Catechol-O-Methyltransferase moderates effect of stress mindset on affect and cognition

Running Title: COMT rs4680 moderates effect of stress mindset on affect and cognition

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ABSTRACT

There is evidence that altering stress mindset—the belief that stress is enhancing vs. debilitating—can change cognitive, affective, and physiological responses to stress. However, individual differences in responsiveness to stress mindset manipulations have not been explored. Given the role of catecholamines in stress, we hypothesized that genetic variation in catechol-O-methyltransferase (COMT), an enzyme that metabolizes catecholamines, would moderate responses to a stress mindset intervention. Participants (N=107) were exposed to a stress mindset manipulation (videos highlighting either the enhancing or debilitating effects of stress) prior to engaging in a Trier Social Stress task and subsequent cognitive tasks. The associations of the COMT rs4680 polymorphism with the effect of stress mindset video manipulations on cognitive and affective responses were examined. Genetic variation at rs4680 modified the effects of stress mindset on affective and cognitive responses to stress. Individuals homozygous for rs4680 low-activity allele (met/met) were responsive to the stress-is-enhancing mindset manipulation as indicated by greater increases in positive affect and attention, improved cognitive functioning, and happiness bias in response to stress. Conversely, individuals homozygous for the high-activity allele (val/val) were not as responsive to the stress mindset manipulation. These results suggest that responses to stress mindset intervention may vary with COMT genotype. These findings contribute to the understanding of gene by environment interactions for mindset interventions and stress reactivity and therefore warrant further investigations.
INTRODUCTION

Cognitive, emotional, and physiological responses to stress are not solely determined by the amount of stress one experiences but also by one’s beliefs about stress. Research on stress mindset—the belief that stress has enhancing versus debilitating properties—has demonstrated that higher indices of health, performance, and well-being can ensue from holding a stress-is-enhancing (SIE) relative to a stress-is-debilitating (SID) mindset. SIE and SID mindsets can also differentially affect physiological and behavioral responses under stress, with SIE mindsets engendering more adaptive responses (e.g., reduced cortisol reactivity) and more approach-related behavior (e.g., greater desire for feedback). Importantly, there is evidence that stress mindset can be changed to improve stress responses. Prior research has demonstrated that participants adopting a SIE mindset, after merely watching a 3-minute video highlighting enhancing (vs. debilitating) effects of stress, demonstrated greater cognitive flexibility, heightened positive affect, and increased anabolic hormonal reactivity in response to an acute stressor relative to those adopting a SID mindset. Further, watching three short (3-minute) videos emphasizing the beneficial aspects of stress at work was associated with adopting a SIE mindset as well as improvements in work performance and self-reported health.

Although research on stress mindset is growing rapidly, the source of variability in individual responses remains unexplored. Identification of genetic polymorphisms associated with sensitivity to mindset manipulations offers one approach to identifying subsets of the population that can be differentially influenced by stress mindset manipulations. Genetic variation has been associated with anxiety and stress as well as placebo response and is therefore a promising potential moderator of stress mindsets.
A rich literature connecting catecholamine function to stress implicates the catecholamine regulatory system as a strong candidate for moderating responses to stress mindset interventions. Catecholamines play an important role in regulating autonomic nervous function, a key pathway involved in the processing of stress. Stress primarily affects catecholamine signaling in the prefrontal cortex (PFC), as conditions of acute stress impair PFC operations via excessive dopamine and norepinephrine release.\textsuperscript{7,8,9,10,11,12} Catechol-O-methyltransferase (COMT) is an enzyme that metabolizes catecholamines including dopamine, epinephrine and norepinephrine. The most well-studied polymorphism in \textit{COMT} is rs4680, which encodes a G (valine or val) high-activity to A (methionine or met) low-activity form of the enzyme.\textsuperscript{13} Given the specific effects of stress on catecholamine release, genetic variation in \textit{COMT} is a potential moderator of stress mindset effects. Here we examine how genetic variation at rs4680 influences a SIE and SID mindset manipulation.

\textbf{METHODS AND MATERIALS}

\textbf{Study Population}

124 participants were recruited from a university study pool for a study on “Stress and Performance.” Participants received $20 for their participation. A subset of 107 participants consented to be genotyped (Table 1).

\textbf{Procedure}

Participants were randomized to either a SIE or SID mindset manipulation elicited through a 3-minute multi-media video using words, music, and corresponding images to emphasize either the enhancing or deleterious properties of stress on cognitive performance (Crum et al., 2013). Following the videos, participants engaged in modified Trier Social Stress
Task\textsuperscript{14} in which the participant was asked to deliver a speech in a mock job interview (in front of a male and female interviewers) followed by question and answer session with feedback designed to engender threat or challenge stress states. Following the stress manipulation, we assessed participants’ mood, cognitive flexibility, and attentional bias. Genotype effects were examined for SIE vs. SID conditions. Additional details on the procedure and results from the main effects of mindset and feedback manipulation are reported elsewhere\textsuperscript{2}. The current manuscript reports analyses on the moderating role of the COMT genotype in shaping affective and cognitive outcomes to the stress mindset manipulation.

**Outcome Measures**

*Self-report measures.* Stress mindset was assessed at baseline and following the video manipulation using the Stress Mindset Measure\textsuperscript{1}. Participants rated agreement with eight statements regarding the effect of stress on a 0-4 Likert scale. Self-reported emotions were assessed using the Positive and Negative Affect Scale (PANAS)\textsuperscript{15} at five time-points: (1) upon arrival (baseline), (2) after watching the stress mindset videos (3) after receiving speech task instructions, (4) after the speech task and (5) after the question and answer component of speech task. Participants rated their feelings on twenty emotional states (ten positive; ten negative) on a 1 (not at all) to 5 (a great deal) scale. “Positive affect” (alphas range from .89 to .92 across time points) and “negative affect” (alphas range from .80 to .85) scales were calculated. We also calculated were “attentiveness” (alphas range from .68 to .81) and “anxiety” (alphas range from .81 to .90) subscales, as those scales were particularly relevant to the stress mindset paradigm.

*Cognitive performance measures.* To assess visual attention to positive and negative stimuli, participants engaged in a computerized dot-probe task.\textsuperscript{16} Black and white pictures of white male
faces identical to those used in Bradley et al\textsuperscript{17} served as stimuli. Reaction time to the probe was used to assess attentional bias. Exposure to the facial expression of the stimuli (happy, angry, or neutral) and target dot position (right or left of fixation) were randomized across all 80 trials presented and latencies were recorded by computer\textsuperscript{1}.

Cognitive interference was measured using the Stroop color-naming task\textsuperscript{18,19}. Participants completed 20 practice and 90 experimental trials. Stroop interference scores were computed as the difference in response latencies (in milliseconds) between incongruent and congruent trials, with higher scores indicating greater cognitive depletion. On the basis of procedures used in other work, incorrect responses and latencies above 2000 ms and below 200 ms were recoded as missing data\textsuperscript{18,19,20}.

Genotyping

Genomic DNA was extracted from saliva using the Qiagen kit (Valencia, CA) following the manufacturer’s protocol. TaqMan SNP Genotyping assays were purchased from Applied Biosystems, (Foster City, CA), and reads were obtained on rs4680 following the manufacturer’s protocol on an Applied Biosystems 7900HT instrument, using SDS version 2.4 software.

Statistical Analysis

Hardy–Weinberg Equilibrium (HWE) and linkage disequilibrium were calculated using the Online Encyclopedia for Genetic Epidemiology studies\textsuperscript{21,22}. We used a gene dosage model for “\textit{COMT} genotype”, that coded each participant’s rs4680 genotype as follows: 0 = met/met; 1 = val/met; 2 = val/val. ANOVAs for all dependent variables 2 (mindset: SIE vs. SID) x 3 (\textit{COMT} rs4680 genotype: met/met vs. val/met vs. val/val) were conducted. Where there were multiple assessments of the same measure (e.g., affect) we conducted repeated measures ANOVAs with time as a within subjects variable and mindset and genotype as a between
subjects variable. Where significant interactions were detected the sample was split by genotype to understand how the mindset manipulation differentially affected met/met vs. met/val vs. val/val participants. We controlled for baseline stress mindset and feedback in the stress task (positive or negative) in all regression models. Race (coded as 1=White, 2=Asian, 3=Black and 4=Other) and gender (coded as 1=female, 2=male) were included as covariates if they were indicated as a significant predictor of the dependent variable. Race was not a significant predictor of any dependent variable. Gender was a significant predictor for happiness bias but no other dependent variable.

RESULTS

Baseline Characteristics

The COMT rs4680 minor allele (A or met-allele) frequency was 0.38 and the SNP was in Hardy-Weinberg Equilibrium ($p = 0.75$), with the following distribution: 14% met/met, 48% val/met, and 38% val/val. Demographics are described in Table 1. Participants were 65.4% female; mean age=24.1 years; SD=5.1 and there were no significant demographic differences across COMT rs4680 genotypes.

Baseline stress mindset did not vary by COMT genotype ($F_{1,107} = 1.54, p = .22$), although met/met participants had a marginally more debilitating (i.e. SID) mindset ($M = 1.54 \pm 0.5$) than participants with met/val ($M = 1.87 \pm 0.6$) and val/val ($M = 1.81 \pm 0.7$) genotypes. There were no significant differences by genotype on baseline levels of positive affect ($F_{1,107} = 2.0, p = .14$), negative affect ($F_{1,107} = 1.8, p = .17$), anxiety ($F_{1,107} = 0.52, p = .6$), or attentiveness ($F_{1,107} = .48, p = .6$), as measured by the PANAS (Table 1).

Mindset Manipulation

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The stress mindset video manipulation produced significant changes in mindset as expected; participants randomized to SIE reported an increased SIE mindset whereas participants randomized to SID reported an increased SID mindset post-manipulation ($F_{1,96} = 92.9, p < .001, \eta^2 = .492$). The changes in mindset did not differ by COMT rs4680 genotype ($F_{2,96} = 1.15, p = .32, \eta^2 = .024$).

**Changes in Affect**

For positive affect, we observed a marginally significant linear time x genotype x mindset effect ($F_{2,92} = 2.73, p = .070, \eta^2 = .056$). Simple effects splitting the sample by genotype revealed a significant linear time x mindset effect ($F_{1,8} = 7.71, p = .024, \eta^2 = .419$) such that the mindset manipulation resulted in greater increases in positive affect for met/met individuals in the SIE condition compared to met/met individuals in the SID condition, whereas there were no significant effects of mindset on positive affect for met/val or val/val participants (Figure 1).

Similarly, for the attentiveness subscale of the PANAS we observed a significant linear time x COMT x mindset effect ($F_{2,92} = 4.12, p = .019, \eta^2 = .082$). Simple effects splitting the sample by genotype revealed a significant linear time x mindset effect ($F_{1,8} = 11.98, p = .009, \eta^2 = .596$) such that the mindset manipulation resulted in greater increases in attentiveness for met/met individuals in the SIE condition compared to met/met individuals in the SID condition, whereas there were no significant effects of mindset on attentiveness for met/val or val/val participants (Figure 1).

For negative affect, a significant quadratic effect was observed ($F_{2,92} = 3.60, p = .031, \eta^2 = .073$). Simple effects splitting the sample by genotype revealed a significant time x mindset effect ($F_{1,8} = 12.77, p = .007, \eta^2 = .615$) such that the mindset manipulation resulted in a sharper rise and fall in negative affect for met/met individuals in the SIE condition compared to met/met
individuals in the SID condition, whereas there were no significant effects of mindset on negative affect for met/val or val/val participants (Figure 2).

Similarly, for the anxiety subscale of the PANAS we observed a significant quadratic time x COMT x mindset effect ($F_{2,90} = 3.25, p = .043, \eta^2 = .067$). Simple effects splitting the sample by genotype revealed a reliable quadratic time x mindset effect ($F_{1,7} = 21.39, p = .002, \eta^2 = .753$) for met/met individuals such that the mindset manipulation resulted in a sharper rise and fall in anxiety for met/met individuals in the SIE condition compared to met/met individuals in the SID condition, whereas there were no significant effects of mindset on anxiety for met/val or val/val participants (Figure 2).

**Cognitive Tasks**

We examined the effect of stress mindset and genotype on participants’ attentional bias to happy and angry faces and cognitive interference by conducting a series of univariate ANOVAs. Results for the attentional bias for happy faces yielded a marginally significant mindset x genotype effect ($F_{2,91} = 2.56, p = .084, \eta^2 = .061$). Simple effects tests indicated that the mindset manipulation had a significant effect on happiness bias for met/met individuals ($F_{1,13} = 7.22, p = .028, \eta^2 = .474$) in that met/met individuals in the SIE condition had more bias towards happy faces and met/met individuals in the SID condition had more bias towards angry faces. Happiness bias did not significantly differ as a function of mindset condition for met/val and val/val participants (Figure 3). There was no interaction between mindset and genotype for attentional bias for threat faces.

With respect to cognitive interference (Stroop task), there was a significant mindset x genotype effect ($F_{2,91} = 3.09, p = .050, \eta^2 = .063$). Simple effects tests indicated that the mindset

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\[ \text{Gender was a significant predictor of happiness bias and therefore was included in the model as a covariate.} \]
manipulation had a marginally significant effect on cognitive interference for met/met individuals \( (F_{1,12} = 4.46, p = .073, \eta^2 = .389) \), such that met/met individuals exhibited less cognitive interference (improved cognitive performance) in the SIE condition compared to the SID condition. Cognitive interference did not significantly differ as a function of mindset condition for met/val and val/val participants (Figure 4).

**DISCUSSION**

Stress has both enhancing and debilitating effects depending on the lens through which it is perceived. Here we present novel evidence suggesting that genetic variation in \( COMT \) can further modify responses to a stress mindset manipulation. Priming with SIE mindset had the greatest effects on met/met compared to met/val and val/val individuals. SIE mindset effects on met/met individuals tended to be favorable. This difference between SIE and SID effects by genotype was evident in the significant increases in positive affect and attention, improved cognitive functioning, and bias toward happy faces post-speech found in the met/met SIE group. In comparison the responses of the met/val and val/val participants were not as affected by the mindset manipulation. Taken together, these results align with existing research suggesting that met/met individuals may be more responsive to placebo effects than val/val individuals\(^6,23\) and suggest that met/met individuals are also more responsive to a stress mindset manipulation. These findings are congruent with evidence that met/met individuals, compared to val/val individuals, are more susceptible to confirmation bias and are likely to be influenced by and have confidence in explicit initial information/instructions\(^24\).
Stress Mindset Theory holds that individuals who believe stress has enhancing properties are more likely to adaptively engage with stress they are experiencing and therefore experience potential positive benefits such as improvements in performance, health and wellbeing\(^1\). The results presented here suggest that this pattern of responses was especially true for met/met individuals who had more anxiety and negative affect in anticipation of stress but also a sharper reduction in negative affect and anxiety after the stress task was complete. Interestingly, met/met individuals exhibited the expected linear increase in positive emotion and attention after enduring stress whereas val/val and met/val individuals did not.

For met/met individuals, adopting a SIE mindset led to improved cognitive performance after the stressor. Whereas met/met individuals in the SID condition exhibited cognitive deficits marked by greater interference on the Stroop task, these deficits were completely eliminated for met/met individuals in the SIE mindset manipulation, marked by three-fold improvements in cognitive function for met/met individuals in the SIE condition compared to met/met subjects in the SID condition. These findings align with research showing that met/met individuals display inferior cognitive functioning under stress that results from the overabundance of prefrontal dopamine\(^{25,26,27}\) and suggest that a SIE mindset manipulation may be especially effective in these individuals to boost their cognitive performance under stress and eliminate—and perhaps even reverse—any comparative deficit to met/val and val/val individuals.

Mirroring these effects on cognitive interference, met/met participants in the SIE condition displayed striking increases in visual attention to positive stimuli; a complete reversal from the met/met participants in the SID condition who showed a bias away from positive faces. Conversely, met/val and val/val participants bias to positive faces was unchanged regardless of the mindset manipulation. These results further support that the effects of stress mindset
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manipulations on cognitive and affective responses to stress are most pronounced in met/met individuals.

Why might met/met individuals be more responsive to mindset manipulations? One potential explanation might be that met/met individuals are more attentive to the manipulation content than val/val or met/val individuals. However, our data do not support this explanation. Although the stress mindset manipulation video produced the expected changes in stress mindset, these effects did not differ by genotype. In other words, all participants, regardless of genotype, changed their mindset in a manner consistent with their respective manipulation. Thus, the effects of the mindset manipulation on cognitive and affective responses to stress did not occur because the mindset manipulation produced greater changes in mindset; rather the impact of the mindset manipulation on cognitive and affective responses was more potent for met/met individuals.

There are some limitations of the present study. Because COMT genotype was analyzed after the conclusion of the study, genotypes were not randomly assigned by condition. Reassuringly however, there were no significant differences by genotype across conditions despite the relatively low number of met/met participants. Another possible limitation is that the study was advertised as a “stress and performance” study, which may have been a disincentive for individuals who tend to be more negatively affected by stress and could have resulted in a self-selection bias toward more functional participants. It is therefore possible that participants were a more resilient group of met/met individuals than is represented in the general population. Finally, behavioral phenotypes arise from a complex interplay of multiple genes. Although we are limited here by the examination of a single gene and polymorphism, the functional effects of the rs4680 polymorphism in the dopamine signaling pathway and the abundance of behaviors
including placebo response that it modifies make it a model genetic variant with which to launch the exploration of genetic effects on mindset. Future work should aim to better understand other genetic moderators of stress that may be susceptible to manipulations of expectations, such as variation in other genes involved in serotonin signaling and dopamine pathways, and to better understand gene by environment interactions for polymorphisms that moderate the availability of key neurotransmitters for affective functioning, behavior, and physiology.

Taken together, the results herein add to our understanding of the effects of stress mindset manipulations by suggesting that some of the variability in mindset manipulation effects may be explained by genetic differences such as the COMT rs4680 polymorphism. The met/met genotype’s sensitivity to a mindset manipulation focused on stress is consistent with COMT’s relationship with stress and placebo responses. Future work is needed to determine if the COMT polymorphism also moderates the effects of mindset manipulations outside the domain of stress, such as mindsets about the nature of intelligence as fixed or malleable. To conclude, we find it critically important to point out that the existence of genetic moderators of mindset effects is not an indicator that these differences are static and uncontrollable. Rather, these differences hint at potential mechanisms linking mindset interventions with outcomes and, as such, can provide important insight for understanding how mindset interventions can be changed to maximize effects where desired (i.e. positive mindset effects and placebo responses) and minimize effects where undesired (i.e. negative mindset effects and nocebo responses), regardless of one’s genotype. Thus, although much remains to be explored, these results lay the preliminary groundwork for understanding not only for whom mindset effects are most effective, but why and how these effects may be optimized to improve important physiological, cognitive and affective outcomes.
CONFLICTS OF INTEREST  The authors declare no conflicts of interest.

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**TABLE 1. Demographic characteristics (n = 107)**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Genotyped participants</th>
<th>met/met 15 (14%)</th>
<th>val/met 51 (48%)</th>
<th>val/val 41 (38%)</th>
</tr>
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<tbody>
<tr>
<td><strong>Female N (%)</strong></td>
<td>70 (65.4)</td>
<td>10 (66.7)</td>
<td>33 (64.7)</td>
<td>27 (65.9)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>24.1 (5.1)</td>
<td>24.8 (5.6)</td>
<td>23.2 (5.7)</td>
<td>24.6 (4.2)</td>
</tr>
<tr>
<td><strong>Race N (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>41 (38.3)</td>
<td>6 (40.0)</td>
<td>25 (49.0)</td>
<td>10 (24.4)</td>
</tr>
<tr>
<td><strong>Asian</strong></td>
<td>32 (29.9)</td>
<td>2 (13.3)</td>
<td>12 (23.5)</td>
<td>18 (43.9)</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>19 (17.8)</td>
<td>1 (6.7)</td>
<td>9 (17.6)</td>
<td>9 (22.0)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>15 (14.0%)</td>
<td>6 (40.0)</td>
<td>5 (9.8)</td>
<td>3 (9.8)</td>
</tr>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Stress Mindset</strong></td>
<td>1.87 (.60)</td>
<td>1.51 (.46)</td>
<td>1.92 (.54)</td>
<td>1.86 (.68)</td>
</tr>
<tr>
<td><strong>Affect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Positive</strong></td>
<td>2.99 (.77)</td>
<td>3.13 (.50)</td>
<td>3.08 (.80)</td>
<td>2.79 (.78)</td>
</tr>
<tr>
<td><strong>Attentiveness</strong></td>
<td>3.28 (.79)</td>
<td>3.28 (.54)</td>
<td>3.38 (.82)</td>
<td>3.17 (.86)</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>1.50 (.50)</td>
<td>1.70 (.63)</td>
<td>1.42 (.44)</td>
<td>1.55 (.27)</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>1.72 (.73)</td>
<td>1.86 (.74)</td>
<td>1.63 (.68)</td>
<td>1.75 (.77)</td>
</tr>
</tbody>
</table>
FIGURE 1. Effects of Genotype and Mindset on Positive Affect (A,B) and Attentiveness (C,D). Error bars represent standard errors of the means.

(A) SIE

(B) SID

(C) SIE

(D) SID
FIGURE 2. Effects of Genotype and Mindset on Changes in Negative Affect (A,B) and Anxiety (C,D). Error bars represent standard errors of the means.

(A) SIE
(B) SID

(C) SIE
(D) SID
FIGURE 3. Effect of genotype and mindset condition on happiness bias. Error bars represent standard errors of the means.

(A) SIE

(B) SID
FIGURE 4. Effect of genotype and mindset condition on cognitive interference. Error bars represent standard errors of the means.

(A) SIE

(B) SID