Taq1A and DARPP polymorphisms are associated with worse working memory updating in high-BMI individuals

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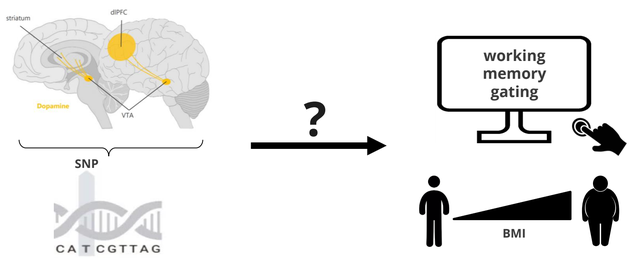
Introduction



Working memory (WM) gating requires stable maintenance and flexible updating of information. These processes are implemented via dopamine-dependent signaling in the dorsolateral prefrontal cortex (PFC) and striatum [1,2]. Two single nucleotide polymorphisms (SNPs), COMT (rs4680) and Taq1A (rs1800497), have been associated with dopamine in PFC and striatum respectively, as well as with working memory functioning [3,4,5]. Furthermore, altered dopamine transmission has been observed in individuals with high BMI [6]. It remains unclear, however, if and how these two SNPs interactively influence working memory gating, depending on BMI.

Research questions:

Do COMT and Taq1A interact to foster differential performance in WM gating, depending on BMI?

Exploratory:
Do other proxies of dopamine modulate WM gating, depending on BMI?

Methods

Participants

- combined data set from 3 studies (fMRI: GREADT, BEDOB; EEG: WORMCRI),
- final N = 318 (152 females; mean Age = 26.93 years (SD = 6.79, min = 12.17, max = 49.75); mean BMI = 26.40 kg/m² (SD = 6.37, min = 17.51, max = 45.54).
- all physically and mentally healthy, right-handed

Proxies for Dopamine Differences

→ **Taq1A:** A1+ associated with less D2 Receptors in Striatum

→ **COMT:** met/met associated with more dopamine in PFC

exploratory:

→ **DARPP:** A/A associated with enhanced striatal D1 efficacy

→ **C957T:** T/T higher D2 receptor availability (PFC & Striatum)

→ **ratio of phenylalanine and tyrosine to large neutral amino acids:** proxy for endogenous dopamine levels

Study Design

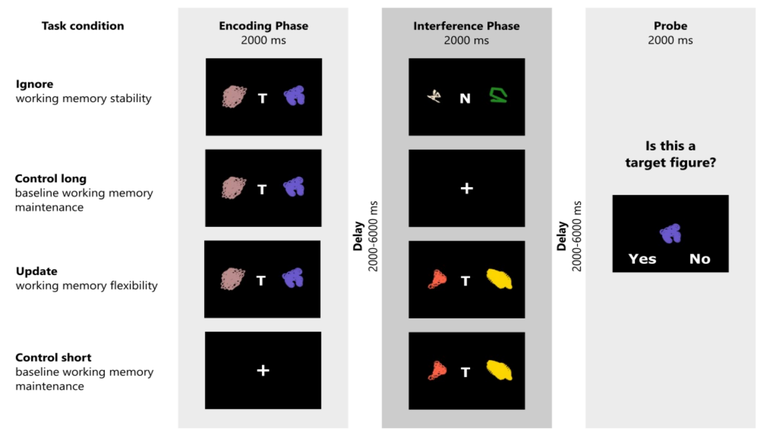
Screening

Inclusion age, health

Testday 1
• neuropsy. tasks
• blood draw

Testday 2
WM task
(during EEG or fMRI)

Working memory gating task



Analysis

trial based analysis: logistic regression for accuracy (correct vs. incorrect)
model comparison approach to find best fitting, least complex model

(1) accuracy ~ ***COMT * Taq1A*** ** condition * zBMI + ztiredness + zIQ + zconcentration + gender + (1|subject)*

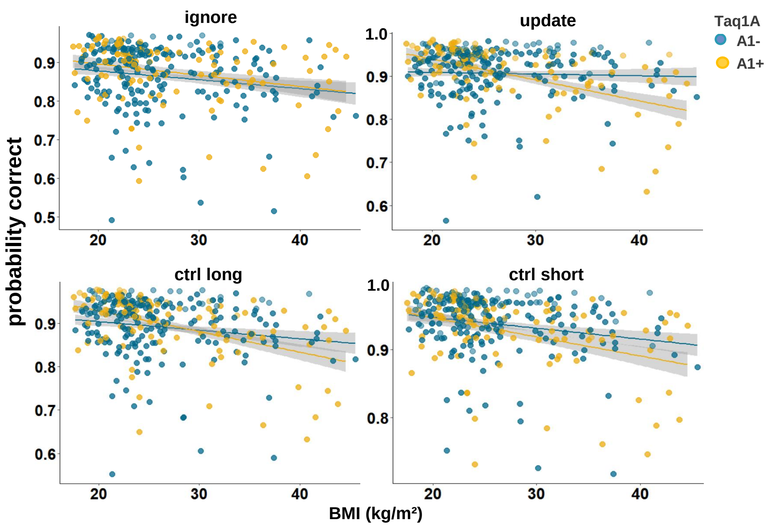
exploratory (corrected for multiple comparisons, p-value time 5)
(2-5) accuracy ~ ***SNP*** ** condition * zBMI + zIQ + ztiredness + zconcentration + gender + (1|subject)*

(6) accuracy ~ ***amino acid ratio*** ** condition * zBMI + zIQ + zconcentration + gender + (1|subject)*

Results

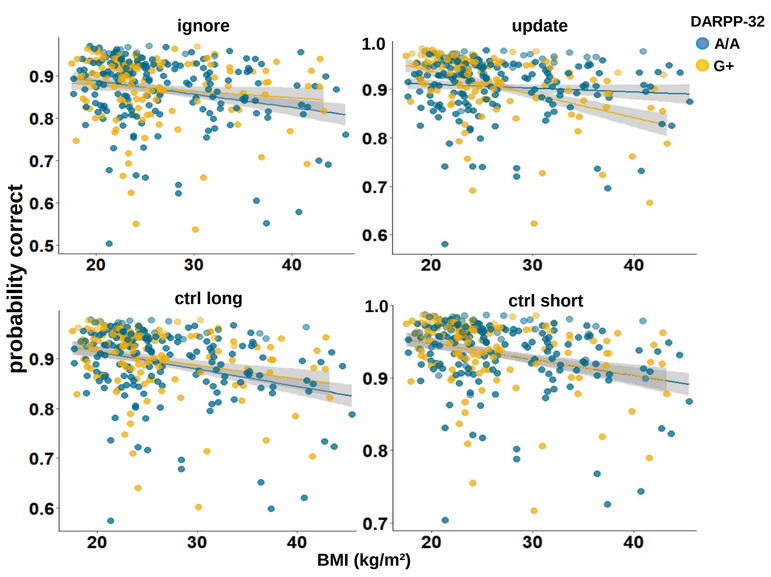
No gene-gene interaction, but BMI-dependent effect of Taq1A on working memory updating

model 1: $p_{COMT*Taq1A*condition*BMI} = 0.106$; $p_{Taq1A*BMI*condition} < 0.000$
Posthoc: $p_{Taq1A*BMI}$ for update = 0.001; $p_{Taq1A*BMI}$ all other conditions > 0.05



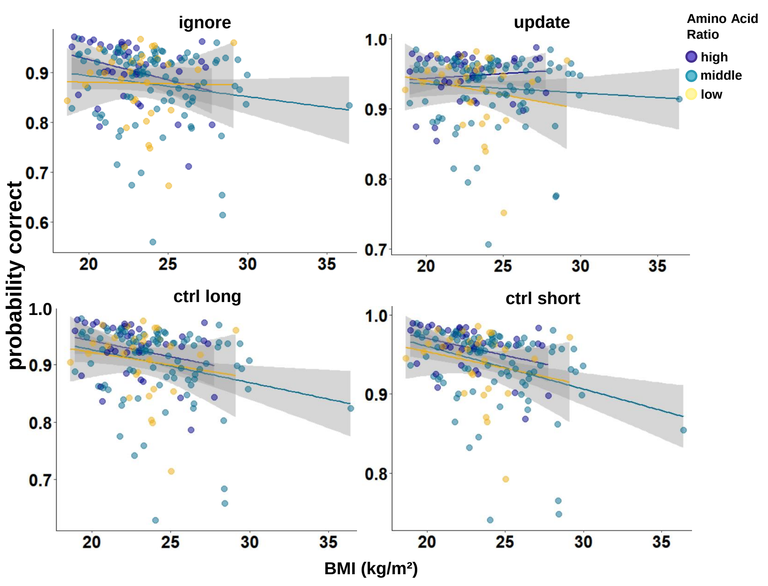
BMI-dependent effect of DARPP on updating of working memory contents

model 2: $p_{DARPP*BMI*condition} = 0.001$
Posthoc: $p_{DARPP*BMI}$ for update = 0.011; $p_{DARPP*BMI}$ all other conditions > 0.189



Amino acid ratio interacts with BMI to foster differential ignoring vs. updating

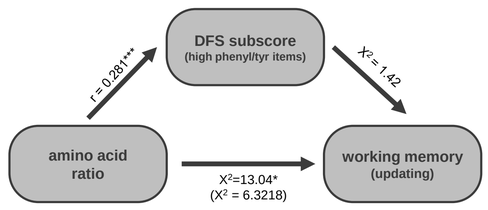
model 6: $p_{AAratio*BMI*condition} = 0.023$
Posthoc: $p_{update\ vs.\ ignore} = 0.011$; all other comparisons [update vs. ctrl_short; ignore vs. ctrl_long; ctrl-short vs. ctrl_long] $p > 0.226$



Association between amino acid ratio and BMI-dependent ignore/update is mediated by food intake

additional mediation analysis: subscore of items high in phenylalanine and tyrosine from the Dietary Fat and Sugar Questionnaire.

1) $p_{subscore\ \sim\ AAratio} < 0.001$ (r = -0.281, 95CI = -0.4180702 - 0.1307529)
2) subscore as a covariate in *model 6*
   → $p_{AAratio*BMI*condition} = 0.097$, indicating a mediation.



The standardized coefficient between amino acid ratio and working memory, controlling for DFS subscore, is in parentheses. *** p < 0.001; * p < 0.05

Discussion

High BMI combined with an "disadvantageous" genotype is associated with worse updating.
Specifically, SNPs associated with striatal dopamine transmission are at play here

→ complies with evidence suggesting that high BMI is associated with impaired dopamine transmission within the striatum [6]
→ first study to show that specifically updating of WM is affected in individuals with high BMI who also possess a disadvantageous genotype

We found no significant associations between COMT or C957T and BMI-dependent working memory gating

→ both SNPs are (also) related to PFC dopamine [3,7]
→ in line with that there are no ignore-related effects
→ emphasizes that specifically updating/striatal effects are at play

Blood amino acid ratio, which is likely to be influenced by intake of foods high in phenylalanine and tyrosine, can affect BMI-dependent WM gating performance

→ suggests that a diet high in phenylalanine and tyrosine could rescue "bad" updating
→ highly speculative!
→ needs specifically designed studies, with explicit measures targeted to quantify food intake properly

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