al., 2018).

Similar diet-associated changes in the dopaminergic system might influence cognition and behavior in humans. In fact, correlational observations provide evidence for a link between HFS and cognition. Higher intake of saturated fat and sugar was associated with poorer global cognition and cognitive decline in aging (Okereke et al., 2012; Zhang et al., 2006) and with reduced hippocampal-dependent learning and memory (Attuquayefio et al., 2016; Francis & Stevenson, 2011). However, the impact of HFS on human dopaminergic signaling and possible behavioral effects

has not been investigated extensively. In a previous study, we found that dietary dopamine depletion decreased working memory performance in a group of participants with low self-reported fat and sugar intake (LFS) but did not affect the HFS group (Hartmann et al., 2020). In line with the inverted u-shaped association between dopamine and cognitive performance, we speculated that the HFS group had higher levels of tonic dopamine than the LFS group (Cools & D'Esposito, 2011; Goldman-Rakic et al., 2000). This hypothesis was further informed by higher levels of peripheral dopamine precursor (pDAP) availability in the HFS group, which may be regarded as a potential proxy for central dopamine availability based on PET studies (Leyton et al., 2004; Montgomery et al., 2003). Based on these findings, we aimed to further disentangle the potential association of HFS with the subprocesses of dopamine-dependent working memory in humans.

In our previous study we did not find baseline differences in complex working memory span between diet groups. Thus, we aimed to specifically investigate subprocesses of working memory: (1) to maintain mental representations of goal-relevant information in the face of distracting sensory input (stability) whilst (2) simultaneously enabling these representations to be updated (flexibility). Dopamine has been proposed to modulate the gating and distractor-resistant maintenance of working memory representations (Chatham et al., 2014; Hazy et al., 2007). Using a pharmacological intervention, Bloemendaal and colleagues could provide evidence that DRD2 activation impaired distractor-resistance (Bloemendaal et al., 2015). Fallon and Cools developed a version of the classical delayed match-to-sample working memory paradigm that specifically probed stability and flexibility of working memory representations. Stability in this task was associated with increased BOLD signal in the PFC and flexibility with increased BOLD signal in the dorsal striatum

(Fallon, van der Schaaf, et al., 2017; Fallon & Cools, 2014). Increasing dopaminergic transmission with methylphenidate improved stability at the expense of flexibility. These results provide causal evidence that stability and flexibility are modulated by catecholaminergic tone, and furthermore support the assumption that working memory relies on a balance between prefrontal and striatal dopamine transmission (Cools & D'Esposito, 2011). To investigate the association of HFS with dopamine-dependent stability and flexibility of working memory representations, we used an adapted version of the paradigm by Fallon & Cools, with controls to take into account temporal confounds in stability and flexibility conditions (Fallon et al., 2018; Fallon, Mattiesing, et al., 2017).

While environmental factors like HFS might be able to modulate the human dopaminergic system, its baseline setup is likely shaped by variations in our genes. The catechol-O-methyltransferase (COMT) is important for dopaminergic activity in the prefrontal cortex and carrying the Val-allele of the COMT Val^{158}Met polymorphism was found to reduce prefrontal dopamine levels in contrast to the Met-allele (Chen et al., 2004; Slifstein et al., 2008). The DRD2/ANKK1 Taq1A polymorphism has been linked to striatal D2 receptor availability. Carrying the Taq1A A1 allele was associated with significantly reduced DRD2 density and binding in the striatum (Eisenstein et al., 2016; Jönsson et al., 1999; Pohjalainen et al., 1998). Both, the COMT Val^{158}Met and Taq1A single nucleotide polymorphism (SNP) have been related to measures of working memory and cognitive stability and flexibility (Berryhill et al., 2013; Fallon et al., 2013; Joober et al., 2002; Naef et al., 2017; Nymberg et al., 2014; Xu et al., 2007). In addition, it has been hypothesized that COMT Val^{158}Met and Taq1A mediate possible effects of HFS on dopamine-related cognition. COMT Val^{158}Met genotype modulated the improving effects of

enhancement of unsaturated fatty acids on memory (Witte et al., 2010) and Sun and colleagues proposed a model whereby carriers of the Taq1A A1 allele have an increased risk for the detrimental effects of HFS on dopamine dependent functions (Sun et al., 2017).

In the present study we investigated the association of HFS with stability and flexibility of working memory representations and tested whether genetic predisposition poses a risk factor for potential HFS effects. To this end, we grouped participants into low (LFS) and high (HFS) consumers based on self-reported HFS intake and assessed COMT Val^{158}Met and Taq1A genotype. Participants then completed a working memory task probing dopamine-dependent stability and flexibility inside an MRI scanner. We hypothesized that stability and flexibility will differ between LFS and HFS, and that this difference is modulated by COMT Val^{158}Met or Taq1A genotype. The putative association of HFS with working memory was expected to parallel diet-related differences in striatal and prefrontal BOLD signal during task execution.

2 Material and Methods

2.1 Participants

Healthy, right-handed, male participants were recruited from the internal participant database of the Max Planck Institute for Human Cognitive and Brain Sciences (Leipzig, Germany) and via advertisements in public places and facilities at the University of Leipzig. We restricted our sample to male participants, because variations in the concentration of the sex hormone estradiol were shown to affect striatal dopamine release in rats (Becker, 1990) and influence working memory

performance in women (Hampson & Morley, 2013; Jacobs & D'Esposito, 2011) and could mask potential diet-associated effects. In total 142 participants were invited to the research facilities to complete a screening for study eligibility (**Fig. 1**). Ninety-nine of those 142 participants were eligible – meaning they were either classified as low or high consumers of HFS, medium consumers were excluded (see 2.2 Study design for details) – and enrolled in the study. Eighty-six participants (Age: *M* = 26.8 years, *SD* = 4.7, range = 18–40 years; BMI: *M* = 24.0 kg/m^2, *SD* = 2.80, range = 18.6–36.4 kg/m^2; IQ: *M* = 109.2, *SD* = 7.3, range = 91–118) completed the study; 13 participants dropped out voluntarily or were excluded post hoc for elevated thyroid hormone levels. Out of the 86 participants that represent the final sample 45 belonged to the low fat/sugar (LFS) group and 41 belonged to the high fat/sugar (HFS) group; the two groups were matched for age (LFS: *M* = 26.6 years, *SD* = 4.5, range = 18–36 years; HFS: *M* = 26.9 years, *SD* = 4.5, range = 20–40 years), BMI (LFS: *M* = 24.2 kg/m^2, *SD* = 2.7, range = 19.7–30.0 kg/m^2; HFS: *M* = 23.8 kg/m^2, *SD* = 2.9, range = 18.6–36.4 kg/m^2) and IQ (LFS: *M* = 109.1, *SD* = 7.8, range = 91–118; HFS: *M* = 109.2, *SD* = 6.7, range = 91–118). All participants were omnivores or vegetarians, and none followed a special dietary regime like low-carb, gluten-free, or paleo diet. None of the participants reported a history of clinical drug or alcohol abuse or neurological or psychiatric disorders or had a first-degree relative history of neurological or psychiatric disorders. None showed moderate or severe depressive symptoms assessed by the Beck Depression Inventory (BDI)(Beck et al., 1996; Kühner et al., 2007), indicated by total scores ≤ 20, or signs of eating disorders assessed by the Eating Disorder Examination Questionnaire (EDE-Q)(A. Hilbert et al., 2007; Mond et al., 2004). All included participants were considered healthy with respect to glucose metabolism and thyroid function.

2.2 Study design

This study was part of a larger project investigating the possible association of HFS intake with changes in the human dopaminergic system and alterations of behavior and decision-making. The detailed study protocol for this project can be found under https://osf.io/w9e5y. Participants were invited to the lab on three occasions, the first of which was a screening day including blood drawings after an overnight fast, anthropometric measurements, BDI and EDE-Q, and assessment of non-verbal IQ by the Viennese Matrices Test (Formann et al., 2011). We used an extreme group design, in which participants were assigned to the low fat/sugar (LFS) or high fat/sugar (HFS) group based on their score on the Dietary Fat and free Sugar Questionnaire (DFS)(Francis & Stevenson, 2013; Fromm & Horstmann, 2019). The LFS group consisted of participants with a total DFS score ≤ 52, the HFS group consisted of participants with a total DFS score ≥ 62. Cutoff scores were defined *a priori* based on previous work and represent the lowest and highest quartile of DFS score distributions (Fromm & Horstmann, 2019). After the screening participants took part in two separate test sessions: one behavioral and one MR session; the order of behavioral and MR session was counterbalanced within groups. Screening and first test session could be on consecutive days, first and second test session were at least two days apart (days between screening and 1st session: M = 8.1 days, SD = 6.3, range = 1–43 days; days between 1st and 2nd session: M = 11.4 days, SD = 13.1, range = 2–70 days). Here we only focus on the working memory task, which was performed during the MR session inside a 3T MRI scanner. During that same session as well as the behavioral session participants completed questionnaires regarding personality traits, motivation, impulsiveness, eating behavior, and physical activity. Furthermore, participants performed the verbal forward and backward digit

span task, as a measure of short-term memory and working memory capacity respectively (S. Hilbert et al., 2014). After completion of test days participants wore a pedometer for seven days to assess mean physical activity levels.

2.3 Delayed match-to-sample working memory task

Participants performed a delayed match-to-sample working memory task with intervening distractor stimuli to assess stability and flexibility of working memory representations (adapted from (Fallon & Cools, 2014)). The main goal of the task was to evaluate whether a remembered figure matched a presented probe or not. Each trial of the task consisted of three different phases, the encoding phase, the interference phase and the probe phase. There were four task conditions: update (measures flexibility), ignore (measures stability), control short delay, or control long delay (**Fig. 2**). In the update condition, participants were presented with two target stimuli (indicated by the letter 'T' centered between the stimuli) in the encoding phase. In the subsequent interference phase, a new pair of target stimuli was presented and had to be remembered instead of the previously shown pair. At the end of the trial, in the probe phase, participants saw one colored pattern and had to indicate whether this corresponded to one of the two last seen target stimuli or not by choosing "yes" or "no" via left or right button press. The presentation of response options on the left or right side was consistent throughout the experiment for each participant and counterbalanced across participants. In the ignore condition, participants again saw two target stimuli in the encoding phase but were presented a pair of non-target stimuli (indicated by the letter 'N' centered between the two stimuli) in the interference phase. Participants were instructed to ignore the non-target stimuli and match the remembered target stimuli from the encoding phase with the

following probe. As in other studies, we included two extra conditions to account for temporal confounds in ignoring and updating (Fallon et al., 2018; Fallon, Mattiesing, et al., 2017). The two control conditions required memorizing only one pair of target stimuli without updating or ignoring interfering stimuli and were included to control for the difference in temporal delay between viewing target stimuli and evaluating the probe in the ignore and update conditions. The control short condition matched the temporal delay between presentation of the to-be-remembered target stimuli and the probe in the update condition (2000–6000 ms) by presenting a fixation cross in the encoding phase and a pair of target stimuli in the interference phase. The control long condition matched the temporal delay between target and probe of the ignore condition (6000–14000 ms) by presenting a pair of target stimuli in the encoding phase and a fixation cross in the interference phase. Stimuli and fixation cross remained on the screen for 2000 ms in both the encoding and interference phase. Encoding, interference, and probe phase were each separated by a variable delay of 2000 to 6000 ms.

Participants were given 2000 ms within which to make a response to the probe item. If they did not respond within 2000 ms the trial was marked incorrect. The task was separated into four runs, with feedback (average accuracy) on performance between each run. Each run consisted of 32 trials (8 per task condition), amounting to a total of 128 trials. Unlike the original version of the task by Fallon and Cools, 2014, which presented ignore and update trials in a block design, the four task conditions were randomly presented within each run in an event-related design. Each trial was separated by an inter-trial interval of 2000 ms. The task stimuli were unique, randomly computer-generated, monochromatic RGB ‘spirographs’. The task lasted approximately 30 minutes and was programmed using the Psychtoolbox (v 3.0.16) in

Octave (v 4.2.2). Responses were collected with a two-finger button box operated with the right-hand index and middle finger. Performance measures of behavior were accuracy and response time (RT).

2.4 Blood measurements

Measures of glucose and lipid metabolism, insulin sensitivity and leptin signaling differ related to obesity and can affect the dopaminergic system (Berland et al., 2016; Dunn et al., 2012). Blood samples collected on the screening day were hence analyzed for markers of fat and sugar metabolism (total cholesterol, LDL and HDL, triglycerides, glucose and long-term sugar marker glycated hemoglobin HbA1c) and metabolic hormones insulin and leptin. Insulin resistance was calculated according to the HOMA-index (Homeostasis Model Assessment) using the formula: fasting insulin (microU/L) x fasting glucose (nmol/L)/22.5 (Matthews et al., 1985). Interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α) and high sensitivity C-reactive Protein (hs CRP) were determined as markers for systemic inflammation, which was shown to modulate dopamine signaling (Petrulli et al., 2017). Furthermore, in line with our previous study (Hartmann et al., 2020), we measured peripheral levels of dopamine precursor amino acids phenylalanine and tyrosine and large neutral amino acids (methionine, valine, leucine, isoleucine, lysine, threonine and tryptophan). The ratio of phenylalanine and tyrosine to the large neutral amino acids represents the peripheral dopamine precursor (pDAP) availability and can be considered a putative proxy for central dopamine levels (Leyton et al., 2004; Montgomery et al., 2003). All blood measures were analyzed at the Institute for Laboratory Medicine, Leipzig, Germany. To assess genetically determined variation in central dopamine transmission we determined COMT Val^{158}Met and Taq1A genotype in our sample.

Analysis of these SNPs was performed in the lab for 'Adiposity and diabetes genetics' at the Medical Research Center, University Leipzig, Leipzig, Germany. For all statistical analyses including COMT Val^{158}Met participants were grouped into Val/Val, Val/Met, or Met/Met allele combinations. Because the frequency of the Taq1A A1 allele is low in the general population, we grouped A1 homozygotes and A1/A2 heterozygotes as A1-carriers in contrast to non-carriers (Noble, 2003).

2.5 Questionnaires

A number of self-report questionnaires was administered for screening purposes and to characterize participants in terms of personality, eating behavior, and physical activity. All questionnaires were administered on-site using the online survey tool LimeSurvey (LimeSurvey GmbH, Hamburg, Germany) hosted on protected servers of the Gesellschaft für wissenschaftliche Datenverarbeitung mbH Göttingen (GWDG, Göttingen, Germany).

2.5.1 Screening Questionnaires

The Dietary Fat and Free Sugar Questionnaire (DFS) is a self-report questionnaire assessing the frequency of diet items high in saturated fat and refined sugars taken in over the last twelve months (Francis & Stevenson, 2013). The Eating Disorder Examination Questionnaire (EDE-Q) is the self-report version of the Eating Disorder Examination interview and assesses eating disorder pathologies (A. Hilbert et al., 2007; Mond et al., 2004). We considered exclusion of participants above a total score of 3.9 (mean + 2 SD for a healthy German population (A. Hilbert et al., 2012)), but none of the participants scored above this cut-off.

2.5.2 Personality, motivation, and impulsivity

Measures of personality, motivation, and impulsivity have been related to working memory before (Entezari et al., 2022; Gray & Braver, 2002; Hinson et al., 2003; Saylik et al., 2018; Studer-Luethi et al., 2012). We measured these constructs to account for their possible effects if group differences emerge. A personality inventory (NEO-FFI), assessing the five personality traits openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism, was completed by participants to characterize the two diet groups (Costa & McCrae, 2008; Körner et al., 2008). Impulsivity was measured using the Urgency, Premeditation, Perseverance, Sensation Seeking Impulsive Behavior Scale (UPPS)(Schmidt et al., 2008) and the Barratt Impulsiveness Scale (BIS 15), which assesses motor, non-planning, and attentional impulsivity (Meule et al., 2011). The behavioral inhibition and behavioral activation systems, which correspond to the motivation to avoid aversive situations and the motivation to approach goal-oriented outcomes respectively, are assessed by the Behavioral Inhibition and Behavioral Activation System Scales (BIS/BAS)(Carver & White, 1994; Strobel et al., 2006). The scale has four subscales that correspond to the BIS, the BAS drive, BAS reward responsiveness and BAS sensation seeking.

2.5.3 Eating behavior and food addiction

The three factors of eating behavior (cognitive restraint, hunger and disinhibition) were assessed by the Three Factor Eating Questionnaire (TFEQ)(Pudel & Westhöfer, 1989; Stunkard & Messick, 1985). The Food Craving Questionnaire Trait (FCQ-T) measures the general frequency and intensity of food craving experiences (Cepeda-Benito et al., 2000). The German version can further be divided into six subscales assessing hunger, reactivity to food cues, rewarding value of food, lack of control and intentions to eat, thoughts and guilt, and emotions (Meule et al., 2012). Finally,

addictive-like eating was assessed by the modified Yale Food Addiction Scale 2.0 (mYFAS 2.0)(Schulte & Gearhardt, 2017).

2.5.4 Physical activity

Because alterations in dopaminergic transmission seem to exert an influence on physical activity, we compared physical activity between the two diet groups (Friend et al., 2017; Kravitz et al., 2016). After completion of test days participants wore a pedometer (PZ270 Power-Walker Pedometer, Yamax, Shropshire, Great Britain) for seven days to assess the number of steps per day. In addition to step count, self-reported physical activity was assessed by the International Physical Activity Questionnaire short form (IPAQ-SF)(Craig et al., 2003). This questionnaire records physical activity of four intensity levels and scores them as MET-minutes (multiples of the resting metabolic rate).

2.6 Neuropsychological tests

Participants performed the Reitan Trail Making Test A and B (TMT A and B) and the Digit Symbol Substitution Task (DSST) as measures of processing speed, mental flexibility, attention, and associative abilities. Both tests were performed with pen and paper under supervision of an experimenter. In brief, during the TMT participants have to connect circles with numbers in ascending order (TMT A) or connect circles with numbers or letters in ascending order, switching between numbers and letters (TMT B). The behavioral measure of the TMT is the time to completion in seconds. During the DSST participants have to assign as many correct symbols to rows of numbers according to a unique key. The behavioral measure of the DSST is the maximum number of correctly assigned symbols.

2.7 Data analysis

2.7.1 Behavioral analysis

All statistical analyses of behavioral data were performed using R in RStudio v4.0.2 (R Core Team, 2015; RStudio Team, 2016). Generalized linear mixed models (GLM) were used to analyze the working memory task's two performance measures: accuracy and reaction time (RT). We excluded trials with RTs < 200 ms from all analyses and used only correct trials for analysis of RT. Accuracy was analyzed using logistic regression with a binomial link function by subjecting all individual trials of each subject with a binary coded response (0 = incorrect; 1 = correct) to the model. We used linear regression on an individual trial basis for the analysis of RTs. We included digit span backward as covariate in all models to control for individual differences in working memory capacity that might mask potential differences in the specific working memory processes of stability and flexibility. Furthermore, it has been shown that effects of dopamine manipulations can be dependent on baseline levels of dopamine synthesis capacity, of which digit span backward can considered a proxy (Cools, 2019; Cools & D'Esposito, 2011; Fallon et al., 2019). Additionally, we included random intercepts for each participant.

To test our main assumption that HFS diet is associated with working memory flexibility and stability, we included diet (LFS vs HFS) as between-subject factor and temporal delay (short vs long) and interference (yes vs no) as within-subject factors, as well as all their interactions (model 1).

(1) *performance ~ diet * delay * interference + digit span + (1|participant)*

To test our secondary hypothesis that dopaminergic gene variants modulate dietary effects we augmented model 1 with the between subject factors COMT Val^{158}Met (model 2a) or Taq1A genotype (model 2b).

(2a) *performance ~ diet * delay * interference * COMT + digit span + (1|participant)*

(2b) *performance ~ diet * delay * interference * Taq1A + digit span + (1|participant)*

To test how pDAP availability is related to task performance we included mean-centered values for pDAP availability as continuous factor, delay and interference as within-subject factors, and the main effect of diet to control for. Because pDAP availability and BMI were found to be weakly positively correlated, $r(84) = .22$, $p = .044$, we included BMI as covariate.

(3) *performance ~ pDAP * delay * interference + digit span + diet + BMI + (1|participant)*

Finally, we investigated how BMI was associated with working memory flexibility and stability, by including mean-centered BMI as a continuous factor, delay and interference as within-subject factors, and the main effect of diet to control for. Similar to model 3, we included pDAP availability as covariate to account for the correlation with BMI.

(4) *performance ~ BMI * delay * interference + digit span + diet + pDAP + (1|participant)*

All GLMs were evaluated using Type III Wald chi-square test. *P*-values were Bonferroni-corrected for the number of models (five models for accuracy and RT, respectively). We used an alpha level of .05 for all statistical tests. Effect sizes for linear regression models are reported as the regression coefficient *β*, effect sizes for logistic regression models are reported as odds ratio OR.

2.7.2 Descriptive analysis

Comparisons between the LFS and HFS group for age, BMI, non-verbal IQ, questionnaire, neuropsychological tests, digit span task, and step count data were done using Welch's t-test. Effect sizes for significant t-tests are reported with Cohen's *d*. The association of BMI with neuropsychological tests and digit span was assessed using Pearson correlation (after exclusion of the statistical outlier for BMI). Group comparisons for blood parameters were corrected for BMI and evaluated by linear regression models with diet group and mean-centered BMI. Group difference in median MET-minutes assessed with the IPAQ was analyzed using Mood's median test. The distribution of COMT and Taq1A genotypes over diet groups was tested with Pearson's chi-square test.

2.7.3 Functional brain imaging

Scans were conducted on a Siemens 3T Skyra magnet resonance imaging system. The structural sequence was a T1-weighted MP2RAGE (magnetization prepared two rapid gradient echo), 192 slices (interleaved), 1.0 x 1.0 x 1.0 mm voxel size, field of view = 256 mm, flip angles α1 = 4°, α2 = 6°, retention time = 7000 ms, inversion time 1 = 945 ms, inversion time 2 = 3770 ms. The functional scan sequence was a T2*-

weighted less voids EPI (echo-planar imaging) sequence, multiband (multi-band factor 3), 60 slices (interleaved), 2.5 x 2.5 x 2.5 mm voxel size, 0.25 mm interslice gap, field of view = 204 mm, flip angle α = 80°, retention time = 2000 ms, echo time = 22 ms. Participants were scanned using a 32-channel head coil.

2.7.4 fMRI preprocessing

All fMRI data was preprocessed using SPM12 (Welcome Department of Imaging Neuroscience, London, UCL, London, UK) run within Matlab 9.10 (Mathworks Inc., Sherborn, MA, USA). Data from all functional runs were preprocessed, which included realignment to the mean image, unwarping, slice-timing correction (referenced to the middle slice of the functional volume), coregisteration to the structural T1 image, segmentation (including skull-stripping), and non-linear normalization (4^{th} degree B-spline) to an EPI template in the Montreal Neurological Institute (MNI) space. The normalized images were smoothed using an 8 mm 3D FWHM Gaussian kernel.

2.7.5 Imaging data analysis

Imaging data was missing for two participants of the LFS and three participants of the HFS group, because they were not eligible for the scanner and performed the task only behaviorally. We used a two-level ('summary statistics') approach for testing our primary hypothesis of differences between diet groups in task condition specific brain responses, in which we computed images for our effects of interest from participants by running individual GLMs for each participant and then performed a second group level GLM with these images (Holmes & Friston, 1998; Mumford & Nichols, 2009). The images computed on the first level were the main effects of

update (to-be-updated stimuli during interference phase) and ignore (to-be-ignored stimuli during interference phase). To choose the first-level model which best explains the functional data we ran two first-level models with varying complexity on a random subsample of 30 participants and compared their model fit on the group level using the MACS toolbox for SPM (Soch & Allefeld, 2018). In brief, this toolbox provides a common pipeline for cross-validated Bayesian model selection. The output is a selected-model map for each model subjected to the comparison, which shows those voxels where the respective model has the highest likeliest frequency to explain the data best. BOLD activations were modeled by convolution of the task regressors with the SPM-default canonical response, high-pass filtering (128 s), and first-order autoregressive error structure. Both models contained task regressors for the onsets of the following task events: initial encoding stimuli (ignore, update, and long no-interference) all under one regressor, to-be-updated stimuli, to-be-ignored stimuli, fixation cross during the interference phase (long no-interference), encoding stimuli during interference phase (short no-interference), probe event, and the feedback screen; the fixation cross during the encoding phase (short no-interference) and delay periods were left unmodelled. Next to these task regressors the simpler model contained six nuisance regressors for the six realignment parameters extracted from preprocessing to account for head motion. The more complex model contained 24 nuisance regressors instead: the six realignment parameters included in the simpler model, the square of these realignment parameters, the first derivate of these realignment parameters, and the realignment parameters used to realign the previous volume to account for spin-history effects (Friston et al., 1996). The more complex model including 24 nuisance regressors explained the data best based on visual inspection of the selected-model maps (i.e.,

406 it showed the most voxels with highest likeliest frequency to explain the data best);
407 results of the second level analysis are based on this model (results of the second
408 level analysis using the simpler model did not differ qualitatively). At the second level
409 we used a full factorial design with the factors diet group (LFS vs HFS) and task
410 condition (update vs ignore). Because we had specific hypotheses about the brain
411 areas involved in working memory updating and ignoring based on previous studies,
412 we used a region of interest (ROI) approach for the analyses comparing updating
413 and ignoring (Fallon, van der Schaaf, et al., 2017; Fallon & Cools, 2014). As ROIs we
414 used activation-based t-maps (regions significantly activated, $p < 0.001$) for update
415 minus ignore and ignore minus update trials based on independent data from Fallon,
416 van der Schaaf, et al., 2017. To investigate the possible interaction of COMT
417 Val^{158}Met and Taq1A with diet we ran two additional full factorial models similar to
418 the main model augmented by the factor COMT Val^{158}Met genotype (Val/Val vs
419 Val/Met vs Met/Met) or Taq1A genotype (A1-carrier vs non-carrier). The alpha-level
420 for significant clusters was set to 0.05 with small volume family-wise error correction
421 using random field theory. The cluster defining threshold was set to 5.

422 We calculated the percent signal change in significant clusters using the SPM
423 toolbox rfxplot (rfxplot.source.net/): % signal change = (Beta(task) x max(HRF) x
424 100)/(Beta(constant)) (Gläscher, 2009). We used a 3-mm sphere around the peak
425 voxels for the contrasts between ignore and update.

426 **2.7.6 Brain-behavior correlates**

427 To test whether better behavioral performance on updating and ignoring is related to
428 higher (or lower) BOLD signal in the striatum and PFC, and whether this relation is
429 different between the two diet groups we investigated brain-behavior correlations

with two different approaches. First, we extracted mean beta values from the significant regions in the dorsal striatum and PFC identified by the previous analysis for each participant. For each region we extracted mean beta values for ignore and update. The beta values for both task conditions and each region were entered as covariate of interest in separate GLMs with accuracy on ignore and update trials as dependent variable, diet group as between-subject factor and task condition as within-subject factor. To extend brain-behavior correlations to regions outside striatal and prefrontal areas, we entered mean accuracy for update and ignore of each participant as two separate regressors in the two-sample *t* test between LFS and HFS for the first-level contrasts update minus ignore and ignore minus update. This model tests whether the relation between BOLD signal and behavioral performance differs between diet groups across the whole brain.

3 Results

3.1 HFS diet is not significantly associated with altered working memory stability and flexibility

Our main model (model 1) revealed no differences in task accuracy between the LFS and HFS group, nor any interaction of diet group with delay or interference (all $p_{corrected} = 1$). The delay between viewing target stimuli and evaluating probes had a significant effect on accuracy, revealing that accuracy was higher for both short-retention period conditions (update ($M = .91$, $SD = .28$; and control short ($M = .92$, $SD = .27$)), than for the long-retention period conditions (ignore ($M = .87$, $SD = .34$) and control long ($M = .88$, $SD = .32$), $\chi^2(1) = 60.50$, OR = 1.29 $p_{corrected} < .001$ (**Fig. 3 A**). The main effect of interference as well as the interaction between delay and interference were non-significant (all $p_{corrected} > .337$). Diet group had no significant

454 effect on RTs and did not interact with delay or interference (all $p_{corrected}$ = 1). The
455 main effects of delay, $\chi^2(1) = 14.10$, $\beta = -8.76$, $p_{corrected} = .001$, and interference, $\chi^2(1)$
456 = 11.48, $\beta = -7.90$, $p_{corrected} = .004$, as well as their two-way interaction, $\chi^2(1) =$
457 101.54, $\beta = -23.50$, $p_{corrected} < .001$, were significant for RTs (**Fig. 3 B**). Simple main
458 effects analysis showed a benefit of update on RTs (M = 914.5 ms, SD = 286.8)
459 compared to control short (M = 980.1 ms, SD = 302.5), $\chi^2(1) = 92.91$, $\beta = -62.8$, $p <$
460 .001, and a cost of ignore on RTs (M = 983.4 ms, SD = 304.6) compared to control
461 long (M = 958.2 ms, SD = 308.2), $\chi^2(1) = 21.83$, $\beta = 31.2$, $p < .001$. The main effect
462 of delay on accuracy and the interaction between delay and interference on RTs
463 were significant in all subsequent models 2a–4 (main effect of delay: all $p_{corrected} <$
464 .001; delay*interference interaction: all $p_{corrected} < .001$). The main effect of the
465 covariate digit span was not significantly associated with accuracy or RTs in any of
466 the five models (all $p_{corrected} > .062$).

467 **3.2 COMT Val^{158}Met and Taq1A are not significantly associated with stability**
468 **and flexibility of working memory representations and do not interact with HFS**

469 In our second analysis (models 2a and 2b) we investigated whether the genetically
470 determined availability of dopamine in the PFC (COMT Val^{158}Met) or striatal density
471 of DRD2 (Taq1A) are associated with working memory stability and flexibility and
472 whether they interact with HFS consumption. For COMT Val^{158}Met the allele
473 frequency of the Val allele was 47.1 % and the allele frequency of the Met allele was
474 52.9 % (25 Val homozygotes, 31 Val/Met heterozygotes, 30 Met homozygotes). The
475 genotype distribution for COMT Val^{158}Met did not conform to Hardy-Weinberg
476 Equilibrium, $\chi^2(1) = 6.58$, $p = .037$. The allele frequency of Taq1A's A1 allele was
477 19.2 % and the allele frequency of the A2 allele was 80.8 % (27 A1 carrier, 59 non-

carrier). The genotype distribution for Taq1A was in Hardy-Weinberg Equilibrium, $\chi^2(1) = 2.64$, $p = .105$. Chi-square tests revealed no diet group differences in the distribution of COMT Val^{158}Met, $\chi^2(2) = .34$, $p = .844$, and Taq1A genotypes, $\chi^2(1) = .57$, $p = .449$. The interaction between COMT Val^{158}Met and diet group as well as all higher order interactions with delay and interference were not significantly associated with accuracy or RTs (all corrected *p*-values > .276). Furthermore, neither the main effect of COMT Val^{158}Met nor the two- or three-way interactions with delay and interference were significantly associated with accuracy or RTs (all corrected *p*-values > .458). The interaction between Taq1A and diet group as well as all higher order interactions with delay and interference were not significantly associated with accuracy or RTs (all corrected *p*-values = 1). Furthermore, neither the main effect of Taq1A nor the two- or three-way interactions with delay and interference were significantly associated with accuracy or RTs (all corrected *p*-values = 1).

3.3 The availability of pDAP was not significantly associated with working memory stability and flexibility

Model 3 investigated the association of pDAP availability with working memory stability and flexibility. Neither the main effect of pDAP availability nor its interactions with delay and interference were significantly associated with accuracy or RTs (all corrected *p*-values > .384).

3.4 BMI is associated with overall lower accuracy on the working memory task

Model 4 investigated the association of BMI with working memory stability and flexibility. One participant with a BMI of 36.4 kg/m^2 was identified as a statistical outlier and excluded from this analysis. Higher BMI was significantly associated with

overall lower accuracy on the working memory task, $\chi^2(1) = 6.76$, OR = .76, $p_{corrected}$ = .047 (**Fig. 4**). *Post hoc* analysis of regression slopes for each of the four task conditions revealed that BMI was negatively associated with accuracy on ignore, z = -2.20, OR = .77, p = .028 , control short, z = -2.67, OR = .71, p = .008, and control long trials, z = -2.80, OR = .71, p = .005, but not with accuracy on update trials, z = -1.22, OR = .86, p = .223.This main effect of BMI was non-significant for RTs ($p_{corrected}$ = 1). BMI did not interact significantly with delay and interference for accuracy or RTs (all corrected p-values > .404). To control for confounding effects of decreased attention during the long test day, we assessed participants' tiredness and focus during the task with a ten-point likert scale after they returned from the MRI scanner. BMI did neither correlate with tiredness, $r(84) = .04$, p = .719, nor focus, $r(84) = .01$, p = .939.

3.5 No evidence that diet group affects striatal and prefrontal BOLD signal during working memory stability and flexibility

To confirm that we find the BOLD signal changes associated with working memory stability and flexibility as in previous studies, we looked at the contrast update vs ignore in the entire sample. Consistent with previous reports (Fallon, van der Schaaf, et al., 2017; Fallon & Cools, 2014), updating relative to ignoring significantly increased BOLD signal in the left and right dorsal striatum and the right thalamus as well as occipital and temporal gyri (**Fig. 5**). Comparing percent signal change within the left and right putamen revealed that this difference between task conditions was caused by positive signal change in update trials compared to ignore trials. Percent signal change within the dorsal striatum in both conditions did not differ between diet groups.

525 The reverse contrast, ignore relative to update, also produced the same pattern of
526 BOLD signal changes as found in previous reports, namely significant increases in
527 middle and superior PFC as well as temporal and parietal gyri (**Fig. 6**). The
528 difference in activation between ignore and update trials in the left and right middle
529 frontal gyrus was driven by negative percent signal change in update trials (**Fig. 6 A**
530 and **B**). The percent signal change in both clusters of the left superior frontal gyrus
531 was negative for both ignore and update trials, but significantly more negative for
532 update trials (**Fig. 6 C** and **D**). Again, as with the update minus ignore contrast,
533 BOLD signal increases for ignoring minus update did not differ between the two diet
534 groups in any of the four prefrontal clusters.

535 Furthermore, we compared activity between COMT $Val^{158}Met$ genotypes or Taq1A
536 genotypes as well as the interaction between diet and genotypes. These analyses
537 revealed no significant voxels for the main effects of genotypes or the interaction
538 with diet. All reported effects stayed the same when excluding participants with
539 maximum head motion larger than one voxel (excluded: LFS: 4; HFS: 7).

540 In summary, together with the results from the striatal clusters, this indicates that the
541 two diet groups do not differ in neural activation during the cognitive processes of
542 updating and distractor-resistance. A full list of significant clusters is presented in
543 **Table 1**. A list of significant clusters for the contrast of task conditions on the whole
544 brain is presented in the supplementary materials **Table S1**. Similar to the ROI
545 approach no other effects were apparent in the whole-brain analysis.

546 **Table 1.** Overview of all clusters with significant neural activation for updating and
547 distractor-resistance of working memory.

Contrast	Brain region	Cluster extent	t	p-value (FWE-corrected, peak-level)	MNI coordinates (x y z)
UPDATE > IGNORE	Right middle occipital gyrus	5233	15.47	.000	34 -86 12
	Left medial occipital gyrus	6081	15.14	.000	-40 -72 -8
	Left putamen	1020	13.18	.000	-20 10 2
	Left supplementary motor area	769	12.26	.000	-4 4 62
	Right inferior frontal gyrus, opercular	668	12.21	.000	48 8 28
	Left inferior frontal gyrus, opercular	1489	11.56	.000	-48 8 28
	Right putamen	115	10.39	.000	20 12 0

	Right inferior frontal gyrus, triangular	123	9.48	.000	48 36 10
	Left hippocampus	84	9.07	.000	-22 -30 -4
	Anterior cingulate gyrus	87	8.94	.000	6 4 28
	Right thalamus	26	8.63	.000	6 -28 -6
	Right hippocampus	39	8.59	.000	22 -30 2
	Right insula	15	7.58	.000	36 -2 12
	Calcarine fissure	337	7.42	.000	14 -74 10
	Right precentral gyrus	280	7.17	.000	28 -2 52
	Left inferior frontal gyrus, triangular	171	7.05	.000	-48 36 12
	Left superior frontal gyrus	76	5.66	.001	-20 -2 50

	Left insula	6	5.64	.001	-34 -6 14
IGNORE > UPDATE	Left inferior parietal gyrus	1519	11.52	.000	-56 -54 38
	Right supramarginal gyrus	959	9.33	.000	60 -46 40
	Left precuneus	1028	8.39	.000	-6 -54 44
	Left medial temporal gyrus	265	7.70	.000	-66 -46 0
	Left superior frontal gyrus, medial	62	5.56	.001	-4 34 48
	Left middle frontal gyrus	68	5.39	.003	-38 18 44
	Left superior frontal gyrus, medial	22	5.08	.010	-6 46 28
	Left medial temporal gyrus	9	5.03	.013	-54 2 -28

	Right middle frontal gyrus	10	4.79	.030	42 20 42

548

549 **3.6 Neural activity does not correlate with task performance**

550 To test whether accuracy on the working memory task is related to BOLD signal in
551 our significant striatal and prefrontal brain regions, we regressed mean activity in
552 these regions onto accuracy on update and ignore trials. Mean beta in none of these
553 regions was significantly associated with accuracy, nor did it interact with diet groups
554 (all corrected *p*-values = 1). To corroborate our findings from the significant region
555 approach and extend it to the whole brain we regressed accuracy on update and
556 ignore trials onto the second level two-sample *t* test between diet groups for update
557 versus ignore. No significant voxels were found for this contrast (FWE-corrected
558 threshold $p < .05$) indicating that behavioral accuracy is not differentially associated
559 with BOLD signal between the LFS and HFS group.

560 **3.7 Description of the LFS and HFS diet groups**

561 **3.7.1 Metabolic parameters**

562 Blood parameters associated with metabolism were compared between diet groups
563 corrected for BMI to check whether reported intake of fat and sugar is represented at
564 the physiological level. Results indicated marginally significant elevated levels of
565 HbA1c in the HFS group (M = 33.3 mmol/mol, SD = 2.5) compared to the LFS group
566 (M = 32.2 mmol/mol, SD = 3.0), $F(1) = 3.63$, $p = .060$, as would be expected (See
567 supplementary table S1 for an overview of all descriptive statistics and group

568 comparisons). No group differences were observed for total cholesterol as well as
569 low-density lipoprotein (LDL) and high-density lipoprotein (HDL), triglycerides,
570 glucose, leptin, insulin and HOMA insulin resistance. Furthermore, no differences
571 between diet groups were observed for markers of systemic inflammation IL-6, hs
572 CRP, and TNF-α.

573 **3.7.2 Personality, impulsivity, motivation, eating behavior, and physical activity**

574 Groups did not differ on any of the personality traits except for neuroticism:
575 participants in the HFS group reported higher neuroticism (M = 2.3, SD = .7) than
576 participants in the LFS group (M = 2.0, SD = .7), t(83.54) = 2.06, p = .042, d = .45.
577 No differences in impulsivity were observed in any of the UPPS and BIS-15
578 subscales. The two diet groups did also not differ in behavioral motivation assessed
579 by the BIS/BAS scale. Cognitive and behavioral domains of eating were measured
580 with the TFEQ. The LFS group reported lower signs of hunger (M = 2.9, SD = 2.5)
581 and higher cognitive restraint (M = 7.0, SD = 4.0) than the HFS group (M = 4.4, SD =
582 2.9), t(78.93) = -3.14, p = .002, d = .69 and (M = 4.29, SD = 3.02), t(81.29) = 3.53, p
583 < .001, d = .76 respectively. The diet groups did not differ in disinhibition. The HFS
584 group reported higher food cravings (M = 78.9, SD = 27.9) than the LFS group (M =
585 68.0, SD = 28.9), t(74.00) = 2.03, p = .046, d = .44. Looking at the FCQ-T subscores,
586 the HFS group reported higher reactivity to food cues (M = 12.2, SD = 4.2) than the
587 LFS group (M = 9.9, SD = 3.7), t(80.76) = 2.62, p = .010, d = .57, and higher
588 reinforcing value of food (HFS: M = 18.6, SD = 7.8; LFS: M = 15.2, SD = 6.4),
589 t(77.73) = 2.15, p = .035, d = .47. The groups did not differ in the other FCQ-T
590 subscales emotions, hunger, lack of control/intentions, and thoughts/guilt. Finally,
591 there was no difference in the expression of food addictive symptoms assessed by

592 the mYFAS 2.0. Physical activity, either assessed by the IPAQ and represented as
593 weekly median MET-minutes or by seven-day mean step count did not differ
594 between diet groups (six participants, three participants from each diet group, did not
595 provide step count data).

596 **3.7.3 Neuropsychological tests**

597 The diet groups did not differ in TMT A, $t(79.68) = -1.08$, $p = .281$, TMT B, $t(71.31) =$
598 -1.72, $p = .090$, DSST performance, $t(83.84) = .18$, $p = .855$, digit span forward
599 $t(82.43) = .52$, $p = .603$, or digit span backward, $t(80.25) = -.39$, $p = .691$. BMI was
600 trend significant associated with TMT A, $r(84) = .21$, $p = .052$, and not significantly
601 associated with TMT B, $r(84) = -.09$, $p = .394$, DSST, $r(84) = -.05$, $p = .653$, digit
602 span forward, $r(84) = -.04$, $p = .692$, or digit span backward, $r(84) = -.02$, $p = .881$.

603 **4 Discussion**

604 In this study, we investigated in a sample of male participants whether a diet high in
605 saturated fat and added sugar (HFS) was associated with behavioral and neural
606 differences in specific processes that support working memory, namely cognitive
607 stability and flexibility. In this cross-sectional study, a delay-match-to-sample task
608 with intervening stimuli was implemented to dissociate between people's ability to
609 shield working memory representations against new irrelevant information (stability)
610 and to adequately update them with new relevant information (flexibility) (Fallon et al.,
611 2018; Fallon, van der Schaaf, et al., 2017; Fallon & Cools, 2014). No evidence was found
612 for an association between HFS (relative to LFS) and working memory stability or
613 flexibility; neither in behavioral performance measures (RT, accuracy) nor in the
614 underlying neural responses as reflected in BOLD signal change. We also found no

615 conclusive evidence for the hypotheses that COMT Val^{158}Met or Taq1A genotype
616 may predispose individuals for detrimental effects of an HFS on cognitive function
617 (Sun et al., 2017; Witte et al., 2010), including working memory, when exploring the
618 interaction between diet group and these common genetic variants. However, in line
619 with previous findings that showed obesity-related working memory impairments
620 (Alarcón et al., 2016; Coppin et al., 2014; Yang et al., 2018), planned exploratory
621 analysis did reveal a negative association of BMI (within the normal- to overweight
622 range) with overall accuracy on this working memory task.

623 **4.1 No evidence for an association of HFS with working memory stability and**
624 **flexibility**

625 The absence of a diet-related difference in working memory stability and flexibility in
626 men, in fact, concurs with control measures from our previous dopamine depletion
627 study conducted in women (Hartmann et al., 2020). In that study, we observed a
628 diet-dependent effect of a dopamine depletion procedure on working memory
629 capacity measured with the automated operation span task, with no significant
630 difference in performance between the groups after the control treatment. Based on
631 the hypothesized inverted U-shaped relationship between dopamine levels and
632 working memory performance (Cools & D'Esposito, 2011; Goldman-Rakic et al., 2000),
633 we speculated that our results may reflect an underlying difference in dopamine
634 between diet groups that does not differentially impact working memory performance
635 at baseline, but it does so after dopamine manipulation shifts people either further
636 away or closer to the putative optimum. Nevertheless, the current null findings are
637 somewhat surprising, because tapping into specific processes of working memory
638 using a delay match-to-sample task, rather than measuring complex working

memory span, could have made subtle group differences surface. We indeed did observe the expected task effects on behavioral performance (RT, accuracy). Furthermore, our imaging results support the finding from previous studies in indicating that resistance against distracting information and the flexible updating of relevant information recruit different nodes within fronto-striatal circuits (Fallon, van der Schaaf, et al., 2017; Fallon & Cools, 2014). Several factors could explain why the hypothesized differences between the diet groups did not surface. First, in our male sample we could not replicate the higher relative peripheral availability of dopamine precursors that was associated with a high intake of saturated fat and sugar in women (Hartmann et al., 2020). The ratio of the dopamine precursors, tyrosine and phenylalanine, to the other large neutral amino acids has been shown to affect central dopamine levels (Leyton et al., 2004; Montgomery et al., 2003). Although indirect and preliminary, this finding was the most direct evidence to date for dopamine differences related to regular dietary intake of fat and sugars in humans. It could be that the groups in the current, all-male sample simply did not differ as much in their underlying dopamine system as the previous all-female sample. It has been shown that women have higher presynaptic dopamine synthesis capacity and endogenous striatal dopamine than men (Laakso et al., 2002; Pohjalainen et al., 1998) – such baseline differences could modulate the effect HFD has on the dopaminergic system in a sex dependent manner. Indeed, one study showed that male and female mice differed not only in the extent to which a high-fat diet altered gene expression of proteins involved in dopamine signal transmission but also dopamine levels in the striatum and PFC (Carlin et al., 2013). Sex specific effects of HFD on dopamine-dependent cognition have neither been investigated in animals nor humans and the use of an all-male sample, for reasons explained in the methods

664 section, is a major limitation of the present study. More research is needed to inform
665 whether HFD impacts women and men differently. Another explanation for why we
666 did not find dopamine-related differences between the two diet groups could be that
667 unspecific differences between the samples in dietary intake on the days of testing
668 led to diverging results. The availability of peripheral dopamine precursors seems to
669 be sensitive to recent dietary intake (Hartmann et al., 2020; Strang et al., 2017).
670 Large scale cross-sectional and well controlled nutrition intervention studies with
671 careful dietary measurements, as well as a measurement of peripheral dopamine
672 precursor availability in all genders could provide more conclusive answers.

673 A further limitation of this study is that we were not able to differentiate associations
674 of dietary fat and added sugar with working memory stability and flexibility. A vast
675 amount of animal research has investigated the effects of fat or sugar alone and both
676 seem to impact various parts of the dopaminergic system and not always in the
677 same manner (Adams et al., 2015; Barry et al., 2018). The items of the DFS
678 questionnaire can be subdivided into high-fat, high-sugar, and high-fat-sugar items
679 but we could not analyze these subscales because no clear groups of low and high
680 consumers emerged. Future studies could focus on recruiting participants on the
681 separate DFS subscales or find more detailed ways of assessing dietary intake.

682 Studying effects of diet in humans poses plenty of obstacles which might explain why
683 only few studies have addressed the link between HFS and cognition or the
684 dopaminergic system and results are not as supportive of this link as the animal
685 literature. As we have outlined before our previous study is the first to our knowledge
686 to find evidence for an association of HFS with dopamine-dependent cognitive
687 processes and dopamine proxies (Hartmann et al., 2020). In this as well as the

688 present study, we grouped participants based on their self-reported intake of HFS
689 food items using the DFS questionnaire developed by Francis and Stevenson
690 because it can easily be administered to a large population, even online, which
691 facilitates recruitment (Francis & Stevenson, 2013). Drawbacks of self-reported data
692 are over- and underreporting, introduced by social desirability bias, memory-related
693 bias, or false entries (Eldridge et al., 2018; Gonyea, 2005) - drawbacks which could
694 be reduced by the future implementation of technology-based tools for dietary intake
695 assessment like smartphone-based applications (Lucassen et al., 2021). Such tools
696 would allow a more fine-grained dietary assessment, which is needed in light of the
697 complex food environment humans live in, especially when considering that different
698 types of the same macronutrient or low-level concentrations could impacted the
699 dopamine system as shown in animals (Barnes et al., 2020; Hakim & Keay, 2019;
700 Hryhorczuk et al., 2016). Support for how relevant knowledge about the exact
701 composition of a meal is comes from Strang and colleagues who could show that the
702 ratio between carbohydrates and protein of a single meal influenced decision-making
703 in an ultimatum game (Strang et al., 2017). The most potent tool to investigate diet
704 effects are dietary interventions because they allow researchers to manipulate
705 individual macronutrients and get closer to the highly controlled diets administered in
706 animal studies. Considering the large variety of food items and ingredients, specific
707 effects on the dopaminergic system like they have been shown in animal studies
708 cannot necessarily be expected, but dietary interventions could close this gap to
709 animal research. Though not investigating dopamine-related cognition, effects of
710 short-term HFS interventions were shown on appetitive control, learning and memory
711 processes. Attuquayefio and colleagues provided either a breakfast high in saturated
712 fat and added sugar or a calorie-matched healthier breakfast over four consecutive

713 days (Attuquayefio et al., 2017); Stevenson and colleagues asked their participants
714 to eat specific foods high in saturated fat and added sugar for breakfast or desert on
715 four days plus to obtain a main meal and drink from fast-food restaurants on two
716 additional days, in contrast to control participants that were asked to maintain their
717 normal non-HFS diet (Stevenson et al., 2020). In both studies, hippocampal-
718 dependent cognitive functions declined in the HFS intervention group relative to the
719 control group, providing causal evidence for an effect of HFS diet on cognition in
720 humans. Interestingly, the association of HFS with impairments in hippocampal-
721 dependent cognitive functions has also been reported in correlational studies that
722 assessed self-reported HFS in the same way we did in the present study
723 (Attuquayefio et al., 2016; Francis & Stevenson, 2011). These results might suggest that
724 diet effects are stronger on the hippocampus than on the dopaminergic system. But
725 first evidence that even short-term interventions could pose an effect on the
726 dopaminergic system comes from Strang and colleagues by showing that decreased
727 plasma levels of the dopamine precursor tyrosine after a single meal with high
728 carbohydrate to protein ratio were causally related to changes in decision-making
729 behavior (Strang et al., 2017). In summary it can be said that the research of dietary
730 effects on cognition and especially the dopaminergic system in humans is still in its
731 infancy and more studies using detailed dietary intake tools or interventions are
732 needed to uncover whether effects seen in animal studies are translatable to
733 humans. On the other hand, animal studies could provide more insight by adopting
734 interventions that are closer to our dietary patterns by incorporating less extreme and
735 more diverse feeding regimens (see review by Janssen and colleagues for more
736 detailed information(Janssen et al., 2019)).

4.2 Dopaminergic gene variants do not seem to predispose individuals to possible diet effects

Although we found no conclusive evidence that COMT Val^{158}Met or Taq1A genotype predisposed individuals for the hypothesized detrimental effects of an HFS on working memory performance and the underlying neural circuitry, our null findings cannot rule out this possibility. As outlined above, our assessment of HFS and LFS based on self-reported food intake might not be accurate enough to obtain experimental groups that show pronounced diet effects. After all, using a three-month dietary intervention, Witte and colleagues could provide evidence that cognition-enhancing effects of unsaturated fatty acids depended on COMT Val^{158}Met genotype (Witte et al., 2010). Interestingly, we did not see a main effect of COMT Val^{158}Met or Taq1A on behavioral as well as neural measures of working memory stability and flexibility though they have been associated with related cognitive processes previously. In a population of healthy older adults, Met-homozygotes showed heightened dorsolateral PFC activation and increased set-like behavior, a process related to cognitive stability and flexibility (Fallon et al., 2013). Joober and colleagues found that patients with schizophrenia and homozygous for the Met-allele performed better on a task of PFC-mediated executive function, but this genotype effect was not observed in healthy controls (Joober et al., 2002). This finding suggests that effects of COMT Val^{158}Met genotype might only emerge when the prefrontal dopamine system is dysregulated as it is the case in schizophrenia (Winterer & Weinberger, 2004). As our study sample consisted of young healthy participants such a dysregulation is highly unlikely but short-term dietary interventions might be able to tip healthy participants into this direction and uncover predisposing effects of COMT Val^{158}Met. Associations of Taq1A with working

762 memory have been reported in healthy participants, where Taq1A effected working
763 memory accuracy and reaction times, and modulated the effects of striatal activation
764 on working memory (Berryhill et al., 2013; Naef et al., 2017; Nymberg et al., 2014).
765 In contrast to our study though, these tasks probed visuo-spatial working memory
766 and not stability and flexibility of working memory representations which might be
767 differently affected by Taq1A.

768 **4.3 Higher BMI is associated with lower overall task performance**

769 Participants with higher BMI showed, independent of diet, overall lower accuracy on
770 the working memory task, in line with previous findings that reported obesity-related
771 working memory impairments (Alarcón et al., 2016; Coppin et al., 2014; Yang et al.,
772 2018). Noteworthy, BMI was associated with lower performance on all task
773 conditions except update, which raises the question whether this reflects an
774 impairment of working memory or rather higher order processes. While ignore and
775 update trials rely on working memory, due to the required manipulation of memory
776 content (or the resistance against that), the control conditions do not require such
777 manipulation and thus probe short-term memory. Though working memory and
778 short-term memory are defined as separate theoretical concepts that reflect different
779 cognitive functions, behavioral studies struggled to separate these two constructs
780 (Aben et al., 2012; Unsworth & Engle, 2007). One higher order process that is implicated
781 in both working and short-term memory and might link the two is the attentional
782 system (Conway et al., 2002; Cowan et al., 2005; Deco & Rolls, 2005; LaRocque et al.,
783 2014). The prevalence of attention deficit hyperactivity disorder has been associated
784 with overweight, increased BMI and fat mass (Martins-Silva et al., 2021; Pagoto et
785 al., 2009). Results regarding the association of BMI with tests of attention remain

inconclusive though, reporting no link with attention or even higher attention in people with increased BMI (Gunstad et al., 2007, 2010). In our sample BMI was not statistically associated with measures of attention Trail Making Test A, Digit Symbol Substitution Task, and Digit Span forward. Furthermore, self-reported tiredness and focus during the task was not associated with BMI, suggesting that perceived attention did not differ between participants. Thus, we cannot say whether the negative association between BMI and overall task performance reported in this study is related to attention as the common construct implicated in short-term and working memory. This finding needs to be replicated in a larger study designed to address this question with a more homogenous distribution of BMI, ideally expanding to individuals with obesity. However, this finding suggests that heightened body weight might have an effect on cognition independent of HFS. Whether dopamine is the causal link for this effect cannot be answered in the present study but the positive correlation between BMI and pDAP availability can be regarded as indirect indication. The correlation between BMI and pDAP availability has been reported by Frank and colleagues in a sample of female participants (Frank et al., 2016). On the other hand, pDAP availability, in contrast to BMI, was not associated with performance on the working memory task, suggesting that the potential mechanism is far more complex. The association between BMI and pDAP availability and how both relate to dopamine-dependent cognition need to be investigated further in larger samples to verify our present results.

4.4 Differences in eating behavior do not seem to be related to working memory stability and flexibility

The two diet groups did not differ in parameters of lipid and glucose metabolism, but also not in the availability of pDAP – in contrast to our prediction. Based on our previous study, we expected to see higher pDAP availability in the HFS group (Hartmann et al., 2020). Personality traits, motivation, impulsivity, or physical activity did also not differ between diet groups, except for higher neuroticism in the HFS group, which is in line with previously reported results (Hartmann et al., 2020). Nevertheless, this difference in neuroticism does not seem to be associated with working memory. Furthermore, the diet groups differed with respect to eating behavior. As reported previously, the HFS group indicated higher signs of hunger and lower cognitive restraint (Hartmann et al., 2020). This finding suggests that the amount of HFS consumed is a consequence of those eating habits (de Lauzon et al., 2004). Using a different version of the TFEQ, Calvo and colleagues could relate uncontrolled eating with reduced working memory (Calvo et al., 2014). The causal mechanism behind this could be that uncontrolled eating and working memory share cognitive processes or that uncontrolled eating leads to increased HFS intake, which in turn alters working memory (based on the animal literature). To shed more light on this causal relationship we propose to include measures of eating behavior in future studies applying HFS interventions. In addition to eating behavior assessed by the TFEQ, the HFS group reported higher overall food cravings, higher reactivity to food cues and higher reinforcing value of food. This finding supports the assumption that increased HFS intake is a consequence of eating habits and traits.

5 Conclusion

The current study did not provide any evidence for the hypothesis that higher intake of HFS is associated with alterations of working memory stability and flexibility,

neither on the behavioral nor on the neural level. Considering the challenges when investigating dietary effects in humans and studies in animals providing causal evidence that HFS alters the dopaminergic system these null findings have to be treated with caution and cannot be regarded as absence of the possible link between HFS and dopamine-dependent cognitive processes like working memory. Further regarding that BMI was associated with overall performance on the working memory task it is paramount to control for body weight when investigating diet effects. With the help of novel tools for dietary intake assessment and dietary interventions, future studies will be able to shed light on the modulatory effects of HFS on the human dopaminergic system.

6 Transparency statement

This study was preregistered after data collection but before data analysis. A preregistration describing the collection of data presented in this article as well as additional data presented elsewhere can be found under https://osf.io/w9e5y. Detailed information about the research question, study design, and proposed data analysis plan for this this study can be found under https://osf.io/8gtfk. We deviated from the detailed preregistered analysis plan in a few points and explain why, but also report the results of those analyses for complete transparency (if applicable). In the study-specific preregistration we state recoding COMT and Taq1A polymorphism according to the equilibrium model, which proposes interaction effects of these two SNPs based on a balance between striatal DRD2 density and COMT activity in the prefrontal cortex (Reuter et al., 2006). Following this model Taq1A genotypes are grouped according to the presence of the minor A1 allele into A1+ (A1 carriers, i.e. A1/A2 heterozygotes and A1/A1 homozygotes) and A1- (non-carriers, i.e. A2/A2

857 homozygotes) individuals. COMT genotypes are grouped according to the presence
858 of the Val-allele into Val+ (Val allele carriers, i.e. Val/Met heterozygotes and Val/Val
859 homozygotes) and Val- (Met/Met homozygotes) individuals. Balanced individuals
860 present the genotype combination A1+/Val+ (low striatal DRD2 density and low
861 prefrontal dopamine) or A1-/Val- (high striatal DRD2 density and high prefrontal
862 dopamine). Unbalanced individuals present the genotype combination A1+/Val- (low
863 striatal DRD2 density and high prefrontal dopamine) or A1-/Val+ (high striatal DRD2
864 density and low prefrontal dopamine). The balance between striatal DRD2 density
865 and prefrontal COMT enzyme activity was reported to be related to the behavioral
866 approach system, cognitive interference, working memory manipulation, and
867 contextual updating of mental representations (Garcia-Garcia et al., 2011; Reuter et
868 al., 2005, 2006; Stelzel et al., 2009). After careful reconsideration we decided
869 against adopting the equilibrium model and stick to the individual post-hoc grouping
870 of COMT and Taq1A genotypes as stated in the first overall study preregistration
871 (https://osf.io/w9e5y). It has been proposed that the effect of the Met allele on COMT
872 enzyme activity is dose-dependent, with Val homozygotes having the highest, Met
873 homozygotes having the lowest, and heterozygotes having intermediate activity
874 (Chen et al., 2004; Lachman et al., 1996). This dosage effect has also been reported
875 for measures of (frontal) cognitive abilities, for example on learning and memory in
876 individuals with schizophrenia (Twamley et al., 2014). Egan and colleagues reported
877 that performance as well as neural activation during a task of frontal lobe function
878 was parametrically modulated by the load of the Met allele (Egan et al., 2001). Some
879 studies associate one of the two COMT Val^{158}Met alleles with performance on
880 cognitive tasks rather than a dosage effect, but which allele seems to drive the effect
881 differs depending on the task and sample studied. Carrying the Met allele impaired

prefrontal cognition in children and adolescents with ADHD, whereas carrying the Val allele was associated with higher error rate in healthy participants (Bellgrove et al., 2005; Caldú et al., 2007). Since the COMT Val158Met polymorphism has not been studied with respect to neither HFS diet nor cognitive stability and flexibility as measured by a paradigm like the one used here, we could not exclude a possible dosage effect or make assumptions about which allele might drive an effect. For these reasons we decided to look at the effects of COMT Val^{158}Met and Taq1A independently and without any a priori assumptions of allelic effects. Nevertheless, we ran the preregistered analyses and report the results in brief. The state of the dopaminergic system according to the equilibrium model did not interact with intake of HFS diet with respect to task accuracy or RT but had a main effect on those measures. Balanced individuals (Val+/A1+ and Val-/A1-) had higher accuracy (M = .92, SD = .28) than individuals with an unbalanced genotype (M = .89, SD = .32), $\chi^2(1) = 4.57$, $p = .033$, and shorter RT (M = 918.34, SD = 149.46) than unbalanced participants (M = 983.06, SD = 154.88), $\chi^2(1) = 4.12$, $p = .042$. Similar to our analysis with individual COMT Val^{158}Met and Taq1A genotypes, genotypes according to the equilibrium model were not associated with neural activation during ignore and update and did not interact with HFS diet.

A second deviation from the present manuscript to the preregistration is the analysis of imaging data. In the preregistration we stated contrasting the experimental conditions, i.e. ignore and update, with the respective no-interference conditions on the first level and subsequently compare those contrasts to investigate the effects of ignore and update. The intention of this analysis at the time of preregistering the study was to control for the difference in temporal delay between ignore and update condition. But since the actual process of updating and ignoring are independent of

said delay there is no need controlling for this. Replicating the finding from Fallon, van der Schaaf, et al., 2017 reassured us that the analysis reported in the manuscript probed update and ignore subprocesses correctly. Furthermore, we stated using anatomical masks from the WFU_PickAtlas for our ROI approach. Because anatomical masks can sometimes be larger than the brain area where an effect is suspected, we used t-maps from an independent study using the original experimental paradigm (Fallon, van der Schaaf, et al., 2017).

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Authors contributions

The authors' contributions were as follows — HH: helped conceptualize study design, led data collection, conducted data analysis, wrote first draft of the manuscript, and revised subsequent drafts based on coauthor input; LKJ: conceptualized study design, assisted in data collection, interpreted the data, critically revised the manuscript; NH: assisted in data collection, supported the development of the preprocessing pipeline and task-based fMRI analysis, interpreted the data, critically revised the manuscript; FM: provided valuable feedback for data analysis, critically revised the manuscript; DF: developed the preprocessing pipeline

for the imaging data; SJF: developed the task paradigm, provided valuable feedback for data analysis, critically revised the manuscript; AH: conceptualized study design, responsible for study supervision and guarantor of this work, provided valuable feedback for data analysis, critically revised the manuscript; and all authors: read and approved the final manuscript.

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Data availability

The data presented in this study are available on request from the corresponding author.

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Figures

Figure 1. Flow diagram with participant enrollment, exclusion and dropouts.

Figure 2. Schematic illustration of the task structure and experimental conditions. The task consists of three task phases. In the encoding phase, participants encoded two target stimuli (signaled by the letter “T”), if any were presented. In the interference phase, participants either had to ignore two non-target stimuli (ignore trials; signaled by the letter “N”) or allow these new stimuli to replace the previously remembered target stimuli (update trials). Control trials do not require ignoring distracting or updating new stimuli. At the end of each trial participants evaluate whether a presented figure was a target figure or not.

Figure 3. Behavioral outcome measures of the WM task. **A.** WM accuracy did not differ between diet groups but was influenced by the delay between viewing target stimuli and evaluating the probe. Accuracy was significantly higher for update and control short trials (short delay) compared to ignore and control long trials (long delay), $p < .001$. **B.** Response times (RTs) for evaluating the presented probe did not differ between diet groups but trial type had a significant effect on RTs. Ignoring distracting stimuli was associated with longer RTs compared to the respective control, $p < .001$; updating working memory representations was associated with shorter RTs compared to the respective control, $p < .001$. Squares represent the statistical mean and error bars represent 95 % confidence intervals.

Figure 4. Association of BMI with WM accuracy. Higher BMI was significantly associated with lower overall accuracy on the WM task ($p_{corrected} = .047$). Separated by four task conditions, BMI was negatively associated with accuracy on ignore, z = -

2.20, OR = .77, p = .028, control long, z = -2.80, OR = .71, p = .005, and control short trials, z = -2.67, OR = .71, p = .008, but not with accuracy on update trials, z = -1.22, OR = .86, p = .223.

Figure 5. Significant voxels for the contrast update minus ignore (p < .05 (FWE-corrected)). **A.** Percent signal change for ignore and update trials in the left putamen. Update trials induced higher positive signal change; this signal change did not differ between diet groups. **B.** Percent signal change for ignore and update trials in the right putamen. Update trials induced higher positive signal change; this signal change did not differ between diet groups. Error bars represent 95 % confidence intervals.

Figure 6. Significant voxels for the contrast ignore minus update (p < .05 (FWE-corrected)). **A.** and **B.** Percent signal change in the left and right middle frontal gyrus was significantly lower for update compared to ignore trials. **C.** and **D.** Percent signal change was negative in ignore and update trials, but significantly lower in update trials in both clusters within the left superior frontal gyrus. Percent signal change did not differ between groups in any of the clusters. Error bars indicate 95 % confidence intervals.

Supplementary Material

Supplementary table S1

Overview of all clusters with significant neural activation for updating and distractor-resistance of working memory on the whole-brain level.

Contrast	Brain region	Cluster extent	t	p-value (FWE-corrected, peak-level)	MNI coordinates (x y z)
UPDATE > IGNORE	Right middle occipital gyrus	33962	15.47	.000	34 -86 12
	Left inferior frontal gyrus, opercular	2016	11.56	.000	-48 8 28
	Right inferior frontal gyrus, triangular	267	9.48	.000	48 36 10
	Right insula	123	8.49	.000	-20 -40 -44
	Calcarine fissure	131	7.88	.000	20 -40 -44
	Right precentral gyrus	94	7.45	.000	20 36 -18
	Left inferior frontal gyrus, triangular	294	7.05	.000	-48 36 12

	Left superior frontal gyrus	72	6.44	.000	-24 32 -16
	Left insula	23	5.64	.001	-34 -6 14
IGNORE > UPDATE	Left inferior parietal gyrus	2393	11.52	.000	-56 -54 38
	Right supramarginal gyrus	1853	9.47	.000	60 -44 40
	Left precuneus	1515	8.39	.000	-6 -54 44
	Left superior frontal gyrus, medial	63	5.56	.001	-4 34 48
	Left medial temporal gyrus	43	5.42	.003	-54 2 -32
	Left middle frontal gyrus	68	5.39	.003	-38 18 44
	Left superior frontal gyrus, medial	23	5.08	.010	-6 46 28

	Right middle cingulate cortex	12	5.07	.011	2 -18 38
	Right middle frontal gyrus	10	4.79	.030	42 20 42

Supplementary table S2

Descriptive statistics for the individual diet groups and comparative statistics (Welch's t-test, if not indicated otherwise)

	LFS N = 45		HFS N = 41		
variable	Mean (SD)	range	Mean (SD)	range	*p*-value
Age [years]	26.6 (4.5)	18-36	26.9 (4.5)	20-40	.811
BMI [kg/m^2]	24.2 (2.7)	19.7-30.0	23.8 (2.9)	18.6-36.4	.512
Non-verbal IQ	109.1 (7.8)	91-118	109.2 (6.7)	91-118	.957
Blood parameters					

Total cholesterol [mmol/l]	4.3 (0.7)	2.9-6.2	4.31 (0.7)	2.7-6.5	.857
LDL [mmol/l]	2.7 (0.7)	1.4-4.2	2.6 (0.7)	1.2-4.3	.565
HDL [mmol/l]	1.5 (0.3)	0.9-2.2	1.5 (0.3)	1.0-2.7	.165
Triglycerides [mmol/l]	1.1 (0.6)	0.4-2.9	1.1 (0.6)	0.4-3.7	.979
Glucose [mmol/l]	5.2 (0.4)	4.2-6.3	5.3 (0.4)	4.5-6.7	.217
HbA1c [mmol/mol]	32.2 (3.0)	22.8-37.2	33.3 (2.5)	28.3-37.9	.078
Leptin [ng/ml]	3.0 (2.7)	0.2-12.8	3.1 (2.1)	0.2-9.6	.784
Insulin [pmol/L]	36.2 (27.6)	8.5-132.3	31.3 (16.4)	14.1-78.4	.318
HOMA-IR	1.4 (1.1)	0.3-5.0	1.3 (0.7)	0.5-3.2	.433
IL-6 [pg/ml]	2.7 (0.9)	2.5-8.8	2.9 (1.5)	2.5-11.3	.386
Hs CRP [mg/L]	0.9 (1.4)	0.2-6.5	0.9 (1.5)	0.2-8.2	.976
TNF-α [pg/ml]	0.7 (0.2)	0.4-1.4	0.7 (0.2)	0.4-1.5	.656

Questionnaires					
DFS	44.3 (4.3)	33-52	71.1 (8.7)	62-97	< .001***
EDE-Q	0.6 (0.6)	0.0-2.9	0.5 (0.6)	0.0-2.4	.746
NEO-FFI					
Openness	3.0 (0.3)	2.3-3.8	3.0 (0.4)	2.3-4.8	.759
Conscientiousness	3.6 (0.4)	2.5-4.2	3.6 (0.4)	2.8-4.3	.611
Extraversion	3.5 (0.6)	2.0-4.8	3.5 (0.5)	2.5-4.3	.751
Agreeableness	2.5 (0.5)	1.5-4.2	2.6 (0.6)	1.5-3.7	.396
Neuroticism	2.0 (0.7)	1.0-3.7	2.3 (0.7)	1.0-3.5	.042*
UPPS					
Urgency	23.5 (4.6)	12-35	25.2 (4.8)	15-34	.108
Premeditation	22.8 (4.7)	13-31	21.7 (4.2)	15-34	.230

Perseverance	19.0 (4.9)	12-33	19.7 (4.6)	10-31	.548
Sensation Seeking	35.4 (6.7)	21-48	35.9 (6.5)	21-47	.736
BIS-15					
Non-planning impulsivity	10.4 (2.8)	5-16	10.7 (3.1)	5-16	.687
Motor impulsivity	10.5 (2.6)	6-16	10.9 (2.7)	6-18	.481
Attentional impulsivity	9.2 (2.1)	6-13	9.4 (2.7)	5-16	.653
BIS/BAS					
BIS	18.1 (3.2)	9-25	18.54 (3.8)	12-26	.575
BAS Fun Seeking	12.2 (2.1)	8-16	11.9 (2.0)	7-16	.583
BAS Drive	12.1 (1.9)	8-15	11.9 (2.2)	7-16	.639
BAS Reward Responsiveness	16.4 (1.8)	12-19	16.1 (2.0)	12-20	.397

TFEQ					
Cognitive restraint	7.0 (4.0)	2-20	4.3 (3.0)	0-12	< .001***
Hunger	2.9 (2.5)	0-10	4.8 (3.0)	0-10	.002**
Disinhibition	3.6 (2.6)	0-14	4.4 (2.9)	0-11	.184
FCQ-T					
Total craving	68.0 (20.9)	39-127	78.9 (27.9)	46-146	.046*
Food cue reactivity	9.9 (3.7)	4-20	12.2 (4.2)	5-23	.010**
Reinforcing value	15.2 (6.4)	8-34	18.6 (7.8)	8-39	.035*
Emotions	6.0 (2.2)	4-15	7.0 (3.8)	4-20	.114
Hunger	9.1 (3.6)	4-18	10.2 (3.8)	4-20	.174
Lack of controls/intentions	14.5 (5.6)	9-29	16.2 (6.9)	9-34	.218

Thoughts/guilt	13.3 (4.8)	10-33	14.8 (6.3)	10-33	.225
mYFAS 2.0					
Number of symptoms	0.2 (0.6)	0-2	0.3 (1.0)	0-6	.799
Genetics and DA proxies					
pDAP availability	0.3 (0.1)	0.2-0.4	0.3 (0.1)	0.27-0.4	.073
Working memory capacity[1]	5.36 (1.17)	3-8	5.46 (1.33)	3-8	.691
Genotype frequencies	balanced	unbalanced	balanced	unbalanced	
	N = 16	N = 29	N = 21	N = 20	. 212[a]
Physical activity					

MET-minutes	Median (interquartile range) 2820 (3189)	0-15887.4	Median (interquartile range) 2839.5 (1989)	82.5-9039	.114[b]
Step count [steps/day]	7010.5 (2995.3)	592.6-15767.7	6768.9 (2536.3)	1844.7-11914.4	.697

[a] Pearson's chi-square test

[b] Mood's median test

[1] measured with the digit span backwards task

whole brain