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Self-reported intake of high-fat and high-sugar diet is not associated with cognitive stability and flexibility in healthy men

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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 **1 Introduction**

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

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

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

37 In our previous study we did not find baseline differences in complex working
38 memory span between diet groups. Thus, we aimed to specifically investigate
39 subprocesses of working memory: (1) to maintain mental representations of goal-
40 relevant information in the face of distracting sensory input (stability) whilst (2)
41 simultaneously enabling these representations to be updated (flexibility). Dopamine
42 has been proposed to modulate the gating and distractor-resistant maintenance of
43 working memory representations (Chatham et al., 2014; Hazy et al., 2007). Using a
44 pharmacological intervention, Bloemendaal and colleagues could provide evidence
45 that DRD2 activation impaired distractor-resistance (Bloemendaal et al., 2015).

46 Fallon and Cools developed a version of the classical delayed match-to-sample
47 working memory paradigm that specifically probed stability and flexibility of working
48 memory representations. Stability in this task was associated with increased BOLD
49 signal in the PFC and flexibility with increased BOLD signal in the dorsal striatum

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

60 While environmental factors like HFS might be able to modulate the human
61 dopaminergic system, its baseline setup is likely shaped by variations in our genes.
62 The catechol-O-methyltransferase (COMT) is important for dopaminergic activity in
63 the prefrontal cortex and carrying the Val-allele of the COMT Val¹⁵⁸Met
64 polymorphism was found to reduce prefrontal dopamine levels in contrast to the Met-
65 allele (Chen et al., 2004; Slifstein et al., 2008). The DRD2/ANKK1 Taq1A
66 polymorphism has been linked to striatal D2 receptor availability. Carrying the Taq1A
67 A1 allele was associated with significantly reduced DRD2 density and binding in the
68 striatum (Eisenstein et al., 2016; Jönsson et al., 1999; Pohjalainen et al., 1998).
69 Both, the COMT Val¹⁵⁸Met and Taq1A single nucleotide polymorphism (SNP) have
70 been related to measures of working memory and cognitive stability and flexibility
71 (Berryhill et al., 2013; Fallon et al., 2013; Joobar et al., 2002; Naef et al., 2017;
72 Nymberg et al., 2014; Xu et al., 2007). In addition, it has been hypothesized that
73 COMT Val¹⁵⁸Met and Taq1A mediate possible effects of HFS on dopamine-related
74 cognition. COMT Val¹⁵⁸Met genotype modulated the improving effects of

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

79 In the present study we investigated the association of HFS with stability and
80 flexibility of working memory representations and tested whether genetic
81 predisposition poses a risk factor for potential HFS effects. To this end, we grouped
82 participants into low (LFS) and high (HFS) consumers based on self-reported HFS
83 intake and assessed COMT Val¹⁵⁸Met and Taq1A genotype. Participants then
84 completed a working memory task probing dopamine-dependent stability and
85 flexibility inside an MRI scanner. We hypothesized that stability and flexibility will
86 differ between LFS and HFS, and that this difference is modulated by COMT
87 Val¹⁵⁸Met or Taq1A genotype. The putative association of HFS with working memory
88 was expected to parallel diet-related differences in striatal and prefrontal BOLD
89 signal during task execution.

90 **2 Material and Methods**

91 **2.1 Participants**

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

98 performance in women (Hampson & Morley, 2013; Jacobs & D'Esposito, 2011) and could
99 mask potential diet-associated effects. In total 142 participants were invited to the
100 research facilities to complete a screening for study eligibility (**Fig. 1**). Ninety-nine of
101 those 142 participants were eligible – meaning they were either classified as low or
102 high consumers of HFS, medium consumers were excluded (see 2.2 Study design
103 for details) – and enrolled in the study. Eighty-six participants (Age: $M = 26.8$ years,
104 $SD = 4.7$, range = 18–40 years; BMI: $M = 24.0$ kg/m², $SD = 2.80$, range = 18.6–36.4
105 kg/m²; IQ: $M = 109.2$, $SD = 7.3$, range = 91–118) completed the study; 13
106 participants dropped out voluntarily or were excluded post hoc for elevated thyroid
107 hormone levels. Out of the 86 participants that represent the final sample 45
108 belonged to the low fat/sugar (LFS) group and 41 belonged to the high fat/sugar
109 (HFS) group; the two groups were matched for age (LFS: $M = 26.6$ years, $SD = 4.5$,
110 range = 18–36 years; HFS: $M = 26.9$ years, $SD = 4.5$, range = 20–40 years), BMI
111 (LFS: $M = 24.2$ kg/m², $SD = 2.7$, range = 19.7–30.0 kg/m²; HFS: $M = 23.8$ kg/m², SD
112 = 2.9, range = 18.6–36.4 kg/m²) and IQ (LFS: $M = 109.1$, $SD = 7.8$, range = 91–118;
113 HFS: $M = 109.2$, $SD = 6.7$, range = 91–118). All participants were omnivores or
114 vegetarians, and none followed a special dietary regime like low-carb, gluten-free, or
115 paleo diet. None of the participants reported a history of clinical drug or alcohol
116 abuse or neurological or psychiatric disorders or had a first-degree relative history of
117 neurological or psychiatric disorders. None showed moderate or severe depressive
118 symptoms assessed by the Beck Depression Inventory (BDI)(Beck et al., 1996;
119 Kühner et al., 2007), indicated by total scores ≤ 20 , or signs of eating disorders
120 assessed by the Eating Disorder Examination Questionnaire (EDE-Q)(A. Hilbert et
121 al., 2007; Mond et al., 2004). All included participants were considered healthy with
122 respect to glucose metabolism and thyroid function.

123 2.2 Study design

124 This study was part of a larger project investigating the possible association of HFS
125 intake with changes in the human dopaminergic system and alterations of behavior
126 and decision-making. The detailed study protocol for this project can be found under
127 <https://osf.io/w9e5y>. Participants were invited to the lab on three occasions, the first
128 of which was a screening day including blood drawings after an overnight fast,
129 anthropometric measurements, BDI and EDE-Q, and assessment of non-verbal IQ
130 by the Viennese Matrices Test (Formann et al., 2011). We used an extreme group
131 design, in which participants were assigned to the low fat/sugar (LFS) or high
132 fat/sugar (HFS) group based on their score on the Dietary Fat and free Sugar
133 Questionnaire (DFS)(Francis & Stevenson, 2013; Fromm & Horstmann, 2019). The LFS
134 group consisted of participants with a total DFS score ≤ 52 , the HFS group consisted
135 of participants with a total DFS score ≥ 62 . Cutoff scores were defined *a priori* based
136 on previous work and represent the lowest and highest quartile of DFS score
137 distributions (Fromm & Horstmann, 2019). After the screening participants took part in
138 two separate test sessions: one behavioral and one MR session; the order of
139 behavioral and MR session was counterbalanced within groups. Screening and first
140 test session could be on consecutive days, first and second test session were at
141 least two days apart (days between screening and 1st session: $M = 8.1$ days, $SD =$
142 6.3 , range = 1–43 days; days between 1st and 2nd session: $M = 11.4$ days, $SD =$
143 13.1 , range = 2–70 days). Here we only focus on the working memory task, which
144 was performed during the MR session inside a 3T MRI scanner. During that same
145 session as well as the behavioral session participants completed questionnaires
146 regarding personality traits, motivation, impulsiveness, eating behavior, and physical
147 activity. Furthermore, participants performed the verbal forward and backward digit

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

151 **2.3 Delayed match-to-sample working memory task**

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

172 following probe. As in other studies, we included two extra conditions to account for
173 temporal confounds in ignoring and updating (Fallon et al., 2018; Fallon, Mattiesing,
174 et al., 2017). The two control conditions required memorizing only one pair of target
175 stimuli without updating or ignoring interfering stimuli and were included to control for
176 the difference in temporal delay between viewing target stimuli and evaluating the
177 probe in the ignore and update conditions. The control short condition matched the
178 temporal delay between presentation of the to-be-remembered target stimuli and the
179 probe in the update condition (2000–6000 ms) by presenting a fixation cross in the
180 encoding phase and a pair of target stimuli in the interference phase. The control
181 long condition matched the temporal delay between target and probe of the ignore
182 condition (6000–14000 ms) by presenting a pair of target stimuli in the encoding
183 phase and a fixation cross in the interference phase. Stimuli and fixation cross
184 remained on the screen for 2000 ms in both the encoding and interference phase.
185 Encoding, interference, and probe phase were each separated by a variable delay of
186 2000 to 6000 ms.

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

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

200 **2.4 Blood measurements**

201 Measures of glucose and lipid metabolism, insulin sensitivity and leptin signaling
202 differ related to obesity and can affect the dopaminergic system (Berland et al.,
203 2016; Dunn et al., 2012). Blood samples collected on the screening day were hence
204 analyzed for markers of fat and sugar metabolism (total cholesterol, LDL and HDL,
205 triglycerides, glucose and long-term sugar marker glycated hemoglobin HbA1c) and
206 metabolic hormones insulin and leptin. Insulin resistance was calculated according to
207 the HOMA-index (Homeostasis Model Assessment) using the formula: fasting insulin
208 (microU/L) x fasting glucose (nmol/L)/22.5 (Matthews et al., 1985). Interleukin 6 (IL-
209 6), tumor necrosis factor alpha (TNF- α) and high sensitivity C-reactive Protein (hs
210 CRP) were determined as markers for systemic inflammation, which was shown to
211 modulate dopamine signaling (Petrulli et al., 2017). Furthermore, in line with our
212 previous study (Hartmann et al., 2020), we measured peripheral levels of dopamine
213 precursor amino acids phenylalanine and tyrosine and large neutral amino acids
214 (methionine, valine, leucine, isoleucine, lysine, threonine and tryptophan). The ratio
215 of phenylalanine and tyrosine to the large neutral amino acids represents the
216 peripheral dopamine precursor (pDAP) availability and can be considered a putative
217 proxy for central dopamine levels (Leyton et al., 2004; Montgomery et al., 2003). All
218 blood measures were analyzed at the Institute for Laboratory Medicine, Leipzig,
219 Germany. To assess genetically determined variation in central dopamine
220 transmission we determined COMT Val¹⁵⁸Met and Taq1A genotype in our sample.

221 Analysis of these SNPs was performed in the lab for 'Adiposity and diabetes
222 genetics' at the Medical Research Center, University Leipzig, Leipzig, Germany. For
223 all statistical analyses including COMT Val¹⁵⁸Met participants were grouped into
224 Val/Val, Val/Met, or Met/Met allele combinations. Because the frequency of the
225 Taq1A A1 allele is low in the general population, we grouped A1 homozygotes and
226 A1/A2 heterozygotes as A1-carriers in contrast to non-carriers (Noble, 2003).

227 **2.5 Questionnaires**

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

234 **2.5.1 Screening Questionnaires**

235 The Dietary Fat and Free Sugar Questionnaire (DFS) is a self-report questionnaire
236 assessing the frequency of diet items high in saturated fat and refined sugars taken
237 in over the last twelve months (Francis & Stevenson, 2013). The Eating Disorder
238 Examination Questionnaire (EDE-Q) is the self-report version of the Eating Disorder
239 Examination interview and assesses eating disorder pathologies (A. Hilbert et al.,
240 2007; Mond et al., 2004). We considered exclusion of participants above a total
241 score of 3.9 (mean + 2 SD for a healthy German population (A. Hilbert et al., 2012)),
242 but none of the participants scored above this cut-off.

243 **2.5.2 Personality, motivation, and impulsivity**

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

260 **2.5.3 Eating behavior and food addiction**

261 The three factors of eating behavior (cognitive restraint, hunger and disinhibition)
262 were assessed by the Three Factor Eating Questionnaire (TFEQ)(Pudel & Westhöfer,
263 1989; Stunkard & Messick, 1985). The Food Craving Questionnaire Trait (FCQ-T)
264 measures the general frequency and intensity of food craving experiences (Cepeda-
265 Benito et al., 2000). The German version can further be divided into six subscales
266 assessing hunger, reactivity to food cues, rewarding value of food, lack of control
267 and intentions to eat, thoughts and guilt, and emotions (Meule et al., 2012). Finally,

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

270 **2.5.4 Physical activity**

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

280 **2.6 Neuropsychological tests**

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

291 **2.7 Data analysis**

292 **2.7.1 Behavioral analysis**

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

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

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

313

314 To test our secondary hypothesis that dopaminergic gene variants modulate dietary
315 effects we augmented model 1 with the between subject factors COMT Val¹⁵⁸Met
316 (model 2a) or Taq1A genotype (model 2b).

317 (2a) *performance* ~ *diet * delay * interference * COMT + digit span + (1|participant)*

318 (2b) *performance* ~ *diet * delay * interference * Taq1A + digit span + (1|participant)*

319

320 To test how pDAP availability is related to task performance we included mean-
321 centered values for pDAP availability as continuous factor, delay and interference as
322 within-subject factors, and the main effect of diet to control for. Because pDAP
323 availability and BMI were found to be weakly positively correlated, $r(84) = .22$, $p =$
324 $.044$, we included BMI as covariate.

325 (3) *performance* ~ *pDAP * delay * interference + digit span + diet + BMI +*

326 *(1|participant)*

327

328 Finally, we investigated how BMI was associated with working memory flexibility and
329 stability, by including mean-centered BMI as a continuous factor, delay and
330 interference as within-subject factors, and the main effect of diet to control for.

331 Similar to model 3, we included pDAP availability as covariate to account for the
332 correlation with BMI.

333 (4) *performance* ~ *BMI * delay * interference + digit span + diet + pDAP +*

334 *(1|participant)*

335

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

341 **2.7.2 Descriptive analysis**

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

352 **2.7.3 Functional brain imaging**

353 Scans were conducted on a Siemens 3T Skyra magnet resonance imaging system.
354 The structural sequence was a T1-weighted MP2RAGE (magnetization prepared two
355 rapid gradient echo), 192 slices (interleaved), 1.0 x 1.0 x 1.0 mm voxel size, field of
356 view = 256 mm, flip angles $\alpha_1 = 4^\circ$, $\alpha_2 = 6^\circ$, retention time = 7000 ms, inversion time
357 1 = 945 ms, inversion time 2 = 3770 ms. The functional scan sequence was a T2*-

358 weighted less voids EPI (echo-planar imaging) sequence, multiband (multi-band
359 factor 3), 60 slices (interleaved), 2.5 x 2.5 x 2.5 mm voxel size, 0.25 mm interslice
360 gap, field of view = 204 mm, flip angle $\alpha = 80^\circ$, retention time = 2000 ms, echo time =
361 22 ms. Participants were scanned using a 32-channel head coil.

362 **2.7.4 fMRI preprocessing**

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

372 **2.7.5 Imaging data analysis**

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

381 update (to-be-updated stimuli during interference phase) and ignore (to-be-ignored
382 stimuli during interference phase). To choose the first-level model which best
383 explains the functional data we ran two first-level models with varying complexity on
384 a random subsample of 30 participants and compared their model fit on the group
385 level using the MACS toolbox for SPM (Soch & Allefeld, 2018). In brief, this toolbox
386 provides a common pipeline for cross-validated Bayesian model selection. The
387 output is a selected-model map for each model subjected to the comparison, which
388 shows those voxels where the respective model has the highest likeliest frequency to
389 explain the data best. BOLD activations were modeled by convolution of the task
390 regressors with the SPM-default canonical response, high-pass filtering (128 s), and
391 first-order autoregressive error structure. Both models contained task regressors for
392 the onsets of the following task events: initial encoding stimuli (ignore, update, and
393 long no-interference) all under one regressor, to-be-updated stimuli, to-be-ignored
394 stimuli, fixation cross during the interference phase (long no-interference), encoding
395 stimuli during interference phase (short no-interference), probe event, and the
396 feedback screen; the fixation cross during the encoding phase (short no-
397 interference) and delay periods were left unmodelled. Next to these task regressors
398 the simpler model contained six nuisance regressors for the six realignment
399 parameters extracted from preprocessing to account for head motion. The more
400 complex model contained 24 nuisance regressors instead: the six realignment
401 parameters included in the simpler model, the square of these realignment
402 parameters, the first derivate of these realignment parameters, and the realignment
403 parameters used to realign the previous volume to account for spin-history effects
404 (Friston et al., 1996). The more complex model including 24 nuisance regressors
405 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 Val¹⁵⁸Met and Taq1A with diet we ran two additional full factorial models similar to
418 the main model augmented by the factor COMT Val¹⁵⁸Met 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

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

442 **3 Results**

443 **3.1 HFS diet is not significantly associated with altered working memory** 444 **stability and flexibility**

445 Our main model (model 1) revealed no differences in task accuracy between the LFS
446 and HFS group, nor any interaction of diet group with delay or interference (all
447 $p_{corrected} = 1$). The delay between viewing target stimuli and evaluating probes had a
448 significant effect on accuracy, revealing that accuracy was higher for both short-
449 retention period conditions (update ($M = .91$, $SD = .28$; and control short ($M = .92$,
450 $SD = .27$)), than for the long-retention period conditions (ignore ($M = .87$, $SD = .34$)
451 and control long ($M = .88$, $SD = .32$), $\chi^2(1) = 60.50$, $OR = 1.29$ $p_{corrected} < .001$ (**Fig. 3**
452 **A**). The main effect of interference as well as the interaction between delay and
453 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 Val¹⁵⁸Met 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 Val¹⁵⁸Met) 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 Val¹⁵⁸Met 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 Val¹⁵⁸Met 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-

478 carrier). The genotype distribution for Taq1A was in Hardy-Weinberg Equilibrium,
479 $\chi^2(1) = 2.64, p = .105$. Chi-square tests revealed no diet group differences in the
480 distribution of COMT Val¹⁵⁸Met, $\chi^2(2) = .34, p = .844$, and Taq1A genotypes, $\chi^2(1) =$
481 $.57, p = .449$. The interaction between COMT Val¹⁵⁸Met and diet group as well as all
482 higher order interactions with delay and interference were not significantly
483 associated with accuracy or RTs (all corrected p -values $> .276$). Furthermore, neither
484 the main effect of COMT Val¹⁵⁸Met nor the two- or three-way interactions with delay
485 and interference were significantly associated with accuracy or RTs (all corrected p -
486 values $> .458$). The interaction between Taq1A and diet group as well as all higher
487 order interactions with delay and interference were not significantly associated with
488 accuracy or RTs (all corrected p -values = 1). Furthermore, neither the main effect of
489 Taq1A nor the two- or three-way interactions with delay and interference were
490 significantly associated with accuracy or RTs (all corrected p -values = 1).

491 **3.3 The availability of pDAP was not significantly associated with working** 492 **memory stability and flexibility**

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

497 **3.4 BMI is associated with overall lower accuracy on the working memory task**

498 Model 4 investigated the association of BMI with working memory stability and
499 flexibility. One participant with a BMI of 36.4 kg/m² was identified as a statistical
500 outlier and excluded from this analysis. Higher BMI was significantly associated with

501 overall lower accuracy on the working memory task, $\chi^2(1) = 6.76$, $OR = .76$, $p_{corrected}$
502 $= .047$ (**Fig. 4**). *Post hoc* analysis of regression slopes for each of the four task
503 conditions revealed that BMI was negatively associated with accuracy on ignore, $z =$
504 -2.20 , $OR = .77$, $p = .028$, control short, $z = -2.67$, $OR = .71$, $p = .008$, and control
505 long trials, $z = -2.80$, $OR = .71$, $p = .005$, but not with accuracy on update trials, $z = -$
506 1.22 , $OR = .86$, $p = .223$. This main effect of BMI was non-significant for RTs ($p_{corrected}$
507 $= 1$). BMI did not interact significantly with delay and interference for accuracy or RTs
508 (all corrected p -values $> .404$). To control for confounding effects of decreased
509 attention during the long test day, we assessed participants' tiredness and focus
510 during the task with a ten-point likert scale after they returned from the MRI scanner.
511 BMI did neither correlate with tiredness, $r(84) = .04$, $p = .719$, nor focus, $r(84) = .01$,
512 $p = .939$.

513 **3.5 No evidence that diet group affects striatal and prefrontal BOLD signal** 514 **during working memory stability and flexibility**

515 To confirm that we find the BOLD signal changes associated with working memory
516 stability and flexibility as in previous studies, we looked at the contrast update vs
517 ignore in the entire sample. Consistent with previous reports (Fallon, van der Schaaf, et
518 al., 2017; Fallon & Cools, 2014), updating relative to ignoring significantly increased
519 BOLD signal in the left and right dorsal striatum and the right thalamus as well as
520 occipital and temporal gyri (**Fig. 5**). Comparing percent signal change within the left
521 and right putamen revealed that this difference between task conditions was caused
522 by positive signal change in update trials compared to ignore trials. Percent signal
523 change within the dorsal striatum in both conditions did not differ between diet
524 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 Val¹⁵⁸Met 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	Left inferior parietal gyrus	1519	11.5	.000	-56 -54 38
>			2		
UPDATE	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
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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 Val¹⁵⁸Met 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

639 memory span, could have made subtle group differences surface. We indeed did
640 observe the expected task effects on behavioral performance (RT, accuracy).
641 Furthermore, our imaging results support the finding from previous studies in
642 indicating that resistance against distracting information and the flexible updating of
643 relevant information recruit different nodes within fronto-striatal circuits (Fallon, van
644 der Schaaf, et al., 2017; Fallon & Cools, 2014). Several factors could explain why the
645 hypothesized differences between the diet groups did not surface. First, in our male
646 sample we could not replicate the higher relative peripheral availability of dopamine
647 precursors that was associated with a high intake of saturated fat and sugar in
648 women (Hartmann et al., 2020). The ratio of the dopamine precursors, tyrosine and
649 phenylalanine, to the other large neutral amino acids has been shown to affect
650 central dopamine levels (Leyton et al., 2004; Montgomery et al., 2003). Although
651 indirect and preliminary, this finding was the most direct evidence to date for
652 dopamine differences related to regular dietary intake of fat and sugars in humans. It
653 could be that the groups in the current, all-male sample simply did not differ as much
654 in their underlying dopamine system as the previous all-female sample. It has been
655 shown that women have higher presynaptic dopamine synthesis capacity and
656 endogenous striatal dopamine than men (Laakso et al., 2002; Pohjalainen et al.,
657 1998) – such baseline differences could modulate the effect HFD has on the
658 dopaminergic system in a sex dependent manner. Indeed, one study showed that
659 male and female mice differed not only in the extent to which a high-fat diet altered
660 gene expression of proteins involved in dopamine signal transmission but also
661 dopamine levels in the striatum and PFC (Carlin et al., 2013). Sex specific effects of
662 HFD on dopamine-dependent cognition have neither been investigated in animals
663 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)).

737 **4.2 Dopaminergic gene variants do not seem to predispose individuals to**
738 **possible diet effects**

739 Although we found no conclusive evidence that COMT Val¹⁵⁸Met or Taq1A genotype
740 predisposed individuals for the hypothesized detrimental effects of an HFS on
741 working memory performance and the underlying neural circuitry, our null findings
742 cannot rule out this possibility. As outlined above, our assessment of HFS and LFS
743 based on self-reported food intake might not be accurate enough to obtain
744 experimental groups that show pronounced diet effects. After all, using a three-
745 month dietary intervention, Witte and colleagues could provide evidence that
746 cognition-enhancing effects of unsaturated fatty acids depended on COMT Val¹⁵⁸Met
747 genotype (Witte et al., 2010). Interestingly, we did not see a main effect of COMT
748 Val¹⁵⁸Met or Taq1A on behavioral as well as neural measures of working memory
749 stability and flexibility though they have been associated with related cognitive
750 processes previously. In a population of healthy older adults, Met-homozygotes
751 showed heightened dorsolateral PFC activation and increased set-like behavior, a
752 process related to cognitive stability and flexibility (Fallon et al., 2013). Joober and
753 colleagues found that patients with schizophrenia and homozygous for the Met-allele
754 performed better on a task of PFC-mediated executive function, but this genotype
755 effect was not observed in healthy controls (Joober et al., 2002). This finding
756 suggests that effects of COMT Val¹⁵⁸Met genotype might only emerge when the
757 prefrontal dopamine system is dysregulated as it is the case in schizophrenia
758 (Winterer & Weinberger, 2004). As our study sample consisted of young healthy
759 participants such a dysregulation is highly unlikely but short-term dietary
760 interventions might be able to tip healthy participants into this direction and uncover
761 predisposing effects of COMT Val¹⁵⁸Met. 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

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

807 **4.4 Differences in eating behavior do not seem to be related to working**
808 **memory stability and flexibility**

809 The two diet groups did not differ in parameters of lipid and glucose metabolism, but
810 also not in the availability of pDAP – in contrast to our prediction. Based on our
811 previous study, we expected to see higher pDAP availability in the HFS group
812 (Hartmann et al., 2020). Personality traits, motivation, impulsivity, or physical activity
813 did also not differ between diet groups, except for higher neuroticism in the HFS
814 group, which is in line with previously reported results (Hartmann et al., 2020).
815 Nevertheless, this difference in neuroticism does not seem to be associated with
816 working memory. Furthermore, the diet groups differed with respect to eating
817 behavior. As reported previously, the HFS group indicated higher signs of hunger
818 and lower cognitive restraint (Hartmann et al., 2020). This finding suggests that the
819 amount of HFS consumed is a consequence of those eating habits (de Lauzon et al.,
820 2004). Using a different version of the TFEQ, Calvo and colleagues could relate
821 uncontrolled eating with reduced working memory (Calvo et al., 2014). The causal
822 mechanism behind this could be that uncontrolled eating and working memory share
823 cognitive processes or that uncontrolled eating leads to increased HFS intake, which
824 in turn alters working memory (based on the animal literature). To shed more light on
825 this causal relationship we propose to include measures of eating behavior in future
826 studies applying HFS interventions. In addition to eating behavior assessed by the
827 TFEQ, the HFS group reported higher overall food cravings, higher reactivity to food
828 cues and higher reinforcing value of food. This finding supports the assumption that
829 increased HFS intake is a consequence of eating habits and traits.

830 **5 Conclusion**

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

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

843 **6 Transparency statement**

844 This study was preregistered after data collection but before data analysis. A
845 preregistration describing the collection of data presented in this article as well as
846 additional data presented elsewhere can be found under <https://osf.io/w9e5y>.
847 Detailed information about the research question, study design, and proposed data
848 analysis plan for this this study can be found under <https://osf.io/8gtfk>. We deviated
849 from the detailed preregistered analysis plan in a few points and explain why, but
850 also report the results of those analyses for complete transparency (if applicable). In
851 the study-specific preregistration we state recoding COMT and Taq1A polymorphism
852 according to the equilibrium model, which proposes interaction effects of these two
853 SNPs based on a balance between striatal DRD2 density and COMT activity in the
854 prefrontal cortex (Reuter et al., 2006). Following this model Taq1A genotypes are
855 grouped according to the presence of the minor A1 allele into A1+ (A1 carriers, i.e.
856 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 Val¹⁵⁸Met 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

882 prefrontal cognition in children and adolescents with ADHD, whereas carrying the
883 Val allele was associated with higher error rate in healthy participants (Bellgrove et
884 al., 2005; Caldú et al., 2007). Since the COMT Val158Met polymorphism has not
885 been studied with respect to neither HFS diet nor cognitive stability and flexibility as
886 measured by a paradigm like the one used here, we could not exclude a possible
887 dosage effect or make assumptions about which allele might drive an effect. For
888 these reasons we decided to look at the effects of COMT Val¹⁵⁸Met and Taq1A
889 independently and without any a priori assumptions of allelic effects. Nevertheless,
890 we ran the preregistered analyses and report the results in brief. The state of the
891 dopaminergic system according to the equilibrium model did not interact with intake
892 of HFS diet with respect to task accuracy or RT but had a main effect on those
893 measures. Balanced individuals (Val+/A1+ and Val-/A1-) had higher accuracy ($M =$
894 $.92$, $SD = .28$) than individuals with an unbalanced genotype ($M = .89$, $SD = .32$),
895 $\chi^2(1) = 4.57$, $p = .033$, and shorter RT ($M = 918.34$, $SD = 149.46$) than unbalanced
896 participants ($M = 983.06$, $SD = 154.88$), $\chi^2(1) = 4.12$, $p = .042$. Similar to our analysis
897 with individual COMT Val¹⁵⁸Met and Taq1A genotypes, genotypes according to the
898 equilibrium model were not associated with neural activation during ignore and
899 update and did not interact with HFS diet.

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

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

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921 **Authors contributions**

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

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

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942 **Data availability**

943 The data presented in this study are available on request from the corresponding
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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	11.5 2	.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)

variable	LFS N = 45		HFS N = 41		p-value
	Mean (SD)	range	Mean (SD)	range	
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