Impaired updating of working memory representations in individuals with high BMI: evidence for dopaminergic mechanisms

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Abstract

Everyday life requires an adaptive balance between distraction-resistant maintenance of information and the flexibility to update this information when needed. These opposing mechanisms are proposed to be balanced through a working memory gating mechanism. Prior research indicates that obesity may elevate the risk of working memory deficits, yet the underlying mechanisms remain elusive. Dopaminergic abnormalities have emerged as a potential mediator. However, current models suggest these abnormalities should only shift the balance in working memory tasks, not produce overall deficits. The empirical support for this notion is currently lacking, however. To address this gap, we pooled data from three studies (N = 320) where participants performed a working memory gating task. Higher BMI was associated with overall poorer working memory, irrespective of whether there was a need to maintain or update information. However, when participants, in addition to BMI level, were categorized based on certain putative dopamine-signaling characteristics (Single Nucleotide Polymorphisms; specifically, Taq1A and DARPP), distinct working memory gating effects emerged. These SNPs, primarily associated with striatal dopamine transmission, specifically influenced updating in high-BMI individuals. Moreover, blood amino acid ratio, which indicates central dopamine synthesis capacity, combined with BMI, shifted the balance between distractor-resistant maintenance and updating. These findings suggest that both dopamine-dependent and dopamine-independent cognitive effects exist in obesity. Understanding these effects is crucial if we aim to modify maladaptive cognitive profiles in individuals with obesity.

INTRODUCTION

In order to function efficiently in a dynamic environment, we must be able to resist distractions while simultaneously being open to update information in response to evolving goals and task requirements. This tension demands a delicate balance, which is thought to be governed by one of our core cognitive control systems - our working memory (WM). Computational and neurophysiological theories propose a metaphorical "gate" that regulates the access to WM (Badre, 2012; O'Reilly and Frank, 2006). When the gate is closed, WM representations are isolated from perceptual input and interference is prevented. When the gate is opened, rapid updating is allowed. Evidence strongly implicates the prefrontal cortex (PFC) in distractor-resistant maintenance, while updating is thought to be supported by the striatum (Miller and Cohen, 2001; D'Ardenne et al., 2012; Braver and Cohen, 2000). Importantly, the neurotransmitter dopamine plays a crucial role in balancing these complementary processes. Within the PFC, tonic dopamine levels mediate maintenance in an inverted-U-shaped manner: very high and very low levels promote gate opening, while medium levels promote gate closing (Cools and D'Esposito, 2011). Within the striatum, phasic increases in dopamine are needed to signal WM updating (Hazy, Frank, and O'Reilly, 2006; D'Ardenne et al., 2012). Importantly, the effectiveness of the phasic rise in dopamine to override PFC tonic dopamine signals depends on the initial striatal tonic level (Cools and D'Esposito, 2011; Schouwenburg, Aarts, & Cools, 2010; Ranganath & Jacob, 2016). Decreases in tonic dopamine levels in the striatum seem to raise the threshold for updating signals, thus potentially hindering updating (O'Reilly and Frank, 2006). Supporting this, worse updating of WM contents can be observed in unmedicated patients with Parkinson's disease (Fallon et al. 2017), older individuals (Podell et al., 2012), or more generally, in individuals with lower dopamine synthesis capacity (Colzato et al., 2013). Notably, dominance in one process typically comes at the cost of the other (Dreisbach & Fröber, 2019; Dreisbach et al., 2005; Fallon and Cools, 2017). Consequently, an individual's capacity to ignore or update (ir)relevant information may vary according to their baseline dopamine levels (e.g. Cools & D'Esposito, 2011; Furman et al., 2021, Jongkees, 2020).

Interestingly, the intricate relationship between dopamine levels and working memory gating might be key in further understanding discrepancies in the literature regarding working memory functioning in obesity. While many studies show reduced (general) working memory in obese individuals (e.g., Yang et al., 2020, 2019, 2018; Gonzales et al., 2010; Coppin et al., 2014), there are others who do not find such associations (e.g., Calvo et al., 2014; Schiff et al., 2016; Alarcon et al., 2016). Based on the above considerations regarding how dopamine supports working memory gating, the failure to reliably find associations between obesity and working memory may be due to prior studies not clearly differentiating between distractor-resistance and updating in the context of working memory. This distinction may indeed be crucial, however, as emerging evidence suggests potential specific impairments in WM gating in obesity. For instance, obesity has been associated with lower dopamine tone (Horstmann et al., 2015), suggesting potential challenges in working memory updating, akin to other populations with diminished dopamine mentioned earlier. Moreover, functional and structural changes in WM gating-related brain areas (Wang et al., 2001; Volkow et al., 2012; Horstmann, 2017). Additionally, individuals with obesity consistently demonstrate a preference for immediate, short-term rewards despite negative long-term outcomes (Horstmann et al., 2011; Mathar et al., 2015), and a tendency to persist with previously rewarded actions despite current devaluation (Horstmann et al., 2015a).

Given the close relationship of such reward-learning processes and working memory (Collins & Frank, 2012), these behavioral patterns may reflect difficulties to update WM contents with new reward information, suggesting cognitive issues that extend beyond mere valuation impairments. However, there is currently a lack of empirical support for this interpretation. To address this gap in knowledge, the present study aims to examine potential obesity-dependent impairments in working memory gating. To this end, we pooled together data on Body-Mass-Index (BMI; kg/m²) and a working memory gating task from three different studies conducted in our lab. In light of the behavioral and neuropharmacological findings discussed above, we hypothesized that individuals with a high BMI would display worse updating, potentially offset by enhanced distractor-resistant maintenance.

Given dopamine's central role in WM gating, such behavioral patterns might be driven by the abnormal dopamine signaling observed in obesity (Horstmann et al., 2015). However, in addition to this, inherent predispositions with respect to dopamine signaling have been shown to further influence WM gating. In this context, several single-nucleotide polymorphisms (SNPs) related to dopamine transmission have garnered significant attention in recent years. For instance, Catechol-O-methyltransferase (COMT) Val158Met activity primarily influences dopamine breakdown in the PFC (Tunbridge et al., 2004; Sesack, Hawrylak, Matus, Guido, & Levey, 1998), and carrying the Met allele of this SNP is associated with reduced COMT activity, leading to higher synaptic dopamine levels (Bilder et al., 2004). Consistent with this, individuals with the Met allele tend to perform better on tasks that require stable maintenance of working memory representations compared to those with the Val allele (Berryhill et al., 2013; Farrell et al., 2012; Savitz, Solms, & Ramesar, 2006). Furthermore, the Taq1A polymorphism has been associated with D2 receptor density in the striatum. A-allele carriers of this polymorphism exhibit lower receptor density and show distinct performance patterns on tasks involving working memory updating (Pohjalainen et al., 1998; Jönsson et al., 1999; Eisenstein et al., 2016; Stelzel et al., 2010; Persson et al., 2015; Li et al., 2019). Interestingly, Taq1A and COMT have been demonstrated to interactively influence working memory functioning (Berryhill et al., 2013; Xu et al., 2007, Reuter et al., 2006, Gracia-Gracia et al., 2011; Stelzel et al., 2009, Wishart et al., 2011, Persson & Stenfors, 2018). Consequently, we aim to examine this interactive effect and assess if it varies with BMI. In addition, the SNPs DARPP-32 and C957T have also been linked to working memory (Hotte et al., 2006; Ma et al., 2022; Smith, Swift-Scanlan & Boettiger, 2014; Xu et al., 2007; Klaus et al., 2019; Jacobsen et al., 2006). DARPP-32, or Dopamine and cAMP-regulated neuronal phosphoprotein, is a protein that potently modulates dopamine D1-dependent synaptic plasticity in the striatum (Ouimet et al., 1984; Calabresi et al., 2000; Lindskog et al., 2006; Girault & Nairn, 2021), and C957T is known to impact dopamine D2 mRNA translation (Duan et al., 2003) and postsynaptic D2 receptor availability in the striatum (Hivonen et al., 2005). Both SNPs have also been associated with (diet-induced) weight gain (Sharma & Fulton, 2013; Hu et al., 2006, Müller et al., 2012). Their effect on BMI-dependent WM gating, however, remains unknown. In order to test the impact of these four candidate polymorphisms we also added participants' genetic information, extracted from their blood, to our analyses. We hypothesized that BMI-dependent distractor-resistant maintenance and/or updating of working memory representations would be modulated by (1) an interaction of COMT and Taq1A, a main effect of (2) DARPP, and/or a main effect of (3) C957T.

In addition to our primary investigations, we further conducted exploratory analyses on a

subsample of our data. Two of the three studies had data available on the ratio of phenylalanine and tyrosine to other large neutral amino acids. This ratio represents the peripheral dopamine precursor availability and can be considered a potential proxy for central dopamine synthesis capacity (Leyton et al., 2004; Montgomery et al., 2003). Existing evidence suggests that this measure may be linked to WM performance in a diet-dependent manner (Hartmann et al., 2020). By looking at amino acid ratio and its connection to BMI-dependent WM gating, we sought to assess the influence of dopamine at the system level.

RESULTS

Sample descriptives

Three participants were excluded from the analyses, as they performed below chance (<50% correct in all four conditions). One subject was excluded as they reported that they didn't perform the task properly during the post-task strategy assessment. The final sample thus consisted of 320 participants. The average age of the sample was 26.93 years (SD = 6.82, min = 12.17, max = 49.75). There were 166 males. Mean BMI was 26.38 kg/m² (SD = 6.35, min = 17.51, max = 45.54). Mean IQ was 105.41 (SD = 10.61, min = 71, max = 122). Data for DFSQ was missing for 5 subjects. Mean DFSQ score was 54.89 (SD = 11.61, min = 33, max = 97). Please refer to Table 1 for a list of full sample characteristics (per study).

BMI-related Impairments in Working Memory Updating Depend on Taq1A, but not COMT Genotype

As expected, results for model 1 showed a significant main effect of BMI on overall task performance (X^2 = 16.80, df = 1, $p_{corrected}$ < 0.001), such that BMI was negatively associated with accuracy (OR = 0.84, CI = 0.78 – 0.91, see Figure 2). Against our main hypothesis, however, there was no difference in this effect between the working memory conditions. The two-way interaction between BMI and condition was insignificant (X^2 = 2.66, df = 3, $p_{corrected}$ > 1), indicating no evidence for BMI to have different effects across our working memory conditions. We found significant main effects of IQ, gender, tiredness, and concentration (all corrected p-values < 0.008). As expected, IQ and concentration were positively associated with task performance (OR_{IQ} = 1.24, CI_{IQ} = 1.14 – 1.35; $OR_{concentration}$ = 1.30, $CI_{concentration}$ = 1.20 – 1.41), while tiredness predicted task performance in a negative manner (OR = 0.87, CI = 0.80 – 0.95). Males performed worse than females on the task (OR = 0.86, CI =0.82 – 0.97). Please refer to Table 2 for the full model output displaying the original, uncorrected p-values.

When investigating the interactive effects of COMT and Taq1A on BMI-dependent WM gating (model 2), results reveal that the four-way interaction of BMI x condition x COMT x Taq1A was non-significant (X^2 = 4.09, df = 6, $p_{corrected}$ > 1). This indicats that the two SNPs did not have the expected differential effects on WM gating. Interestingly, however, we could observe a significant three-way interaction between Taq1A genotype, BMI, and condition (X^2 = 12.40, df = 3, $p_{corrected}$ = 0.024), indicating that Taq1A genotype might moderate BMI-dependent effects on gating. There were no main effects of COMT (X^2 = 0.159, df = 2, $p_{corrected}$ > 1) or Taq1A (X^2 = 1.13, df = 1, $p_{corrected}$ > 1), and all other two- or three-way interactions involving COMT were insignificant (all corrected p-values > 0.34). Please refer to Table 3 for the full model output with original, uncorrected p-values.

To further investigate the significant Taq1A x condition x BMI interaction, we ran simple effects analyses, testing the Taq1A-BMI interaction separately for each condition. These analyses showed that the BMI-genotype interaction was significant in the update condition (p = 0.002). In this condition, A1-carriers had 33.9% (SE = 7.58) lower probability to score correctly with one unit increase of BMI, whereas for non-carriers there was only -1.22% (SE = 7.21%) change. BMI-Taq1A interactions for all other conditions were insignificant (all p-values > 0.079), suggesting that the effect was specific to updating and hence might drive the observed overall three-way interaction (Fig. 3).

In order to determine whether our results stemmed from mere match/non-match response

biases or from proper ignoring/updating, we conducted a follow-up analysis, investigating the effects of the probe type presented at the end of each trial. The probe could either be the target item, a completely novel item, or a distractor item, meaning that the probe was one of the items that had to be encoded initially, but then be overwritten. Thus, a distractor probe measures the cognitive challenge of updating in its most exact form, while a target or novel item primarily assay match/non-match responses. For this analysis, we thus subsetted our data, including updating trials only, and re-ran our model augmented with the factor probe type. Results showed a significant main effect of probe type (X^2 = 94.11, df = 2, p < 0.001). trials where the probe was a distractor were the hardest (mean accuracy = 86.44%), followed by target probe trials (mean accuracy = 91.58%), and novel probe trials (94.96%). The three-way interaction between probe type, BMI, and Taq1A genotype was not significant (X^2 = 1.645, df = 2, p = 0.439), indicating that the probe type did not affect the BMI-Taq1A interaction in updating trials. High-BMI A-allele carriers were worse than non-carriers in all three probe trial types similarly. However, this pattern was most pronounced in the distractor condition (see Figure 4).

BMI-related Impairments in Working Memory Updating Depend on DARPP-32

Investigation of the effects of DARPP on BMI-dependent working memory gating, revealed a significant 3-way interaction of DARPP-32, BMI, and condition (X^2 = 20.21, df = 3, $p_{corrected}$ < 0.001), such that there was a DARPP-32 x BMI interaction in the update condition only ($p_{posthost}$ = 0.006, see Figure 5). G-carriers had a 32.4% (SE = 7.86) lower probability to score correctly per increasing unit of BMI, while the probability was only 4.39% (SE = 6.61) lower in A/A homozygotes. Post hoc tests for all other conditions were insignificant (all p-values > 0.216). Main effects stayed similar to our previous model (all corrected p-values < 0.008). The main effect of DARPP-32 was insignificant (X^2 = 0.03, df = 1, $p_{corrected}$ > 1), as well as the interaction of DARPP-32 with BMI (X^2 = 0.18, df = 1, $p_{corrected}$ > 1) and with condition (X^2 = 1.00, df = 3, $p_{corrected}$ > 1). For the full model output with original, uncorrected p-values, please refer to Table 4.

Again, to pinpoint where this effect comes from, we ran a follow-up analysis, investigating whether the type of probe item had an influence. We subsetted our data, including only updating trails, and re-ran our model augmented with the factor probe type. Results revealed a significant main effect of probe type (p < 0.001), and a significant three-way interaction between probe type, BMI, and DARPP genotype (X^2 = 10.792, df = 2, p = 0.005). Post hoc analyses indicated that this interaction was driven by a significant DARPP-BMI interaction in distractor (p = 0.046) and target (p = 0.008) trials, while there was no such interaction in novel trials (p = 0.242; see Figure 6).

No Association of C957T with BMI-dependent Working Memory Gating

Our analysis revealed no significant main effect of the C957T polymorphism (X^2 = 0.03, df= 1, $p_{corrected}$ > 1). All other main effects stayed significant (all corrected p < 0.012), except for the effect of BMI (X^2 = 3.49, df= 1, $p_{corrected}$ = 0.247). Furthermore, we found no substantial evidence for two- or three-way interactions involving the C957T polymorphism (all corrected p > 0.186), suggesting that C957T does not significantly interact with BMI or one of our working memory conditions. See Table 5 for the full model output.

BMI-dependent Alterations in Working Memory Gating are Influenced by Peripheral Dopamine Synthesis Capacity

When investigating potential influences of dopamine changes on the system level (model 5), we

found a significant three-way interaction between amino acid ratio, BMI, and condition (X^2=10.88, df = 3, $p_{corrected}$ < 0.049). Post hoc simple effects analyses suggested that this interaction seems to be driven by differential performance specifically in update vs. ignore (X2 = 5.57, df = 1, p = 0.018). As BMI increases, higher ratios of amino acids promote better performance in updating, but worse performance in ignoring (see Figure 7, upper panel). All other comparisons (update vs. control short; ignore vs. control long; control long vs. control short, update vs. control long, ignore vs. control short) did not yield significant differential relationships between amino acid ratio and BMI (all p values > 0.168).

The main effects of BMI, condition, and amino acid ratio were insignificant (all $p_{corrected}$ > 1). The main effect of z-IQ (X^2= 11.64, df = 1, $p_{corrected}$ = 0.002) and z-concentration (X^2= 18.60, df = 1, $p_{corrected}$ < 0.001) were significant, both relating positively to performance (OR_{IQ} = 1.28, $OR_{concentration}$ = 1.33). The interactions between BMI and condition (X^2= 9.80, df = 3, $p_{corrected}$ = 0.081), and between amino acid ratio and condition (X^2= 8.69, df = 3, $p_{corrected}$ = 0.135) were not significant. BMI and amino acid ratio showed no significant two-way interaction (X^2 = 0.322, df = 1, $p_{corrected}$ > 1). Because there was an extreme BMI data point, we re-ran the model excluding this data point to check whether the results still hold. The three-way interaction between Amino Acid Ratio, BMI, and condition became trend-significant ($p_{corrected}$ = 0.063, see Table S1 & Figure S1).

DISCUSSION

The present investigation sought to evaluate whether obesity might be associated with impairments in working memory gating. Consistent with previous literature (Yang et al., 2020, 2019, 2018; Gonzales et al., 2010; Coppin et al., 2014, Hartmann et al., 2023) we found evidence for impairments in overall working memory in individuals with a high BMI. Yet, we could not observe the expected interaction of BMI and condition, indicating no specific effect of BMI on WM gating. Interestingly, however, distinct effects of BMI on gating became apparent when taking into account potential changes in inherent dopamine signaling. Specifically, individuals carrying a risk-allele of Taq1A or DARPP-32 performed significantly worse on updating with increasing BMI. This finding is compelling as we are the first to show such selective effects. Against our expectation, however, we did not find evidence for a BMI-dependent interaction effect of COMT and Taq1A on working memory gating, nor did we find any effects of C957T.

Selective BMI-Genotype Effects on Working Memory Updating

Our findings are partially in line with our hypothesis. While we did observe the expected worsening in updating in individuals with a high BMI, this effect became apparent only when participants - along with BMI - were categorized based on certain putative dopamine-signaling characteristics. This finding is compelling as we are the first to show such selective effects.

Notably, it were the Taq1A and DARPP-32 SNPs that selectively modulated WM updating in a BMI-dependent manner. Intriguingly, both of these SNPs are associated with, predominantly, striatal dopamine signaling (Hemmings & Greengard, 1986, Meyer-Lindenberg et al., 2007, Gluskin & Mickey, 2016), implying a targeted modulation of processes occurring within the striatum. The decline in updating performance was notable only among individuals carrying either the A-allele (Taq1A) or the G-allele (DARPP-32). Both of these alleles have previously been considered risk alleles for various conditions and behaviors involving maladaptive cognitive flexibility, such as addiction (Smith et al., 2008; Munafo, Matheson, & Flint, 2007; Deng et al., 2015), Schizophrenia (Meyer-Lindenberg et al., 2007; González-Castro, 2016; Albert et al., 2002), or impaired reinforcement learning (Frank et al., 2007; Doll et al., 2011). In non-risk-allele carriers, however, performance remained stable despite increasing BMI. This pattern suggests that possessing the more advantageous genotype could potentially mitigate the impact of a high BMI on working memory updating. Moreover, in the normal-weight BMI range, carriers of a risk allele (in both, Taq1A and/or DARPP) slightly outperformed their non-risk allele carrying counterparts. This distinction was particularly pronounced in trials where the probe was a distractor, suggesting that the effect is primarily due to "real" updating, i.e. when initially encoded items need overwriting, as opposed to simple match/non-match responses (as in novel vs. target probe items). This is especially intriguing as it emphasizes that carrying a ”risk allele” can in fact be advantageous under certain cognitive demands – a claim that has also been put forward by e.g. Stelzel et al. (2010). It is only when the risk allele is combined with other adverse factors (such as high BMI) that its detrimental potential is unleashed.

Mechanistic Accounts for our Findings

Mechanistically, our findings are potentially due to differential go/no-go path activation in the basal ganglia – pathways that are crucially involved in governing working memory gating. In essence, the D1 pathway modulates the 'go' signaling responsible for updating, while the D2 pathway facilitates 'no-go' signaling crucial for distractor-resistant maintenance (Frank & O`Reilly, 2006).

Considering Taq1A, evidence points at increased striatal dopamine synthesis and corresponding increases in striatal BOLD signals in A-carriers compared to non-carriers (Laakso et al. 2005; Stelzel et al., 2010). These findings suggest that the phasic dopamine signal needed to trigger "go" (i.e. updating), might be enhanced in A-carriers. This aligns with the idea that A-carriers, who possess fewer D2 receptors (Thompson et al., 1997; Pohjalainen et al., 1998; Jönsson et al., 1999) fall more within the ambit of the D1/go-dominant regime (Klein et al., 2007). Our data support this speculation by displaying slightly better updating performance in A-carriers in the normal-weight BMI range. However, as BMI increases, this trend seems to become maladaptive, as updating performance deteriorates in A-carriers. We propose two possible explanations for this. First, with increasing BMI, there might be a form of "over-updating", that is, also unnecessary information is kept in an accessible state throughout the experiment. This would pertain to theories put forward by Durstewitze and Seamans (2001) in which they argue that both, too little or too much dopamine, can lead to too shallow barriers between distinct cognitive networks, potentially promoting excessive cognitive flexibility. It might hence be that in high-BMI A-carriers there is a more salient gating signal, facilitating the updating of *all* task representations. Indeed, the BMI-dependent decline in updating performance in A-carriers was qualitatively larger in trials where the probe was a distractor - possibly attributed to difficulties in disposing of the distractor, because it remained in this more accessible cognitive state. Alternatively, the combination of reduced D2 receptors (in A-carriers) and diminished tonic dopamine (as in obesity), could impair the efficiency of signal transmission necessary for updating, thereby leading to improper updating. Further research is needed to disentangle which of these explanations is more plausible.

Regarding DARPP, the G-allele has been associated with reduced striatal D1 efficacy (Meyer-Lindenberg et al., 2007). Moreover, Frank et al. (2007) and Doll et al. (2011) showed that carrying a G-allele was associated with worse go-learning – a process requiring activation of the same pathway that is likely to be activated during updating of working memory contents. Similarly, Frank and colleagues (2009) demonstrate that the G-carrier group compared to the A/A allele group displayed worse approach learning – again a process relying on go-path activation. However, there were no effects of DARPP on no-go learning (Frank et al., 2007), which requires activation of the same pathway that is likely to be activated during distractor-resistant maintenance. Our results related to DARPP hence broadly align with the literature and suggest that, particularly, markers of inefficient striatal go-signaling (G-carriers) predict BMI-dependent effects on working memory updating.

Collectively, our observations hint at potential abnormalities in go/no-go path signaling in high-BMI risk-allele carriers.

Possible Accounts for the Absence of COMT and C957T Effects

Considering that according to the prevailing models, PFC and striatum interact to foster effective WM gating, the question arises as to why we could not observe the expected COMT-Taq1A interaction on BMI-dependent working memory gating. We posit several explanations for the absence of the anticipated interaction.

Firstly, these polymorphisms may indeed exert a limited interactive effect on working memory gating. In line with this notion, prior findings concerning the interactive effects of COMT and Taq1A on working memory have yielded contradictory results. For instance, Garcia-Garcia

et al. (2011) and Stelzel et al. (2009) reported patterns of COMT-Taq1A interactions in the context of working memory updating that were consistent with each other. In contrast, Wishart et al. (2011) observed an opposing interaction pattern, while Persson & Stenfors (2018) did not identify any COMT-Taq1A interaction at all. Notably, all these studies explored genotype interactions using paradigms that either assessed the two memory processes separately (Gracia-Garcia et al., 2011; Wishart et al., 2011; Persson & Stenfors, 2018) or in a manner that they were not distinctly discernible (Berryhill et al., 2013). None of these studies examined the comprehensive interaction of COMT, Taq1A, and working memory updating vs. ignoring within a single paradigm, as we did here. We hoped to shed more light on the possible origins of the contradictions, as with our design we could specifically probe the distinct associations of each genotype with each memory process. However, we couldn't achieve this as we didn't find an interaction between COMT, Taq1a, and the conditions. We can hence not make any clear conclusions. Secondly, it has recently been debated whether COMT actually has a noteworthy effect on cognition at all. Some meta-analyses find (small) effects (Barnett et al., 2007), while others don't (Geller et al., 2017, Barnett et al., 2008; also see Goldman et al., 2009; Wacker, 2011; and Barnett et al., 2011 for a discussion on the meta-analysis from Barnett et al., 2008).

Beyond this, the absence of significant effects related to COMT could further be interpreted as underscoring the selectiveness of our observed effects. COMT effects are predominantly observed in the PFC (Mier, Kirsch & Meyer-Lindenberg, 2010; Egan et al., 2011; Käenmäki et al., 2010) and rather tied to maintenance of working memory contents (Nolan et al., 2004; Rosa et al., 2010). This lends weight to the interpretation that distractor-resistant maintenance, or prefrontal processes, remain unaffected by BMI. In a similar vein, also our findings concerning the C957T polymorphism bolster the selective nature of our findings. Much like COMT, this polymorphism is presumably more involved in working memory maintenance, that is, prefrontal-related functioning. Supporting this notion, Xu and colleagues (2007) found an association between the C957T polymorphism and specifically maintenance of (phonological and serial) information, but not with other tasks requiring updating. Furthermore, this polymorphism has also been associated with D2 binding potential in extrastriatal regions (Hirvonen et al., 2009b) and greater WM-related activity in PFC (Li, Bäckmann & Persson, 2019). Last but not least, the results with respect to C957T involvement in striatal-dependent cognition are mixed (see e.g. discussion part in Baker, Stockwell, & Holroyd, 2013). It hence seems that C957T effects are not as specific to striatal processes.

Selective Modulation of Working Memory Gating: System-Level Dopamine versus Genetic Profiles

Our findings are the first to show a selective modulation of working memory updating, as opposed to the previously observed trade-off between ignoring and updating (e.g. Fallon and Cools, 2017; see Cools (2019) for an extensive review). To the best of our knowledge, none of the previous studies investigating working memory gating in relation to dopamine signaling have found such a selective modulation. We speculate that this is because these studies looked at broader changes in the dopamine system, i.e. by using drug manipulations or comparing Parkinson's vs. healthy controls, rather than particular genetic profiles. Such broad "system-level" dopamine changes may impact both, PFC signaling pertaining to distractor-resistant maintenance, and striatal signaling associated with updating. This, in turn, might foster the commonly observed inverted-U-

shaped relationship between dopamine and cognition: In cases where baseline dopamine levels are low, a dopamine increase (for instance, through agonists) would enhance ignoring, albeit at the expense of updating. Conversely, at medium baseline dopamine levels an increase would lead to impaired ignoring, potentially benefiting updating (for a more detailed discussion, see Cools and D'Esposito, 2011). Indeed, we also see this pattern, when looking at system-level dopamine changes: depending on BMI, low (or high) peripheral dopamine synthesis capacity (as indicated by blood amino acid ratios) was associated with worsening of distractor-resistant maintenance, while improving updating (or vice versa). It should be noted that the sample for our amino acid analyses was much smaller (N = 160) than the one used in our SNP analysis (N = 320), and the BMI-range for this sub-sample was narrower (mean = 23.63, SD = 2.78, min = 18.63, max = 36.42). This was because only two of the three studies had the data on amino acids available. Interestingly the system-level effect of amino acid ratio becomes visible in a healthy- to overweight BMI range, indicating that already small changes in BMI can promote different dopamine-dependent cognitive profiles.

Strengths and Limitations

A major strength of this study is that it was the first to probe gene-gene interactions on a direct working memory maintenance and updating comparison. This is a notable advantage, as previous studies have usually examined these aspects in separate paradigms, which might have contributed to the heterogeneous results regarding SNP interaction effects on working memory (see above). Another main strength of our study is the sizable sample. However, despite the relatively large size, our sample was still not big enough for systematic and reliable analysis of multiple gene-gene interactions. This would be of interest however, as possible interactions of all SNPs presented in this paper have been shown (Zmigrod & Robbins, 2021; Frank & Hutchison, 2009; Smith, Swift-Scanlan & Boettiger, 2014, Xu et al., 2007). Such analyses would require even larger cohorts, however, as the effect sizes of single SNPs are usually small. We nevertheless report the outcome of such highly explorative models in our supplements for the purpose of transparency and to guide future studies. Yet, those results should be interpreted with caution. Last but not least, the sample used for this study was very heterogeneous, as it was pooled together from three separate studies. The BMI distribution, for instance, was significantly different depending on gender ($p = 0.01$). BMI was higher in females. This was because females were overrepresented in the BEDOB study, which had the largest BMI range (refer to Table 1). Although we ran control analyses to account for this heterogeneity, we cannot exclude the possibility that certain properties of the data distribution could have influenced our results.

Overall Conclusions

Overall, our data aligns with previous evidence for working memory impairments in obesity. However, selective effects of BMI on working memory gating - specifically updating - become visible only when accounting for genetic markers of striatal dopamine transmission. Our study is the first to show such selective effects. Previous research, that generally utilized drug manipulations, consistently demonstrated system-level modulations, leading to a trade-off between ignoring and updating information. While we also observe this trade-off when examining more comprehensive system-level relationships (i.e. blood amino acid ratio), the specificity of our SNP-related findings to updating sets them apart from previous studies. Our results hence pave

the way for new individualized treatments for obesity, as they 1) highlight that carrying a risk-allele may produce particular cognitive impairments, which may be masked when genotypes are not taken into account, and 2) suggest that the previously documented deficits in reward learning might span beyond just (food) rewards and could be rooted in broader issues concerning information updating, particularly in those with a genetically predisposed susceptibility.

MATERIALS AND METHODS

Participants

The data used in this study were collected in the scope of three separate pre-registered cross-sectional studies, which are all part of a larger line of research in the O'Brain Lab: GREADT (see https://osf.io/w9e5y), BEDOB (see https://osf.io/fyn6q), and WORMCRI (see https://osf.io/zdmkx). Prior to participation, participants were screened for a history of clinical drug or alcohol abuse, neurological or psychiatric disorders, and first-degree relative history of neurological or psychiatric disorders. Symptoms of depression were assessed via a screening interview using the Structured Clinical Interview for DSM-IV (SCID, Wittchen 1997; in BEDOB & WORMCRI) or Beck Depression Inventory (BDI, Beck et al., 1996; in GREADT).

Study Design

All measures relevant to the present study were collected in a comparable manner. In all studies, participants were first asked to come to the lab for a screening session where in- and exclusion criteria were checked. Weight and height were measured to calculate BMI. After inclusion, blood samples were taken from the participants to assess COMT $Val^{158}Met$, Taq1A, C957T, and DARPP-32 genotypes. Analysis of these SNPs was performed in the laboratory for 'Adiposity and diabetes genetics' at the Medical Research Center, University Leipzig, Leipzig, Germany. In WORMCRI and GREADT, we also took serum blood samples in order to extract information on the amino acid profiles. Participants, therefore, came overnight-fasted for these two studies. Serum blood samples were analyzed at the "Institut für Laboratoriumsmedizin, Klinische Chemie und Molekulare Diagnostik (ILM)" Universitätsklinikum Leipzig, Germany. After the blood draw, participants did a number of neuropsychological tests among which were the digit span task (Wechsler, 2008; assessing baseline working memory), and a proxy for IQ (in BEDOB: "Wortschatztest" (Schmidt & Metzler, 1992; assessing verbal IQ); in GREADT and WORMCRI: "Wiener Matrizen Test" (Formann, Waldherr & Piswanger, 2011). After that, participants filled in several questionnaires, of which the Dietary Fat and free Sugar Questionnaire (DFSQ; Francis & Stevenson, 2013; Fromm & Horstmann, 2019; assessing eating behavior), was subject to all three studies. On the second test day, participants completed the working memory task (described below), either during fMRI (GREADT & BEDOB) or during EEG (WORMCRI). After completion of the task, all participants were asked to indicate the level of tiredness and concentration they felt during the task on a 10-point Likert scale. For a more detailed description of each study's design, please refer to the respective pre-registration mentioned above.

Working Memory Task

Participants completed a modified version of a delayed match-to-sample task originally designed by Fallon and Cools (2014). This modified version has already been described in Hartmann et al. (2023) and Herzog et al. (2023). The task comprises 4 conditions (Fig. 1). In the ignore condition, testing distractor-resistant maintenance, participants first have to memorize two target stimuli, signaled by the letter "T" centered in between the two. Next, they are presented with two new stimuli, this time marked by a centered "N", indicating non-targets which have to be ignored. After that, participants are presented with a probe stimulus and have to determine whether one of the first two target stimuli matches the presented probe. In the update condition, participants are first shown two target stimuli (centered "T"). After that, they see a new set of target stimuli (again indicated by a centered "T"). These two new stimuli replace the previously presented stimuli as the target and thus have to be evaluated for a match when the probe is presented subsequently. The two control conditions do not have any interference and are matched to the temporal delay between encoding the to-be-matched targets and probe. The probe is presented for 2000 msec. The task is separated into four blocks, with each block entailing 8 trails of each condition, interleaved among all blocks. Each block thus consists of 32 trials. The total number of trials in the task amounts to 128. Feedback is presented after each of those blocks. Each trial is separated

by a jittered inter-trial interval ranging from 2000 to 6000 msec. The stimuli are randomly computer-generated, monochromatic RGB “spirographs”. The primary outcome measure is accuracy. The total duration of the task is approximately 30 minutes.

Statistical Analyses of Behavioral Data

All behavioral analyses were performed in R in RStudio v4.2.2 (R Core Team, 2015; RStudio Team, 2016). Generalized linear mixed models (GLM) of the ‘*lme4’* package were used to analyze the primary outcome measure of the working memory task: accuracy. We ran a logistic regression using *glmer()* with a binomial link function. We used trial-by-trial information for each subject with binary coded response (0 = incorrect; 1 = correct). Trials with a reaction time < 200 ms and > 2000 ms were excluded, as those trials can be considered false alarms and misses, respectively. Trials with a reaction time > 2000 ms were excluded, as they reflect misses. To first test our main hypothesis that working memory gating is altered, depending on BMI, we built a trial-based regression model including the interaction of the within-subject factor condition (ignore vs. update vs. control long vs. control short) and the continuous between-subject factor BMI. We further probed the influence of several potential covariates: study (GREADT vs. BEDOB vs. WORMCRI), IQ, Age, DFSQ, binge-eating phenotype, tiredness, concentration, and gender. Using the *anova()* function from the *‘stats’* package, we compared AIC and BIC (Akaike, 1979; Stone, 1979) of the full model against a simpler version of the model. We found the best-fitting model (lowest AIC and BIC) to include IQ, tiredness, concentration, and gender (see supplementary materials). Due to model convergence problems, the continuous predictors BMI, IQ, tiredness, and concentration were z-scored. Furthermore, the model did not converge with a maximal random structure (including the factor ‘condition’). The random structure of the model was thus reduced to include the factor ‘subject’ only. The final model was:

*(1) accuracy ~ condition * BMI + IQ + tiredness + concentration + gender + (1 |subject)*

To test how BMI-dependent working memory gating is influenced by the respective dopamine proxy (SNP or amino acid ratio), we ran 4 additional models, each including the respective between-subject factor as an additional factor of interest. Model fit was again assessed using AIC and BIC for each model (see supplementary materials). Again, due to converges, the random structure of the models included the factor ‘subject’ only. The final models were:

*(2) accuracy ~ COMT * Taq1A* condition * BMI + IQ + tiredness + concentration + gender + (1|subject)*

*(3) accuracy ~ DARPP * condition * BMI + IQ + tiredness + concentration + gender + (1|subject)*

*(4) accuracy ~ C957T * condition * BMI + IQ + tiredness + concentration + gender + (1|subject)*

*(5) accuracy ~ amino acid ratio * condition * BMI + IQ + concentration + gender + (1|subject)*

As we ran 4 additional models testing similar hypotheses, all main results for these models were corrected for multiple comparisons using bonferroni correction, i.e. p-values were multiplied by 4. Model outputs were called using the *Anova()* function, from the *‘car’* package.

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Author contribution statement
NH and AH designed the study. NH, HH, and MW collected the data. NH analyzed the data. NH drafted the manuscript. Code review was done by HH. HH, AK, PK, AV, MW, LD, SF, and AH critically revised and approved the final manuscript.

Conflict of interest statement
No potential conflicts of interest relevant to this article were reported

Data availability statement
Data and scripts used for the analysis will be available at https://github.com/O-BRAIN/WM_SNP upon publication

Declaration of Generative AI and AI-assisted Technologies in the writing process
During the preparation of this work, the author used ChatGPT in order to improve readability and language. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication

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FIGURES AND TABLES

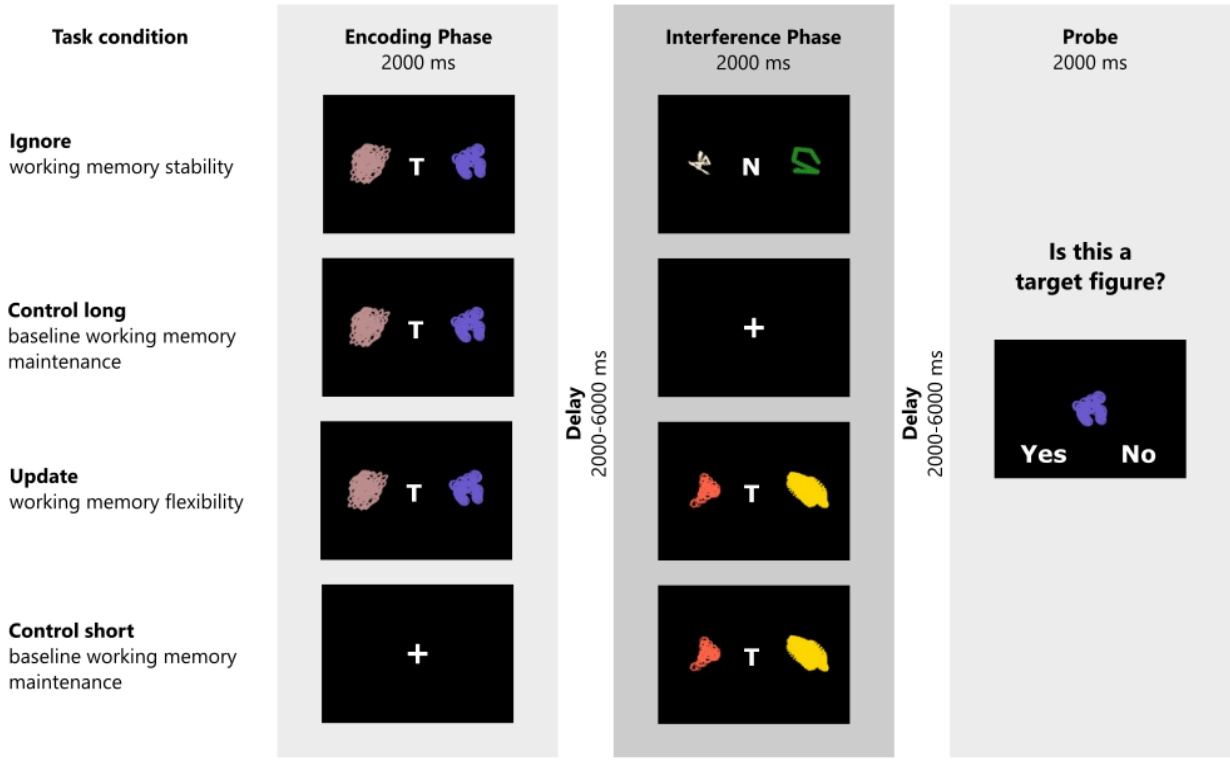

Figure 1. Schematic illustration of the task structure and experimental conditions. The task consists of three task phases. In the encoding phase, participants have to remember two target stimuli (signaled by the letter "T"), or are presented with a centered cross (short control trials). In the interference phase, participants either have to ignore two non-target stimuli (ignore trials; signaled by the letter "N") or allow two new stimuli (again marked by a "T") to replace the previously remembered target stimuli (update trials). No-interference trials (short and long control) do not require any manipulations in the interference phase. At the end of each trial, participants evaluate whether a presented figure was a target figure or not. Figure reused from Hartmann et al. (2023) with permission.

Table 1. Sample Characteristics

project	all			BEDOB			GREADT			WORMCRI		
N (male)	320 (166)			156 (43)			86 (86)			78 (37)		
	mean (sd)	min	max	mean (sd)	min	max	mean (sd)	min	max	mean (sd)	min	max
BMI	26.38 (6.35)	17.51	45.54	29.172 (7.695)	17.51	45.54	24.025 (2.799)	18.632	36.419	23.217 (2.735)	18.929	29.888
IQ	105.41 (10.61)	71	122	101.575 (11.979)	71	122	109.151 (7.249)	91	118	107.731 (10.416)	74	118
Age	26.93 (6.82)	12.17	49.75	26.879 (8.907)	12.167	49.75	26.756 (4.474)	18	40	26.799 (3.859)	20.106	36.290
DFS	54.89 (11.61)	33	97	55.839 (10.163)	35	91	57.046 (15.107)	33	97	50.584 (8.546)	34	71

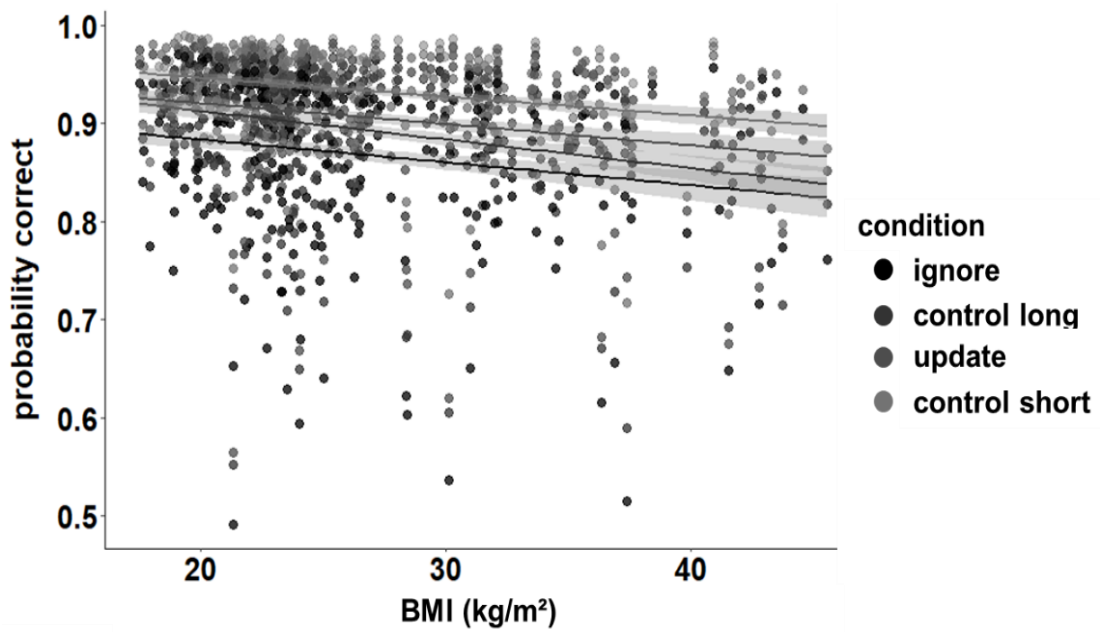

Figure 2. Main effect of BMI on working memory performance (model 1). Increasing BMI was associated with worse performance ($p_{corrected} < 0.001$, OR = 0.84). This trend was similar for all four conditions, as there was no interaction between BMI and condition ($p_{corrected} > 1$). Shaded areas represent the 95% confidence intervals.

Table 2. Full output model 1 with uncorrected p-values.

	Chisq	Df	Pr(>Chisq)
(Intercept)	3623.78	1	<0.001
condition	282.00	3	< .001
zBMI	16.80	1	< .001
zIQ	25.10	1	< .001
Gender	10.50	1	0.001
zWM_tired	36.00	1	< .001
zWM_conc	9.19	1	0.002
condition:zBMI	2.66	3	0.447

N = 320

Marginal R^2 / Conditional R^2 = 0.069 / 0.172

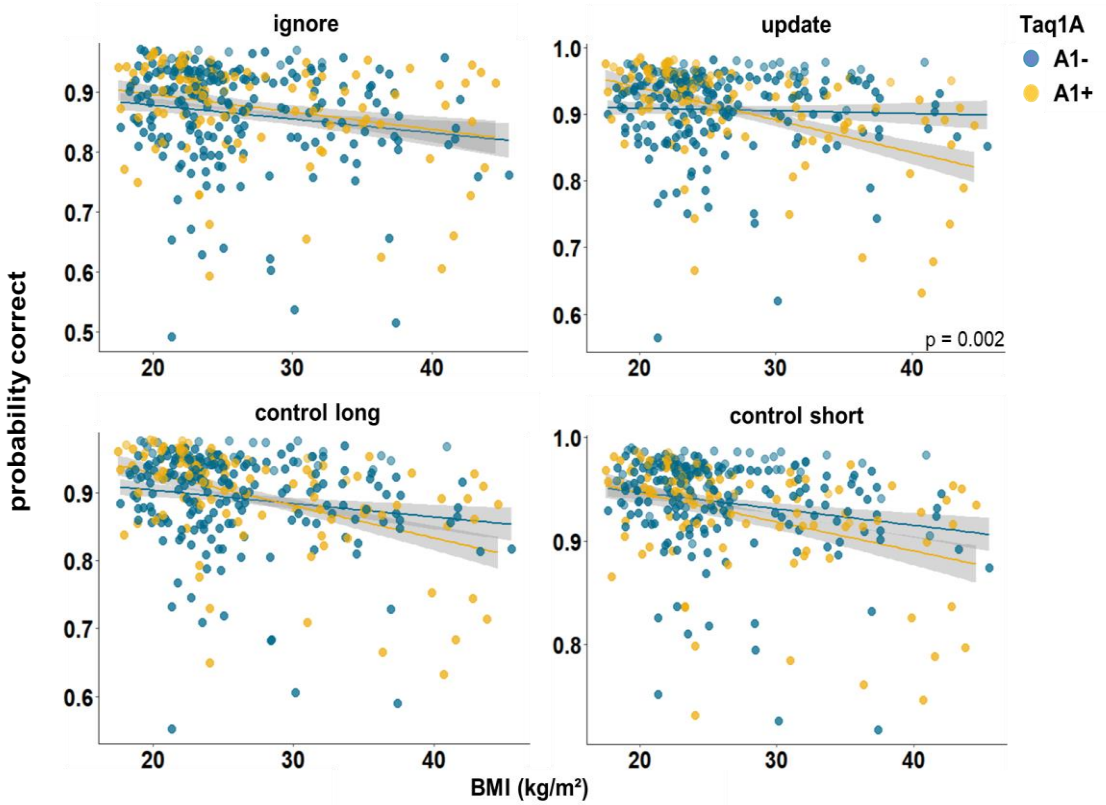

Figure 3. Interaction of Taq1A genotype, BMI, and condition on working memory performance (model 2). The two-way interaction of Taq1A and BMI was significant in the update condition only (p = 0.002). In this condition, carrying the A-allele led to a decrease in performance with each increasing unit of BMI (33.9%; SE = 7.58), while there was only -1.22% (SE = 7.21%) change in non-carriers. Shaded areas represent the 95% confidence intervals.

Table 3. Full output model 2 with uncorrected p-values.

	Chisq	Df	Pr(>Chisq)
(Intercept)	3228.77	1	<0.001
condition	212.81	3	< .001
COMT	0.16	2	0.923
Taq1A	1.13	1	0.288
zBMI	22.15	1	< .001
zIQ	24.09	1	< .001
Gender	7.53	1	0.006
zWM_tired	12.39	1	< .001
zWM_conc	30.80	1	< .001
condition:COMT	10.30	6	0.113
condition:Taq1A	4.69	3	0.196
COMT:Taq1A	2.47	2	0.291
condition:zBMI	3.49	3	0.322
COMT:zBMI	0.86	2	0.650
Taq1A:zBMI	2.98	1	0.085
condition:COMT:Taq1A	2.09	6	0.911
condition:COMT:zBMI	6.29	6	0.391
condition:Taq1A:zBMI	12.40	3	0.006
COMT:Taq1A:zBMI	3.68	2	0.159
condition:COMT:Taq1A:zBMI	4.09	6	0.665

N = 318

Marginal R^2 / Conditional R^2 = 0.076 / 0.173

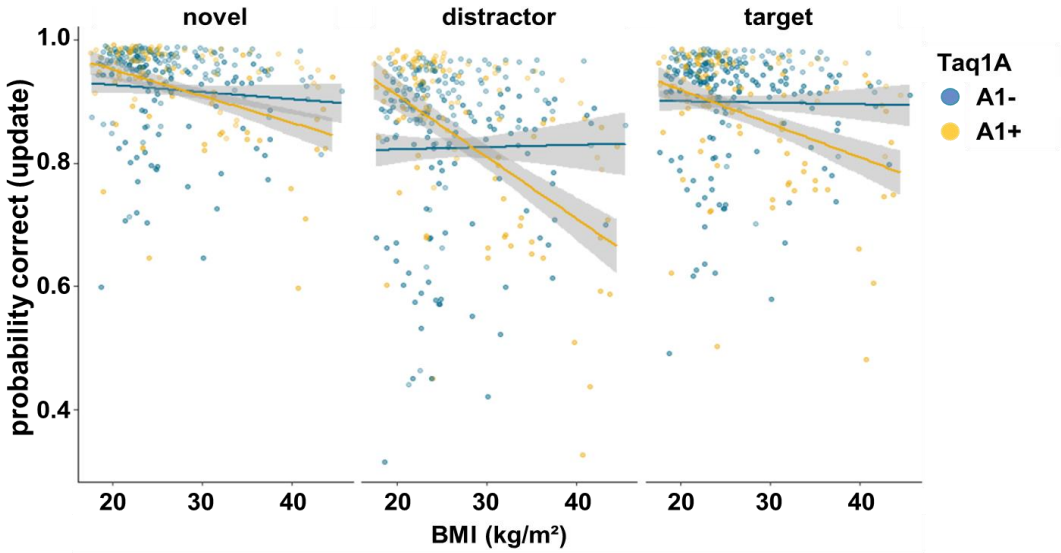

Figure 4. Interaction of Taq1A genotype, BMI, and probe type in updating trials only. There was no significant three-way interaction between probe type, BMI and Taq1A ($p = 0.439$). The BMI - Taq1A interaction was in a similar direction in all trials. There was a significant main effect of probe type ($p < 0.001$). Trials where the probe was a distractor had lowest probability to be correct. Shaded areas represent the 95% confidence intervals.

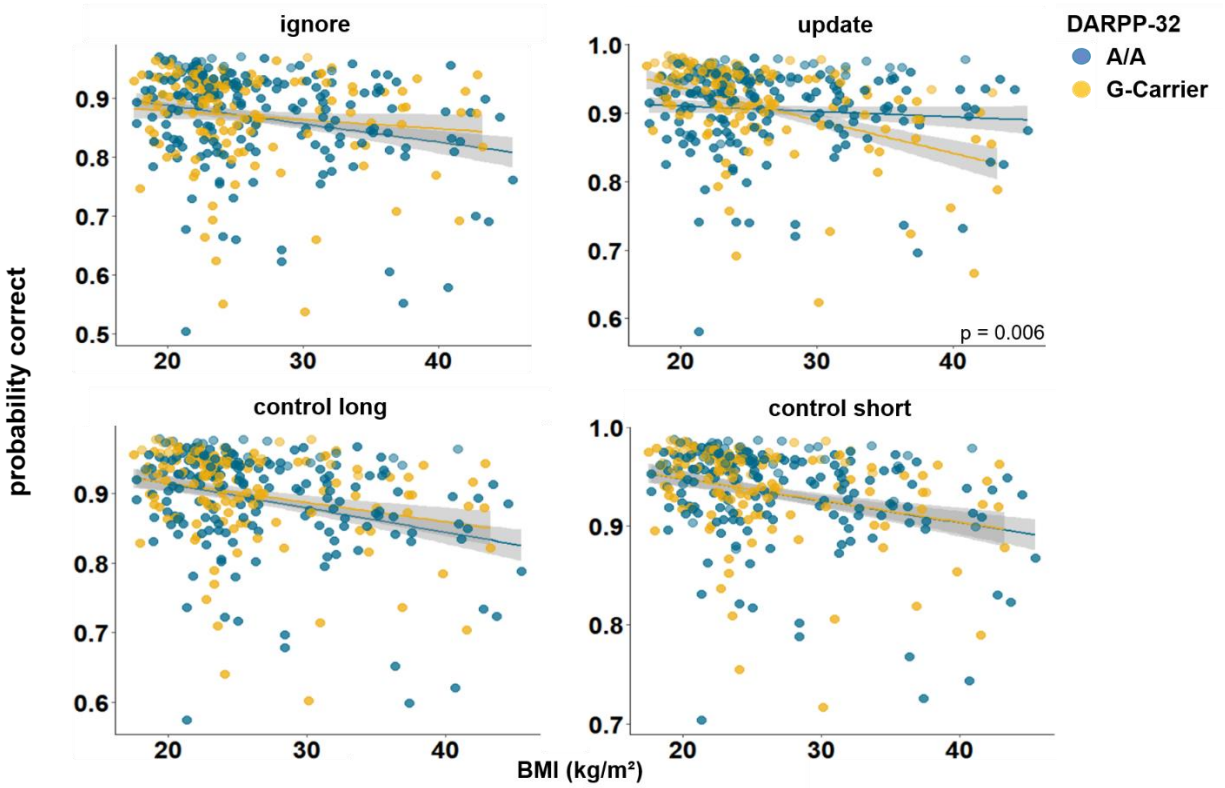

Figure 5. Interaction of DARPP-32, BMI, and condition on working memory performance (model 3). The two-way interaction of DARPP-32 and BMI was significant in the update condition only ($p = 0.006$). In this condition, carrying the G-allele led to a decrease in performance with each increasing unit of BMI (32.4%; SE = 7.86), while there was only -4.39% (SE = 6.61) change in A/A homozygots. Shaded areas represent the 95% confidence intervals.

Table 4. Full output final model 3 with uncorrected p-values.

	Chisq	Df	Pr(>Chisq)
(Intercept)	3511.81	1	< .001
DARPP	0.03	1	0.853
zBMI	17.18	1	< .001
condition	274.62	3	< .001
zIQ	25.10	1	< .001
zWM_conc	35.27	1	< .001
zWM_tired	10.52	1	0.001
Gender	9.17	1	0.002
DARPP:zBMI	0.18	1	0.668
DARPP:condition	1.00	3	0.801
BMI:condition	3.61	3	0.307
DARPP:BMI:condition	20.21	3	< .001

N = 320

Marginal R^2 / Conditional R^2 = 0.071 / 0.173

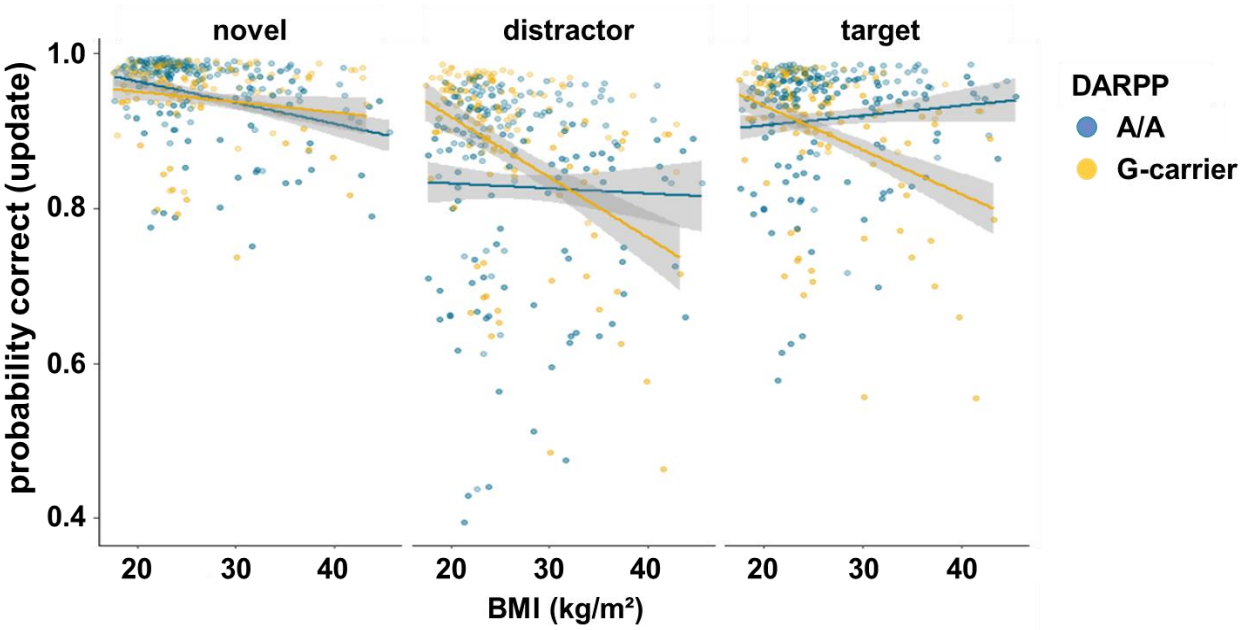

Figure 6. Interaction of DARPP-32 genotype, BMI, and probe type for update trials only. There was a significant three-way interaction between probe type, BMI and DARPP-32 (p = 0.005). Post hoc analyses showed that the BMI - DARPP interaction was significant in distractor (p = 0.046) and target (p = 0.008) trials, but not in trials where the probe was a novel item (p = 0.242). There was a significant main effect of probe type (p < 0.001). Trials where the probe was a distractor had lowest probability to be correct. Shaded areas represent the 95% confidence intervals.

Table 5. Full output final model 4 with uncorrected p-values.

	Chisq	Df	Pr(>Chisq)
(Intercept)	328.55	1	< .001
C957T	0.03	1	0.859
zBMI	3.49	1	0.062
condition	48.06	3	< .001
zIQ	25.30	1	< .001
zWM_conc	33.66	1	< .001
zWM_tired	10.54	1	0.001
Gender	8.85	1	0.003
C957T:zBMI	0.36	1	0.548
C957T:condition	7.97	3	0.047
BMI:condition	0.31	3	0.958
C957T:BMI:condition	0.07	3	0.995

N = 318

Marginal R^2 / Conditional R^2 = 0.070 / 0.171

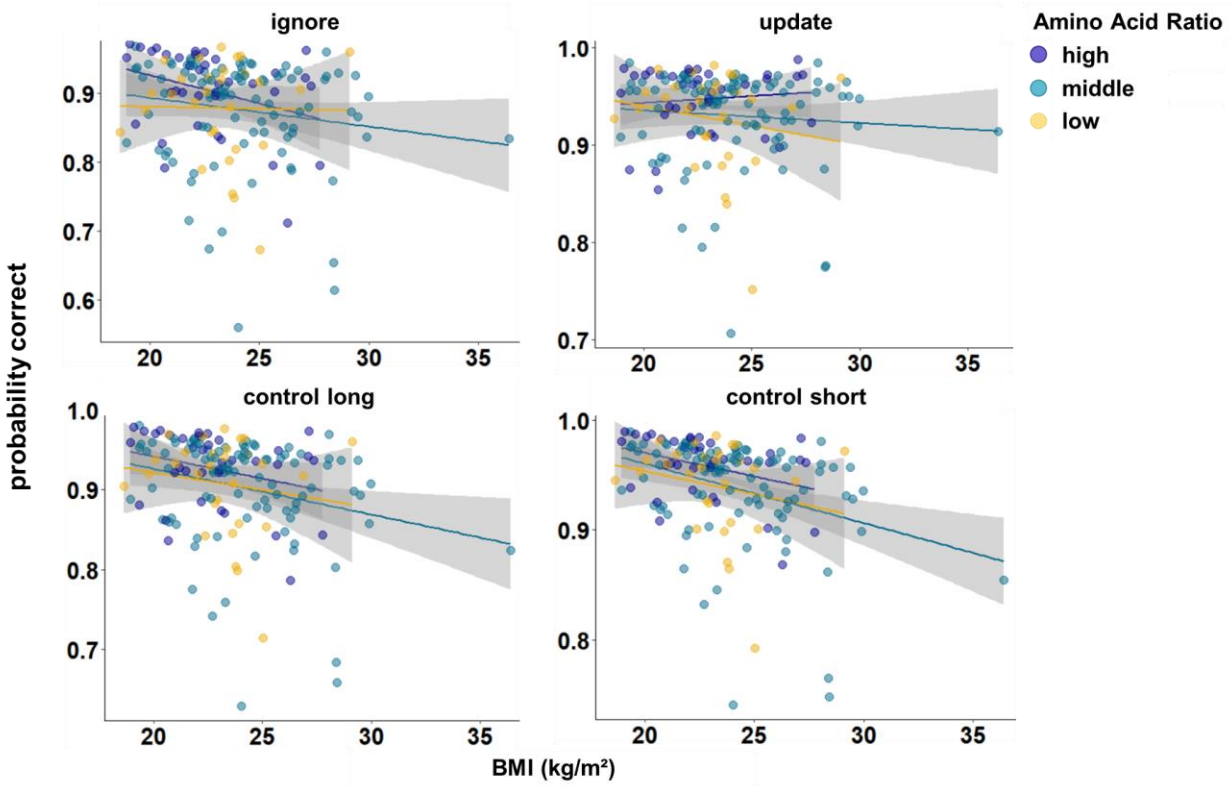

Figure 7. Interaction of Amino Acid Ratio, BMI and condition (model 5). For illustration purposes, amino acid ratio was artificially grouped into high, middle, and low. The difference in condition ($p_{\text{ignore vs. update}} < 0.001$) becomes especially apparent when looking at individuals with high amino acid ratios: With each increasing unit of BMI, performance gets worse in ignore, but better in update. There were no significant differences in the relationship of amino acid ratio and BMI comparing all other conditions against each other (all p > 0.168). Shaded areas represent the 95% confidence intervals.

Table 6. Full output final model 5 with uncorrected p-values.

	Chisq	Df	Pr(>Chisq)
(Intercept)	13.31	1	< .001
AAratio	0.58	1	0.444
zBMI	0.98	1	0.321
condition	3.43	3	0.330
zIQ	11.64	1	< .001
zWM_conc	18.60	1	< .001
Gender	5.08	1	0.024
AAratio:zBMI	0.32	1	0.570
AAratio:condition	8.69	3	0.034
BMI:condition	9.80	3	0.020
AAratio:BMI:condition	10.88	3	0.012

N = 160

Marginal R^2 / Conditional R^2 = 0.068 / 0.170