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RESEARCH ARTICLE

Investigating interactive effects of worry and the catechol-o-methyltransferase gene (COMT) on working memory performance

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Abstract

Extant research indicates that worry is associated with reduced working memory. It remains unclear, however, what mechanisms contribute to impaired performance in worriers. Critically, dopamine in the prefrontal cortex heavily influences the stability of mental representations during working memory tasks, yet no research has probed its role in associations between worry and working memory. To address this gap, the current study was designed to examine the moderating role of dopamine on the association between worry and working memory, using the catechol-o-methyltransferase (COMT) gene as a proxy for basal levels of dopamine. Across four assessments, we examined within- and between-person variation in worry and its interactive effects with COMT to predict working memory performance. Within-person variation in worry interacted with COMT to predict accuracy, such that higher worry across time predicted less accuracy for homozygous Val carriers but not Met carriers. Our findings demonstrate that basal dopamine plays an important role in how increases in worry across time for an individual negatively impact working memory performance.

Keywords Worry · Working memory · Catechol-o-methyltransferase gene (COMT) · N-back · Dopamine · Anxiety

Introduction

Anxiety is one of the most prevalent psychiatric conditions. Research indicates that women are nearly twice as likely to experience anxiety than men (Altemus et al., 2014; Kessler et al., 2012). Worry is a specific dimension of anxiety that often is associated with impaired working memory (Moran, 2016)—a core component of executive function. Cognitive models of anxiety have hypothesized that worry disrupts working memory by co-opting cognitive resources, thereby leading to difficulties achieving task goals (Eysenck et al., 2007; Moser et al., 2013; Shackman et al., 2006). Importantly, dopamine in the prefrontal cortex (PFC) is critical for the maintenance of task goals and, therefore, also impacts working memory performance. While evidence supports the importance of dopamine in other clinical conditions associated with impaired cognitive performance, such as Parkinson's disease (Lewis et al., 2005), schizophrenia (Meyer-Lindenberg et al., 2005), and attention deficit hyperactive disorder (Lou et al., 2004), no studies have probed the role of dopamine in the association between worry and working memory performance. To address this gap in the literature, the current study investigated the role of dopamine in the association between worry and working memory in a female sample.[1]

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[1] We use the term "female" throughout this text to refer those who are assigned female sex at birth. It is important to make the distinction between sex and gender, neither of which are binary, nor do they have to overlap. In addition, the term "female" to describe sex assigned at birth can be elusive, as sex can refer to many factors, including genitals, hormones, and chromosomal make-up. Here, we solely use it to refer to those who experience menstrual cycles. We do not intend to extend "female" to signify or speak to any other biological, social, or identity-related factors in the current text. Furthermore, we use the term "women" when referring to the literature, as this is the term most often used when discussing gender differences in anxiety.

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Worry and working memory

Working memory refers to the ability to maintain and manipulate mental representations of stimuli that are no longer present in the external environment (Baddeley, 2012; Baddeley & Hitch, 1974; D'Esposito, 2007). A key component of working memory is the ability to stabilize mental representations to execute task-relevant goals. Cognitive models of worry posit that it impairs cognitive function by co-opting working memory resources, thereby affecting goal-directed behaviors. Attentional Control Theory (ACT; Eysenck et al., 2007) puts forth a specific account of worry's effect on cognitive performance, stating that it impairs attentional control (i.e., the central executive), which balances top-down (i.e., goal-directed processes) and bottom-up (i.e., stimulus-driven processes) resources to complete task demands (Eysenck et al., 2007; Moser et al., 2013). ACT has garnered empirical support with studies finding that worry impairs working memory performance, particularly when task demands are high (Hayes et al., 2008; Leigh & Hirsch, 2011; Sari et al., 2017). A recent meta-analysis further confirmed that the relationship between worry and working memory is quite robust (Moran, 2016) across phonological and spatial domains. Together, these data indicate that worry impairs the influence of the top-down goal-directed control system to impact cognitive performance.

Dopamine and working memory

While the effect of worry on working memory is robust, the factors that may explain this relationship remain opaque. Dopamine is a potential mechanism to investigate, as its actions in the prefrontal cortex (PFC) contribute to working memory performance (Goldman-Rakic, 1988). Dopaminergic activity can be categized into two main classes that uniquely influence brain function (Arnsten et al., 2015). The D1-class (D1 and D5 receptors) is more densely populated in the PFC, and therefore highly influential for PFC-mediated cognitive functions (e.g., working memory). On the other hand, D2-class (D2, D3, and D4 receptors) is more densely populated in the striatum, and therefore influential for functions that depend on the striatum (e.g., task switching, flexibility) (Bilder et al., 2004; Durstewitz & Seamans, 2008). Based on this, the dual state theory of dopamine function suggests that the dominance of the D1 class (i.e., D1-state) increases the stability of mental representations whereas the dominance of the D2-class (i.e., D2-state) increases flexibility (Cools & D'Esposito, 2011; Durstewitz & Seamans, 2008). Supporting this, seminal work in nonhuman primates has demonstrated that dopamine depletion in the PFC relates to poor working memory performance in tasks that require delayed recall (Brozoski et al., 1979; Sawaguchi & Goldman-Rakic, 1991). More recent work has established that extracellular dopamine in the PFC, in particular, is critical for the maintenance and stability of representations (Arnsten, 2015). Research also has replicated this effect in humans (Cools & D'Esposito, 2011). Therefore, the ability to maintain task goals to execute goal-directed behavior is heavily influenced by dopamine in the PFC.

The relationship between dopamine and working memory follows an inverted-U pattern, such that moderate levels in the PFC promote optimal performance and too much or too little dopamine impairs performance (Egan et al., 2001; Gibbs & D'Esposito, 2005). This pattern is based on a signal-to-noise ratio hypothesis of D1 signaling in the PFC during working memory tasks. When dopamine is too low or too high, the signal-to-noise ratio is reduced and mental representations are not as clear (Arnsten & Li, 2005; Witte & Flöel, 2012). This association between dopamine and working memory has been studied in humans using the $Val^{158}Met$ polymorphism in the catechol-o-methyltransferase (COMT) gene as a proxy for basal extracellular dopamine in the PFC. The COMT gene codes for the enzyme that catabolizes dopamine; its activity has been shown to contribute to 50% of dopamine degradation in the PFC (Männistö & Kaakkola, 1999; Yavich et al., 2007). Those with low levels of the COMT enzyme (homozygous Met allele carriers) have optimal levels of dopamine, and those with high levels of the enzyme (homozygous Val allele carriers) have too little dopamine in the PFC. Following the inverted-U pattern, Met/Met carriers (compared to Val/Val carriers) have been shown to perform better on working memory tasks, have more efficient activation in the PFC and more appropriate levels of PFC activation when needed during high demand conditions (Cools & D'Esposito, 2011; Egan et al., 2001; Jacobs & D'Esposito, 2011; Malhotra et al., 2002; Meyer-Lindenberg et al., 2005; Mier et al., 2010). In addition, Val/Val carriers show increased D1 receptor binding compared to Met carriers in fronto-cortical regions, while there is no difference between the two groups in the striatum, highlighting the importance of COMT for dopamine availability in the PFC (Slifstein et al., 2008). Further evidence for the importance of dopamine in the PFC comes from a study that investigated the effect of working memory training on D1 binding. Bäckman et al. (2011) found that working memory training reduced D1 binding and improved task performance (Bäckman et al., 2011). Importantly, the effect of COMT also depends on task difficulty, such that when task conditions become more demanding Met/Met carriers show enhanced performance (Cools & D'Esposito, 2011).

Worry, dopamine, and working memory

Evidence for the association between dopamine and anxiety comes from studies in populations of those with Parkinson's Disease—a condition characterized by dopamine depletion. Anxiety is one of the most prevent psychological disorders in Parkinson's disease, of which the most pervasive is

Generalized Anxiety Disorder, a condition characterized by chronic uncontrollable worry (Broen et al., 2016). Thus, higher rates of anxiety in Parkinson's patients might result from their lower dopamine levels. Some work in nonpatient samples also has supported a hypodopaminergic hypothesis of anxiety in humans (Berry et al., 2019).

Studies that have attempted to directly examine the role of COMT in anxiety, however, have reported mixed findings. Several studies have found that the Met allele is associated with higher self-reported anxiety (Eley et al., 2003; Enoch et al., 2003; Olsson et al., 2005; Stein et al., 2005) and fear processing measured by the startle response (Montag et al., 2008) in female samples. On the other hand, some studies have found that the Val allele was associated with greater self-reported anxiety (Kim et al., 2006) and panic disorder (Domschke et al., 2004). Others still have reported null effects of COMT on anxiety (Ohara et al., 1998). Therefore, the role of COMT in anxiety remains unclear.

Importantly, the purpose of the current study was to investigate the interaction of dopamine availability—via COMT genotype—and anxiety on working memory performance. Not to understand how dopamine availability relates to anxiety per se. Accounting for dopamine in studies of worry-related working memory impairments can more directly speak to a potential mechanism by which anxiety impairs cognition. Our predictions for the impact of COMT on the association between worry and working memory were driven by both the signal-to-noise ratio hypothesis of dopaminergic signaling in the PFC and the dual state theory of PFC dopamine function. As stated prior, the signal-to-noise hypothesis suggests that moderate levels of dopamine in the PFC enhances the signal to noise ratio which supports stable mental representations. Per the dual state theory, then, moderate levels of dopamine may support a D1 dominated state, which enhances goal representations in the PFC, whereas comparatively less dopamine in the PFC likely supports a D2 dominated state (Durstewitz & Seamans, 2008).

Empirical efforts attempting to understand the interaction between anxiety and dopamine on cognition have mostly been done so by experimentally inducing stress (Armbruster et al., 2012; Buckert et al., 2012). Animal models of stress and dopamine interactions postulate that stress increases dopamine release in the PFC and reorganizes brain function such that the PFC loses its regulatory influence and regions sensitive to heightened emotionality (i.e., amygdala and striatum) take control (Arnsten, 2009; Arnsten, 2015; Shansky & Lipps, 2013). This effect may partially depend on levels of basal dopamine in the PFC, which are strongly influenced by the COMT genotype (Tunbridge et al., 2019).

In contrast, no evidence indicates that individual differences in worry increases extracellular dopamine as stress might. However, because worry interferes with working memory function (Eysenck et al., 2007; Moran, 2016) and Val/Val carriers tend to be in a D2-domonaited state, characterized by decreased dopamine availability in the PFC that may lead to more distractibility and less goal representation (Witte & Flöel, 2012), we predicted that Val/Val carriers would perform particularly poorly when worry was present (Bilder et al., 2004; Durstewitz & Seamans, 2008). That is, the combined distracting effects of worry and reduced dopamine availability in the PFC would lead to the worst working memory function and therefore lowest performance.

The present study

In sum, the present study attempts to build on prior work by investigating the role of dopamine in the relationship between both acute worry (i.e., within-person change over time) and chronic worry (i.e., between-person differences) and working memory performance. Importantly, most of the studies on anxiety's interactive effects with dopamine have been done in animals. Animal models often use experimental stressors to induce a state of anxiety while studying the effect of dopamine (i.e., within effects) on working memory performance. However, it is unclear how these effects translate to individuals who experience chronic levels of worry. Importantly, due to differences in measurement variance at the group and individual level, within-person state effects (e.g., of induced stress) cannot be translated to between-person effects (e.g., of different levels of trait worry) and vice versa (Fisher et al., 2018). We predicted that worry and dopamine would interact to predict working memory performance, such that higher levels of worry would lead to reduced performance for Val carriers but not for Met carriers. We predicted that this would be the case for both acute and chronic worry.

Method

Participants

Participants were recruited from the Michigan State University campus and greater Lansing and East Lansing communities as part of a larger study examining the role of ovarian hormones across the menstrual cycle in the relationship between anxiety and cognition. Participants were not screened for anxiety and depression before participation in the study, as the aim was to capture a spectrum of worry scores. To investigate our goals, 94 individuals were genotyped for the COMT Val158/Met (rs4680) polymorphism (described below). The final sample consisted of 51 female participants who were homozygous allele carriers. Therefore, we proceeded with this sample size. All participants had regular menstrual cycles (i.e., 22-32 days) and were not taking birth control. They came into the laboratory for four in-person visits to complete the task. Participants could not have any

disruptions to their neuroendocrine system, nor could they be on any psychotropic medication. Participants were screened for cigarettes and e-cigarette use before every lab visit. Participants were not smokers, but they were asked if they had smoked either of these substances in the past 24 hours before every visit. One subject for one session smoked a cigarette in the 24 hours before a visit, and 2 subjects for one of their visits smoked an e-cigarette 24 hours before their sessions. Their mean age was 20.78 (*SD* = 1.65). Race of the participants were as follows: 61% white, 27% black, 6% Asian, and 6% identified as more than one race. All but one participant identified as women. Participants' levels of education were as follows: 51% completed partial college; 33% completed college; 14% had a high school-level education; 2% completed graduate level education; and one person did not report. Income levels were such that 53% of the sample reported an annual household income of $50,000 or less, whereas 47% of the sample reported an annual household income >$50,000.

Materials

N-back Working memory was assessed using the verbal N-back task. The task used is the same as that reported by Jacobs and D'Esposito (2011) in which dopamine effects were reported on behavior and neural activity. During each trial, one letter was presented on the screen for 1,000 ms. Participants were asked to indicate whether each letter is a "target" (i.e., the correct response) or "non-target" (i.e., incorrect response). The task consisted of 320 trials (0-back – 160; 2-back – 80; 3-back – 80). In the 0-back condition, participants were simply asked to respond to the letter "X" as a target and all other letters as non-targets. Memory load was manipulated by asking participants to respond to the letter based on whether they had seen it *n*- trials back. For instance, in a two back condition with a four trial sequence involving the letters A,D,C,D, the participant would indicate that the letter on the fourth trial is a "target," because it was presented two trials prior. On the other hand, if it were a three-back condition, it would be a "non-target." In 2 and 3 back conditions, lure trials also were included. Lure trials occur when a familiar letter is presented an incorrect number back. Lure trials add an additional "load' complexity, because they require participants to not only remember the letters presented previously but also require the inhibition of an automatic response to the target due to familiarity. Reaction times (RTs) and accuracy were calculated for correct responses only on each trial type. Correct trials were further trimmed for reaction times greater than 200 ms and accuracy greater than 30% across all trial types.

Penn state worry questionnaire (PSWQ; Meyer et al., 1990) The PSWQ is a self-report measure that consists of 16 items assessing an individual's degree of worry. The internal consistency of the PSWQ has been shown to be high in adult samples ($\alpha = 0.91$). Participants completed the PSWQ items anchored to each day. Items were summed to produce a total score that ranged between 16 and 80, with higher scores indicating more worry on that day. Internal consistency of the daily PSWQ was computed by taking the average of the alpha of PSWQ scores at all four time points ($\alpha = 0.94$). The mean PSWQ score was 38.13 (SD = 15.07).[2] To examine the amount of within-person variability in the PSWQ, we calculated an individual standard deviation (iSD) to examine the average intra-individual variability across subjects. This was done by calculating the standard deviation for each subject. The mean iSD was 8.02 (SD = 6.23), indicating there was significant within-person variability in worry scores.

COMT analysis Participants provided approximately 1.8 mL of saliva daily across their menstrual cycle (approximately 35 days) using the passive drool method. Participants were instructed to keep the saliva samples in their freezer, until transported to the lab, where they were kept in a −80 °F freezer. One saliva sample for each participant were shipped to CD Genomics (Shirley, NY) where they performed genotyping of the COMT Val158/Met (rs4680) polymorphism using SNaPshot Multiplex System for SNP Genotyping. Of the 94 participants that were genotypes, 51 participants were homozygous allele carriers. Therefore, our final sample consisted of 24 Met/Met and 27 Val/Val carriers.

Procedure and data analysis

As part of the larger investigation, participants were instructed to complete both the PSWQ and saliva samples daily throughout their participation in the study (approximately 35 consecutive days). Within the 35 days, participants also came into the laboratory to complete the N-back task across four laboratory visits meant to correspond to phases of their menstrual cycle. Data (PSWQ and N-back performance) from the four laboratory visits were used for the current analyses.

Analyses were conducted using the "lme4" package (Bates et al., 2014) in R Version 3.5.1. First, the analyses aimed to investigate basic task effects. We aimed to replicate that lure trials were cognitively demanding by testing whether participants were less accurate and slower compared with targets and nontargets as per Jacobs and D'Esposito (2011). Similarly, we probed effects of load on accuracy and reaction time. We expected that participants would be slower and less accurate on lure trials during two and three back load conditions. To examine this, we used multilevel models to account for repeated visits for each participant. Separate models were estimated for load and trial type to examine their effects on reaction time

[2] Between-centered SD = 12.83; Within-centered SD = 8.40.

and accuracy. Load (0-back, 2-back, 3-back) and Trial Type (Not-Target; Target; Lure) were entered as dummy-coded predictors. Time was entered as an effects-coded predictor to control for practice effects.

Within-person centering for PSWQ (i.e., examining variation from a person's own mean) was conducted by computing a mean for each participant and subtracting their mean from each of their own four observations (Hoffman & Stawski, 2009). For these models COMT (Met, Val) was entered as an effects-coded between-person predictor and PSWQ was entered as a continuous within-person predictor of accuracy and reaction time. A cross-level interaction was also included to examine whether the effect of worry varies by COMT genotypes. Between-person centering for worry was conducted by computing a mean for each participant, followed by computing an overall mean (i.e., mean of means), which was then subtracted from each participant's mean score. This approach allowed us to estimate relative differences between people's average worry scores. For these models, COMT was included as an effects-coded predictor, PSWQ as a continuous between-person predictor of reaction time and accuracy, and their interaction. All models included time as an effect-coded predictor to control for practice effects. The random effect structure for all models only included a random intercept, and no random slopes, and the variance-covariance matrix followed a compound symmetry structure. Partial eta squared η^2_p is reported as an estimate of effect size: 0.05 represents a small effect, 0.1 a medium effect, and 0.2 a large effect (Cohen & Taylor, 1973). Confidence intervals also were reported for significant effects. For all models, assumptions were examined, and Cook's distance was computed to assess for leverage.

Our analysis was the first to investigate the effect of dopamine and worry on working memory performance, and therefore a priori expectations of the magnitude of the effect size were unknown. However, our study had the benefit of repeated measurements over time that strengthened our ability to detect an effect. In addition, the use of MLMs provided the ability to patrician within and between variance to reduce residual error. Furthermore, we conducted a sensitivity power analysis to investigate the size of the effect we could detect with our sample size using G Power. The test family was specified as "F tests" and the statistical test was specified as "ANOVA: Repeated measures, within-between interaction" for within person effects and "ANOVA: Repeated measures, between factors" for between person effects. The alpha probability level was set to 0.05 and the power probability level was set to 0.8 to determine the expected effect size of a between-within interaction at 80% power. The sample size was set to 51, number of groups was 2 (Met/Val), and the number of repeated measurements was set to 4. Four different sets of sensitivity-based analyses for reaction time and accuracy on two and three back lure trials were estimated. Average correlations across repeated measurements were as follows for two-back reaction time and accuracy and three back reaction time and accuracy, respectively r's = 0.55, 0.56, 0.61, 0.34. A conversion was used to estimate the f value provided by G Power to partial-eta squared (η^2_p). The results of the sensitivity analyses for between-within analyses revealed that given our sample size, we were powered to detect a small effect for two back reaction time ($\eta^2_p = 0.022$) and accuracy ($\eta^2_p = 0.022$), as well as three back reaction time ($\eta^2_p = 0.019$) and accuracy ($\eta^2_p = 0.03$). The results of the sensitivity analyses for between-centered analyses revealed that given our sample size, we were powered to detect a small to medium effect for two back reaction time ($\eta^2_p = 0.09$) and accuracy ($\eta^2_p = 0.09$), as well as three back reaction time ($\eta^2_p = 0.10$) and accuracy ($\eta^2_p = 0.07$). Therefore, we proceeded with the analyses with the ability to detect small effects for our cross-level interaction and small to medium effects for between-centered analyses.

Results

Basic task effects

Descriptive statistics for the task can be found in Table 1. Overall, basic effects replicated the effects found by Jacobs and D'Esposito (2011).

Table 1 Descriptive statistics for the N-Back task

	Met/Met	Val/Val	p
Reaction time			
0-back targets	486.98 (60.75)	508.49 (71.19)	NS
0-back nontargets	408.29 (55.08)	439.57 (87.22)	NS
2-Back targets	594.80 (101.03)	636.67 (132.91)	NS
2-Back nontargets	513.30 (90.14)	537.49 (107.61)	NS
2-Back lures	658.44 (146.59)	672.47 (147.75)	NS
3-Back targets	635.69 (113.35)	675.97 (137.27)	NS
3-Back nontargets	517.45 (95.85)	546.38 (111.06)	NS
3-Back lures	630.31 (137.62)	631.33 (173.91)	NS
Accuracy			
0-back targets	0.93 (0.06)	0.88 (0.12)	.02
0-back nontargets	0.99 (0.00)	0.99 (0.00)	NS
2-Back targets	0.82 (0.14)	0.77 (0.19)	NS
2-Back nontargets	0.99 (0.02)	0.98 (0.03)	NS
2-Back lures	0.81 (0.17)	0.74 (0.20)	NS
3-Back targets	0.66 (0.14)	0.66 (0.15)	NS
3-Back nontargets	0.98 (0.02)	0.08 (0.03)	NS
3-Back lures	0.68 (0.16)	0.66 (0.19)	NS
Worry			
	37.73 (13.75)	37.71 (16.09)	NS

NS not significant

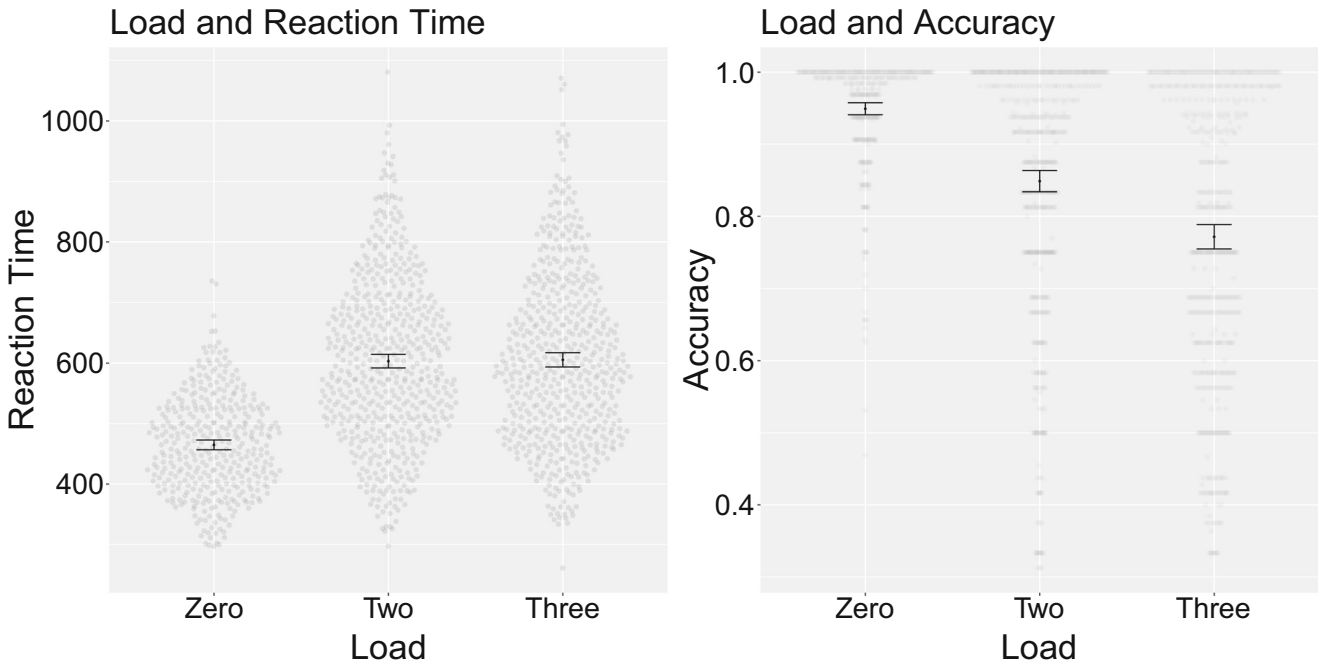

Fig. 1 Load Effects on Reaction Time and Accuracy. The findings replicated that of Jacobs and D'Esposito (2011), such that participants were significantly slower on two and three back load conditions. In addition, participants were significantly less accurate on the three-back condition

Load The results revealed the expected effect of load on reaction time ($\eta^2_p = 0.29$), such that participants were significantly faster on 0- back than 2-back ($b = 138.44$, $p < 0.001$, 95% CI [125.83, 151.06]) and 3-back ($b = 140.63$, $p < 0.001$, 95% CI [128.02, 153.25]) trials. However, 2-back and 3-back RTs were not significantly different from each other ($p = 0.70$). For accuracy, results revealed a significant effect of load ($\eta^2_p = 0.16$), such that participants were significantly more accurate on 0-back than 2-back ($b = 0.10$, $p < 0.001$, 95% CI [0.12, 0.08]) and 3-back ($b = 0.18$, $p < 0.001$, 95% CI [0.16, 0.20]) trials. In addition, participants were more accurate on 2-back than they were on 3-back ($b = 0.08$, $p < 0.001$, 95% CI [0.06, 0.10]) trials. In sum, these effects were in line with predictions, demonstrating that 3-back trials proved to be most difficult for participants, as they were slower and less accurate (Fig. 1).

Trial type Results for reaction time revealed the expected of effect of trial type ($\eta^2_p = 0.29$) such that participants were slower on lures than targets ($b = 53.18$, $p < 0.001$, 95% CI [40.54, 65.81]) and nontargets ($b = 148.66$, $p < 0.001$, 95% CI [136.02, 161.30]). Participants were also significantly slower on targets than they were on non-targets ($b = 95.48$, $p < 0.001$, 95% CI [84.18, 106.78]). Similarly, there was a significant effect of trial type on accuracy ($\eta^2_p = 0.43$), such that participants were significantly less accurate on lures than nontargets ($b = -0.27$, $p < 0.001$, 95% CI [0.25, 0.28]) and targets ($b = 0.064$, $p < 0.001$, 95% CI [0.05, 0.08]). They were also significantly less accurate on targets compared to nontargets ($b = -0.20$, $p < 0.001$, 95% CI [0.19, 0.22]) (Fig. 2). These results mirror expected effects, and therefore we proceeded to examine our effects on lure trials.

Worry and COMT

Within-person centered worry There were no significant effects for RTs (all $ps > 0.30$). For 2-back lure accuracy, there was a trend effect of COMT in the expected direction such that Met carriers were more accurate ($b = -0.07$, $p = 0.08$). Importantly, there was qualified by a significant COMT x PSWQ interaction ($p = 0.03$, $\eta^2_p = 0.04$) (Table 2).[3] Consistent with hypotheses, analysis of simple slopes revealed that worry significantly predicted lower accuracy on 2-back lure trials for Val carriers ($b = -0.004$, $p = 0.01$, 95% CI [0.007, 0.008]) but not Met carriers ($p = 0.50$) (Fig. 3). Similar effects were seen for 3-back lures, such that worry marginally predicted lower accuracy on 3-back lures in Val ($b = -0.004$, $p = 0.06$) but not Met carriers ($p = 0.40$) (Table 3).

Between-person centered worry For reaction time, no effects reached significance for 2-back lures (all $ps > 0.20$) or 3-back lures (all $ps > 0.43$). For accuracy, there continued to be a marginal effect of COMT in the expected direction, such that

[3] We tested whether this effect remained with Met/Val carriers and found that the interaction was still present ($p = 0.03$), evidencing a significant effect for Val carriers.

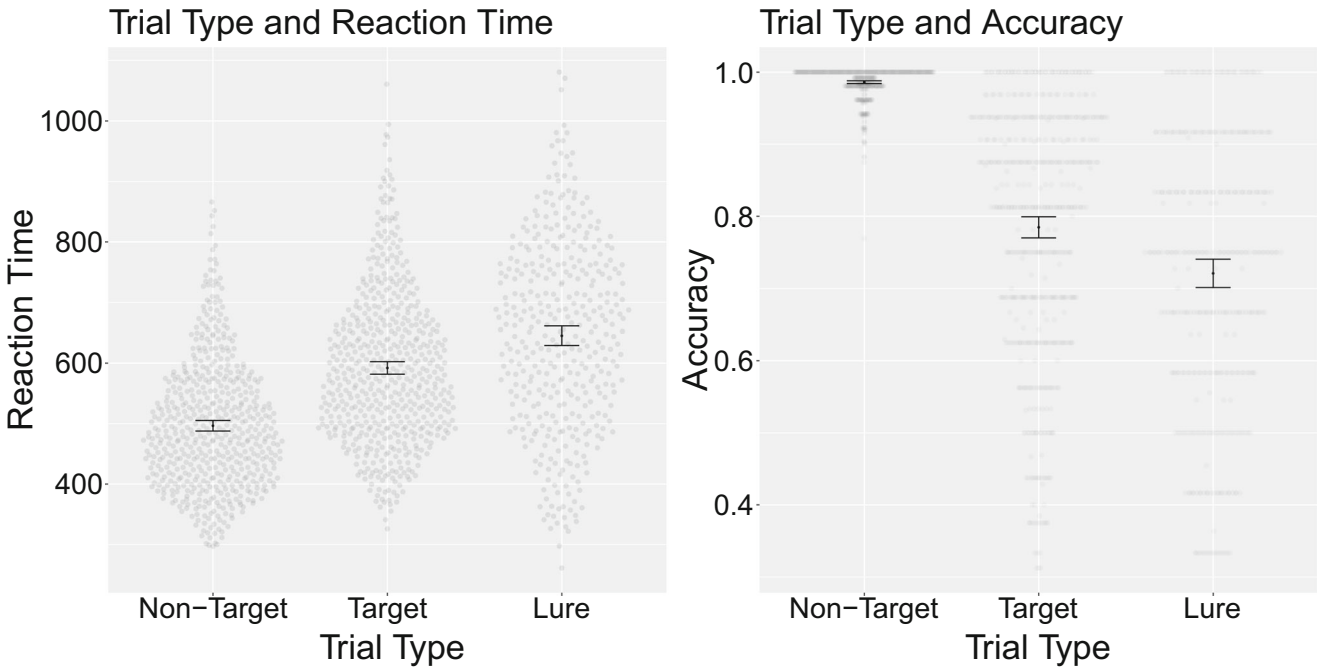

Fig. 2 Trial Type Effects on Reaction Time and Accuracy. These results also replicated Jacobs and D'Esposito (2011), revealing that participants were slower and less accurate on lure trials

Met carriers were more accurate on 2-back lures than Val carriers ($b = 0.08$, $p = 0.08$). However, there was no main or interaction effects involving worry (all ps > 0.49).

Discussion

The aim of this study was to examine the role of dopamine in the association between worry and working memory performance in a female sample. To do so, we investigated within- and between-person variation in worry and their interactions with the COMT gene as a proxy of basal dopamine levels (Gibbs & D'Esposito, 2005; Tunbridge et al., 2019). We predicted that those with low basal levels of dopamine (Val/Val carriers) would show a stronger relationship between higher worry and poorer performance on demanding lure trials than those with high basal levels of dopamine (Met/Met carriers). Consistent with our hypothesis, we found that, indeed, higher worry was associated with lower accuracy on lure trials in Val/Val carriers but not Met/Met carriers. This association was clearly demonstrated for within-person variation in worry and was not apparent for between-person variation suggesting that the interaction between state worry and basal dopamine is most important for working memory performance.

Our findings provide support for the role of dopamine in the association between worry and working memory performance. Interestingly, our results indicated that dopamine plays a more critical role in how worry relates to accuracy than reaction time. Dopamine's influence on working memory

Table 2 Worry and COMT predicting Two-Back accuracy

Fixed effect	Estimate	Standard error	t	p
Intercept	0.65	0.38	20.14	0.000**
Worry	−0.004	0.001	−2.44	0.016*
COMT	0.07	0.04	1.79	0.08
COMT x Worry	0.005	0.002	2.171	0.03*
Variance components	Variance	Standard deviation		
Intercept	0.017	0.13		
Residual	0.01	0.11		

COMT was included as a dummy-coded variable, and Val is the base in the model presented here. Time also was included in this model as an effect coded predictor ($p < 0.001$)

Table 3 Worry and COMT predicting Three-Back accuracy

Fixed effect	Estimate	Standard error	t	p
Intercept	0.59	0.031	19.04	0.000**
Worry	−0.004	0.001	−1.925	0.056
COMT	0.03	0.04	0.86	0.39
COMT x Worry	0.005	0.002	1.97	0.051
Variance components	Variance	Standard deviation		
Intercept	0.009	0.09		
Residual	0.02	0.13		

COMT was included as a dummy-coded variable, and Val is the base in the model presented here. Time also was included in this model as an effect coded predictor ($p < 0.001$)

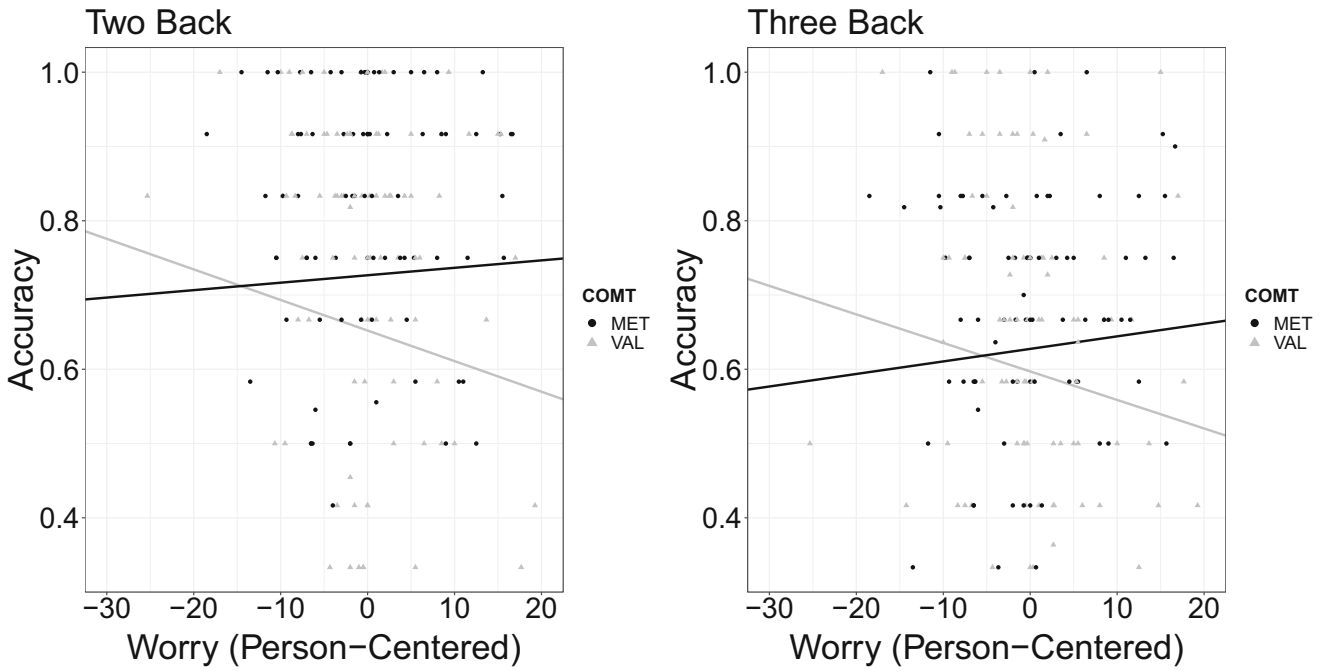

Fig. 3 Worry and COMT on Lure Accuracy. This line graph demonstrates that worry and dopamine interact to predict accuracy on lure trials. Each point on the graphs represents an observation. The results show that for Val/Val carriers, worry relates to less accuracy

tasks is characterized as reflecting the maintenance and stability of mental representations (Arnsten & Li, 2005; Sawaguchi & Goldman-Rakic, 1991). It is therefore plausible that dopamine would affect the ability to correctly identify the target (i.e., accuracy) more so than how long it takes to do so (i.e., reaction time). In this way, perhaps worry impairs working memory performance through impairing one's ability to maintain mental representations in mind, providing a novel candidate mechanism to further explore in future research.

Our results also suggest that dopamine's effect on working memory performance in the presence of worry may be different than that of acute stress (Arnsten, 2015). Stress increases dopamine release, and it is therefore hypothesized that Val/Val carriers benefit from stress's DA-agonist effects that move them closer to an optimal position on the inverted-U, while Met/Met carriers demonstrate impaired performance (Armbruster et al., 2012; Buckert et al., 2012) . Our findings suggest that instead, heightened levels of worry for an individual may pose an additional load that hampers performance. This supports cognitive models of worry, such as ACT, suggesting that worry leads to an additional load on working memory resources, and as such, increases "noise" in the PFC, hindering goal stability and therefore performance for those with low-circulating dopamine (Val/Val carriers) (Eysenck et al., 2007; Moran, 2016).

The longitudinal design allowed for the examination of within- and between-person effects of worry (i.e., individual variation from a person's own mean and chronic worry). It has been noted that within- and between-person variability have unique predictive ability and using one to characterize the other can lead to false generalizations (Fisher et al., 2018). Our results support the importance of separating the two, as we found that within-person variation in worry (i.e., experiencing more worry than a person is accustomed to) impacted accuracy, whereas chronic, between-person levels did not. These findings indicate that dopamine plays less of a role for individuals who are chronically high in worry, as they may have identified other mechanisms to compensate for the added load of worrisome thoughts. On the other hand, experiencing more worry than one's own average may lead to impairments that are not as easily compensated for.

One way to understand the role of dopamine in the decision to compensate for worrisome thoughts may be to consider the involvement of the striatum in evaluating mental effort (Cools, 2015). Cools (2015) proposes that dopaminergic activity in the striatum is involved in evaluating whether or not to execute effortful functions, such as goal stabilization. The dual state theory of dopaminergic activity suggests that a D2-dominated state influences striatum-dependent functions, leading to increases in susceptibility to distraction and enhanced flexibility (Durstewitz & Seamans, 2008). Thus, those with lower D1 signaling (Val/Val carriers) in the PFC, who are likely in a D2 state, are more apt to weigh the costs and benefits of alternative actions. It could be, then, that Val carriers who experience a rise in their average levels of worry symptoms decide that increasing mental effort is not worth the cost and therefore decide to forgo the demands of goal stabilization. As such, reduced accuracy during times of higher

worry and greater demands on working memory resources in Val carriers could reflect their "mental demand avoidance" (Cools, 2015). That is, Val carriers who experience increases in worry may decide that enhancing effort on a task to overcome low D1 signaling and worry is too costly. Further examining these possibilities represents an important direction for future research.

Critically, our findings point to the importance of translational science to inform human psychiatric conditions. Research investigating COMT-stress interactions have mostly focused on nonhuman primates and rats, and very little work has probed this in humans. Although preclinical work benefits from the ability to directly assess and manipulate stress and neural function, the experience in humans is more complex. While worry is a specific kind of anxiety that is common in humans, it is not an experience that can be easily induced and measured in animals. As such, identifying the nuanced ways that human psychological experiences may mimic or diverge from animal findings is vital for enhancing translational science (Grillon et al., 2019).

Our findings provide novel insights regarding the role of dopamine in the association between worry and working memory but should be interpreted with a few limitations in mind. While our analyses were conducted on a sample of similar size as past work investigating genotype-cognition associations (Buckert et al., 2012; Jacobs & D'Esposito, 2011), replication in larger samples would be fruitful. In addition, our work was conducted in a sample of naturally cycling female participants. Research has shown that estradiol may down-regulate COMT enzyme activity (Jacobs & D'Esposito, 2011), and therefore, work in larger samples also should investigate interactive effects between COMT, worry and estradiol to predict working memory performance.

Conclusions

Our findings point to the importance of dopamine in worry-cognition associations as a potential explanatory mechanism for how worry impacts working memory. Our analyses also show the necessity to evaluate within- and between-person variation in worry to differential the roles of state and trait worry in working memory.

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Code availability Code can be made available upon request.

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Declarations

Competing interest The authors declare no conflicts of interest related to this publication.

Ethics approval This study was approved by the Human Research Protection Program at Michigan State University (approval number: CGA #141791).

Consent to participate Written informed consent was obtained from all participants.

Consent for publication Participants signed informed consent regarding publishing data.

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