WORRY AND WORKING MEMORY FUNCTION: INVESTIGATING INTERACTIVE EFFECTS OF WORRY, BASAL DOPAMINE, AND ESTRADIOL ON THETA-GAMMA COUPLING IN A FEMALE SAMPLE

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ABSTRACT

Anxiety is a leading cause of disability worldwide and is two times more prevalent in female than male populations. Importantly, anxiety is associated with reduced prefrontal cortex (PFC) function in areas critical for cognitive processes such as working memory. Attentional Control Theory (ACT) suggests that worry, a core cognitive feature of anxiety, places an additional load on working memory resources, thereby leading to cognitive impairments and enhanced effort to maintain performance. Ample evidence supports that worry is associated with impaired working memory performance. However, fewer studies have clarified the association between worry and working memory-related neural function. Preclinical models have proposed that anxiety may interact with dopamine and estradiol to influence lateral prefrontal cortex function, a region critical for working memory. However, no study has examined their interactive effects in humans. This project aims to address this gap by examining dopamine and estradiol's effects on the relationship between worry and oscillatory neural activity (i.e., theta-gamma coupling; TGC) involved in working memory function in a female sample. The study aims are to (1) establish the relationship between worry and TGC; (2) examine the role of tonic dopamine (measured by the COMT gene) in the association between worry and TGC; and (3) examine whether estradiol moderated the association between worry and TGC. I hypothesized two plausible directions for the association between worry and TGC based on previous literature. Research suggests that those with chronic psychiatric conditions evidence less TGC compared to controls due to reduced prefrontal cortex function (i.e., *hypoactivation hypothesis*). Alternatively, aligned with the predictions of ACT, it is plausible that worry may be related to enhanced TGC indicating exaggerated neural activity to maintain favorable performance (i.e., *processing inefficiency hypothesis*). For the second aim, I predicted that lower dopamine levels would strengthen the

association between worry and TGC, irrespective of the direction of the association. Lastly, I expected the association between worry and TGC to be enhanced when estradiol is low. The sample consisted of 135 female participants who completed a verbal working memory task (N-back) up to four times in-person. Saliva samples on the day of N-back completion were used to assay for estradiol concentrations and extract COMT gene polymorphisms (rs4680). Worry was within- and between-person centered to examine the role of within-person changes in worry over time and between-person differences in worry averaged across a whole menstrual cycle. TGC was computed on correct trials of the N-back task. I found evidence for both the hypoactivation and processing inefficiency hypotheses on two-back lure trials – trials that were of moderate difficulty. Specifically, within-person increases in worry were associated with reduced TGC for those with high average symptoms of worry. In contrast, within-person increases in worry were associated with increased TGC for those with low average levels of worry. I also found that increases in within-person worry were associated with enhanced TGC for Val/Val carriers (those with less tonic dopamine), whereas there was no association for Met/Met carriers. Further, this association was enhanced for Val carriers when estradiol was high. The findings demonstrate that the association between within-person increases in worry and TGC may depend on the amount of worry one experiences on average and tonic dopamine levels. This study further highlights the utility of incorporating dopaminergic neurotransmission in our understanding of worry-related cognitive impairments.

I dedicate this dissertation to my family – for your sacrifice and belief in me. I carry it with me everywhere, every day. This is for you. Mwen renmen nou anpil; mèsi pou tout sa nou fè pou mwen.

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1. INTRODUCTION

Attempting to understand the relationship between anxiety and cognition has been the topic of debate and inquiry for decades (Diamond, 2005; Gray, 1984; Mogg & Bradley, 1998). Anxiety disorders are the most prevalent class of mental health disorders, and are associated with substantial economic burden and reduced capacity for daily functioning (Baxter et al., 2014; Konnopka & König, 2019; Marciniak et al., 2004). Understanding the association between anxiety and cognition can improve our knowledge of anxiety's impact on functioning more broadly.

One facet of cognition that is often associated with anxiety is working memory (Moran, 2016; Shackman et al., 2006). Working memory refers to the ability to maintain, manipulate and update information no longer present in the external environment (Baddeley, 2012; D'Esposito, 2007). Working memory supports tasks such as solving a math problem, maintaining the digits of a new phone number for immediate use, and retaining the first two examples in this sentence. It is an essential process that contributes to a wide range of other cognitive functions and guides behavior on-line to achieve a goal. Research has offered convincing evidence that anxiety is related to impaired working memory performance (Eysenck et al., 2007; Eysenck & Derakshan, 2011; Moran, 2016). What remains unclear, however, are the neural correlates involved. Neural correlates of working memory dysfunction in anxiety are only recently being integrated into anxiety frameworks (Eysenck et al., 2022). Uncovering associations between anxiety and neural correlates of working memory function may have important implications for elucidating how anxiety impairs cognition and lay the foundation for developing novel interventions targeting anxiety-related cognitive impairments.

Critically, anxiety disorders are more prevalent and have a more severe and chronic course in female populations (Altemus et al., 2014; Kessler et al., 2012). Cognitive models of anxiety generally fail to consider sex-specific factors that may uniquely contribute to the association between anxiety and working memory. Preclinical studies have offered insight in this regard and have proposed that ovarian hormones and their effects on neurotransmitter systems, such as dopamine, interact to influence working memory in female rats (Shansky et al., 2004; Shansky & Lipps, 2013). However, the translational utility of these models remains unclear. The current study therefore aimed to examine the translational utility of preclinical models of anxiety-related cognitive impairments by examining relevant neurobiological factors.

1.1. Terminology and Study Aims

I use the term "female" within this text to refer to individuals assigned female sex at birth. Sex assigned at birth is distinct from gender and is intentionally not used interchangeably within the text. It is important to note that sex assigned at birth is often used ubiquitously to refer to numerous factors, including sex chromosomes (e.g., XY or XX), gonads, and/or sex hormones. However, sex is not binary, and there can be variability across chromosomes, gonads, and hormones that do not align with the "female" and "male" differentiation. Sex can be an elusive term that refers to any or all of these factors. Here, I use the term "female" to refer to those who experience menstrual cycles and have varying levels of estradiol.

The focus on ovarian hormones (namely 17-β estradiol) and its effect on dopamine is intentional as a means to focus on female health, which has been historically neglected in the literature (Beery & Zucker, 2011). Neuroscience research tends to omit female populations precisely because of varying levels of ovarian hormones across the menstrual cycle. This omission has caused direct harm (Correa-de-Araujo, 2006; Parekh et al., 2011) and has led to a

relative shortage of knowledge on estradiol's effects on health. In recent years, there have been substantial strides to address this harm and improve our understanding of sex hormone milieu in cognitive neuroscience and anxiety (Beery & Zucker, 2011; Li & Graham, 2017; McEwen et al., 2001; McEwen, 2010; Taylor et al., 2021). This study joins in these efforts by integrating literature on ovarian hormones and cognition into a framework that may improve our understanding of anxiety's influence on cognition in human populations. Finally, although work has attempted to investigate the role of estradiol in sex differences, the aim of the current study is not to make a statement on "sex dimorphism," "sex differences," or "sex convergence/divergence" (McCarthy et al., 2012). Instead, the aim is to focus on how estradiol and dopamine may contribute to our understanding of anxiety-related cognitive impairment in a historically underrepresented population in the cognitive neuroscience literature.

The current study aimed to build toward a comprehensive understanding of the association between worry and a neural marker of working memory function in a female sample. Research has provided ample evidence that worry is associated with reduced working memory performance. Examining whether and how worry is associated with neural mechanisms involved in working memory dysfunction during task completion is also useful to advance our understanding of worry-related cognitive dysfunction (Eysenck et al., 2022). I specifically focused on worry, a transdiagnostic dimension of anxiety (Heller et al., 1997; Nitschke et al., 2001; Snyder et al., 2022), and its association with a neural marker of working memory function, theta-gamma coupling (TGC). I also examined how dopamine and estradiol, critical neuromodulators of working memory, influence the association between worry and TGC. Together, the approach of the current study was to identify a novel association between worry

and a neural marker of working memory function in a female sample while taking relevant neurobiological factors into account.

1.2. The Association Between Worry and Working Memory Performance

One of the most influential theories of working memory was proposed by Baddley and Hitch nearly 50 years ago (Baddeley & Hitch, 1974). Various revisions of this theory over the years have led to a prominent understanding of working memory as the ability to store, update, and manipulate mental representations that are no longer present in the physical environment. Baddley and colleagues proposed that working memory involves the temporary storage of information in "stores" based on sensory input (e.g., visual, phonological/verbal and episodic). In addition to maintaining information, working memory also involves utilizing stored information to guide behavior toward a goal (e.g., a task goal). This process was proposed to be executed by an overarching system called the "central executive" (Baddeley, 2000, 2012; Baddeley & Hitch, 1974; Baddeley & Logie, 1999; Norman & Shallice, 1986). The central executive is an attention-based, capacity-limited system that biases and coordinates lower-order stores for the purposes of a task goal. Miyake and colleagues specified the functions of the central executive as the ability to shift attention, update mental representations, and inhibit irrelevant information, the latter of which is seen as a core component of all executive functions (Miyake et al., 2000; Miyake & Friedman, 2012). Therefore, working memory is a complex, "multicomponent" construct that involves both the storage of information *and* the control processes (i.e., executive functions) for the maintenance and use of that information to guide and support a task goal (see Figure 1A) (D'Esposito, 2007; D'Esposito & Postle, 2015; RepovŠ & Baddeley, 2006). As such, when working memory is affected, it may broadly impact various cognitive functions.

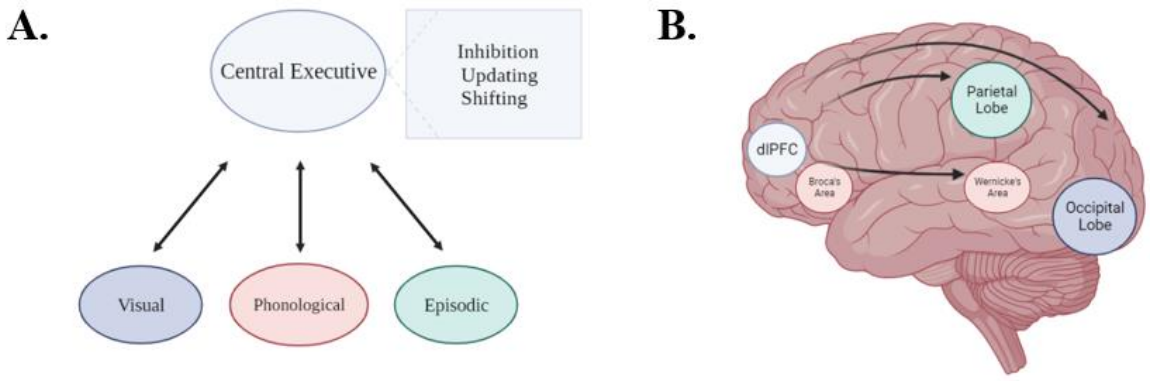

Figure 1. Working Memory Model. **A.** Graphical depiction of components of working memory and executive functions integrating the models from Baddley & Loggie (1999) and Miyake et al. (2000). **B.** Neural model of working memory components, adapted from the figure presented by Chai et al. (2018).

Drawing from cognitive models of working memory, Eysenck and colleagues put forth Attentional Control Theory (ACT) to propose a framework for worry's impact on cognitive performance (Eysenck et al., 2007). ACT proposes that worry impacts the ability to balance top-down control and bottom-up input (termed attentional control). Specifically, worry poses an internal interference that co-opts working memory resources and leads to executive function impairments. That is, ACT posits that worry leads to difficulties managing top-down control functions implemented by the central executive. ACT outlines many key assumptions; however, I will focus on two for the purposes of this study. First, ACT makes the distinction between trait and state anxiety, and posits that within-person increases in worry (e.g., state worry) are more likely to be experienced by those high in trait anxiety. As such, in those with high trait anxiety, increases in state anxiety levels are more likely to negatively impact working memory function. Secondly, ACT proposes that increases in worry are more likely to be associated with processing *inefficiency* (i.e., longer reaction time) rather than *ineffectiveness* (i.e., accuracy). ACT assumes

that those who experience increased worry are motivated to reduce its deleterious impacts by implementing more effort and adopting compensatory strategies to maintain performance.

Empirical support for ACT has corroborated that state worry indeed affects working memory. Studies have found that inductions in state worry are associated with reduced working memory capacity for high worriers (Hayes et al., 2008; Leigh & Hirsch, 2011; Stefanopoulou et al., 2014) and a non-affected sample (Sari et al., 2017). These studies suggest that active worry indeed affects the ability to store information, and this effect may be more prominent for high trait worriers.

Evidence also supports that trait worry impacts *both* processing inefficiency and ineffectiveness across executive functions. For instance, in tasks that require inhibition, those with generalized anxiety disorder (GAD) and high trait worry evidenced slower reaction times and reduced accuracy (Hallion et al., 2017; Price & Mohlman, 2007; Rosa-Alcázar et al., 2020). For shifting, studies have found that worry was related to reduced performance on working memory tasks under a dual task condition (Crowe et al., 2007), and a self-report measure of switching using the Attentional Control Scale (Williams et al., 2017). Studies have also found that worry was associated with reduced accuracy on updating tasks (Crowe et al., 2007; Gustavson & Miyake, 2016a; Hallion et al., 2014; Held et al., 2020; Stefanopoulou et al., 2014). Together, two conclusions can be drawn from the existing data. First, evidence suggests that worry is associated with processing efficiency and effectiveness impairments. The context in which worry impacts either is likely dependent on task context (e.g., cognitive demand and task difficulty) (Berggren & Derakshan, 2013). Second, because worry is associated with impaired performance across executive functions, it is likely that worry affects the central executive, aligned with ACT's predictions.

1.3 The N-back Task: A Promising Task for Understanding Working Memory Dysfunction in Worry

The verbal N-back task allows for measuring cognitive performance across varying levels of cognitive demand. The N-back is considered a "dynamic span" task. In a recent meta-analysis, worry was found to have robust effects on dynamic span tasks compared to simple (e.g., digit span) and complex span tasks (O- or R-span) (Moran, 2016). During the task, individuals must continuously maintain and update information to correctly identify whether a stimulus was seen *n* trials back. For instance, on 2-back conditions, participants must remember whether they have seen a letter two trials back to identify whether the letter is a "target" (a correct match) or a "non-target" (an incorrect match). The task allows for the investigation of performance with varying levels of cognitive demand, by increasing the amount of information that must be stored for accurate task performance (e.g., 2-back vs 3-back conditions; see Figure 2). Some iterations of the task include an additional complexity called "lures." Lures are when a stimulus matches a previously shown letter but is presented the incorrect *n* trials back (see Figure 2). These trials require inhibiting a prepotent response due to familiarity in addition to remembering the correct order of previously presented stimuli.

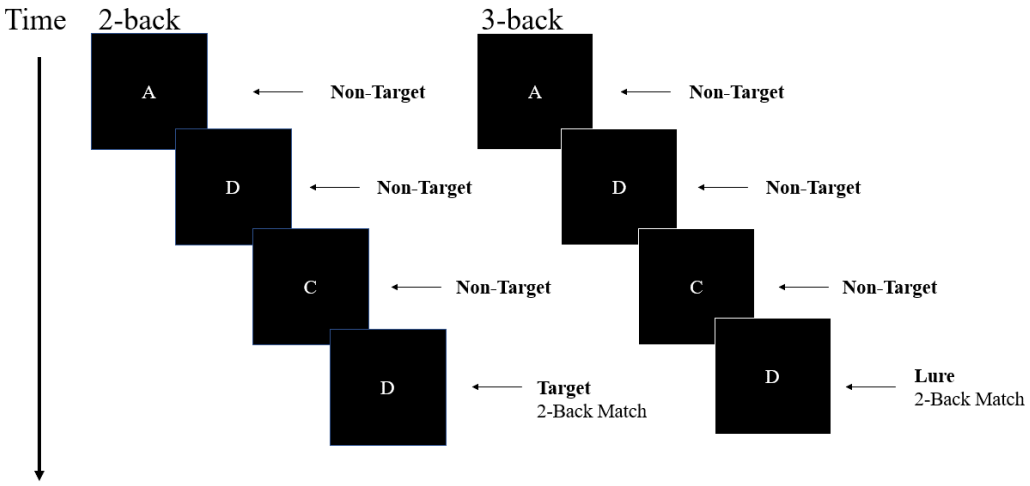

Figure 2. Graphical representation of 2- and 3-back conditions on the verbal N-back task. Each black box represents a trial, during which a letter is presented one at a time. Participants must respond to every letter. During 2-back conditions, participants must identify whether a letter matches the one shown two trials before (a "target"). In 3-back conditions, participants must determine whether the letter was seen three trials before. All other letters are "non-targets." Within 2- and 3-back conditions, participants may also be presented with lure trials, a special kind of non-target. When this occurs, participants are shown a letter that was previously seen but is the incorrect number of trials back to be considered a target.

The N-back therefore relies on various processes, such as verbal storage and inhibition (a core executive function), to support successful task completion. Indeed, studies have shown that the N-back may represent a more complex measure of working memory as the task does not often converge with other working memory tasks, such as complex span tasks (Jaeggi et al., 2010; Kane et al., 2007; Redick & Lindsey, 2013). This may be because the N-back represents multiple functions that rely on working memory (e.g., maintenance and updating) (Schmiedek et al., 2014). Studies using the N-back task to investigate the effects of worry have found that those with high levels of worry evidence lower accuracy and longer reaction times, specifically under high load conditions (Balderston et al., 2017; Stefanopoulou et al., 2014). Gustavon and Miyake (2015) suggest that updating may be a critical feature to assess in worry because it involves the balance between top-down control and bottom-up processing. That is, the task requires individuals to be attentive to new information while using control processes to maintain and use

that information for a specific goal. Therefore, the N-back task is useful for measuring worry's association with working memory processes that involve maintenance, updating, and inhibition (Gustavson & Miyake, 2016).

1.4 The Association between Worry and Neural Processing: A Focus on the Lateral Prefrontal Cortex

ACT leverages empirical data on cognitive performance to formulate predictions on worry's influence on cognition. Cognitive neuroscience scholarship can also provide insight to elucidate the nuanced relationship between worry and cognition. The dorsal lateral prefrontal cortex (dlPFC), in particular, is a critical region involved in working memory and top-down control (Braver, 2012; Braver et al., 2007; Brozoski et al., 1979; Goldman-Rakic, 1988; Kane & Engle, 2002). Specifically, the dlPFC is necessary to maintain information (Smith & Jonides, 1999) and coordinate brain function to implement top-down control (Braver et al., 2007; D'Esposito et al., 1995; Miller & Cohen, 2001). The neural recruitment needed to maintain goals is implemented by the dlPFC (Curtis & D'Esposito, 2003). In this way, the dlPFC serves as a critical region for maintaining task set and exerting control, which is critical for working memory functions (Barbey et al., 2013; D'Esposito & Postle, 2015b) (see Figure 1B).

Higher levels of worry are associated with altered dlPFC activity at rest and during active periods of worry. Studies have found that worry is linked to left-lateralized activity that includes the dlPFC (Heller et al., 1997), increased resting state activity in the left dlPFC (Bijsterbosch et al., 2014), and more dlPFC activation and associated regions during active worry (Mohlman et al., 2017). At rest, worry is also associated with enhanced resting state functional connectivity between the amygdala and the dlPFC (Feurer et al., 2021). Further, another study found heightened intra-network connectivity in the fronto-parietal network (which includes dlPFC) in

higher worriers at rest (Gerlach et al., 2021). These studies suggest that worry is associated with heightened dlPFC activity and connectivity with the dlPFC at rest.

There is additional evidence that worry is associated with dlPFC activity on cognitive tasks, but the results are mixed. Warren and colleagues found that worry was associated with heightened activity in the left posterior dlPFC during conflict on the Stroop task when anxious arousal was also low (Warren et al., 2013), suggesting that it is specific to this cognitive dimension of anxiety. However, another study found no association between worry and lPFC activity on the Stroop task (Silton et al., 2011). In addition, Fales and colleagues (2008) found that anxious individuals only evidenced increased activation in the PFC during lure trials of the N-back, suggesting worriers may attempt to manage their effort by periodically engaging the PFC. Balderstron et al. (2017) found, however, that those diagnosed with anxiety disorders (including GAD) evidence reduced lPFC activation compared to controls on high load conditions of the N-back, although they did not investigate lure trials specifically (Balderston et al., 2017). Other studies using emotional conflict have also found increased lPFC activation (Barker et al., 2018; Park et al., 2016). Therefore, the association between worry and lPFC is nuanced and partially modulated by cognitive demand. When task demands are high (such as lure trials of the N-back), worry may be associated with hyperactivation of the dlPFC due to increased effort (or processing inefficiency). However, it also plausible hypoactivation of lPFC may be present when working memory is excessively taxed (Silton et al., 2010).

1.5 Theta-Gamma Coupling: A Maker of Working Memory Function

While imaging studies have offered great insight into the role of the dlPFC in cognitive tasks for high worriers, advanced signal processing with electroencephalography (EEG) data can further augment our understanding of lPFC activity and cognitive processing. EEG offers

temporally precise measurements of neural oscillations. Neural oscillations reflect the synchronized synaptic activity of neuronal populations (Canolty & Knight, 2010), and their activity can provide the ability to understand complex cognitive processing.

Oscillatory activity is grouped into specific frequency bands that are thought to be important for different cognitive processes. Commonly studied frequency bands include delta (1-3 Hz), theta (4-8 Hz), and alpha (9-12 Hz), which are considered slower rhythms that are important for higher-order processing, such as cognitive control and inhibition. Beta (13-30 Hz) and gamma (30 Hz or higher) are faster rhythms linked to motor function, sensory input, and attention. Further, there are three components of oscillatory activity – (1) phase, which refers to a particular location on a sine wave measured in radians or degrees; (2) amplitude (or power which is amplitude squared), which refers to the strength of the signal; and (3) frequency, typically measured in hertz (Hz), and measures cycles per second (i.e., 2 Hz is two cycles per second). Using what we know about frequency bands and oscillatory activity, we can begin to understand their integration for cognitive processing.

For instance, these frequency bands often demonstrate "cross-talk," that is, some sort of coordination, to perform higher-order cognitive processes and support neural integration (Fries, 2005). One way to measure this is cross-frequency coupling (CFC; Canolty and Knight, 2010). While several CFC metrics exist, phase-amplitude coupling (PAC) has gained traction in recent years. PAC occurs when a low frequency brain rhythm modulates the amplitude of a higher brain rhythm. This was first discovered in the rat hippocampus (Bragin et al., 1995). Since then, it has been observed in the human hippocampus (Axmacher et al., 2010) and neocortex (Canolty et al., 2006).

Theta-gamma coupling (TGC) is a specific type of PAC that serves as a "neural code" for the sequential ordering and maintenance of information (Lisman & Jensen, 2013; Roux et al., 2012). Theta oscillations in frontal recording sites have been linked to cognitive control functions and the maintenance of sequential storing of information (Cavanagh & Shackman, 2015; Sauseng et al., 2010). On the other hand, gamma activity is important for storing information (Honaken, 2014; Vidal, 2006). Gamma activity in the lateral frontal cortex is modulated by working memory load, with higher load associated with higher gamma power (Roux et al., 2012). Therefore, gamma is critical for storing items in working memory (Roux & Uhlhaas, 2014; Tallon-Baudry & Bertrand, 1999). TGC occurs when gamma amplitude is nested at specific phases of the theta cycle (see Figure 2). In this way, multiple items can be organized along a theta cycle (Axmacher et al., 2010; Lisman & Jensen, 2013; Roux et al., 2012; Roux & Uhlhaas, 2014; Sauseng et al., 2019). Higher TGC strength indicates that gamma amplitude is a strong function of theta phase, reflecting enhanced integration between neuronal assemblies (Lisman & Jensen, 2013). Relatively less coupling reflects reduced integration between neuronal assemblies (see Figure 2).

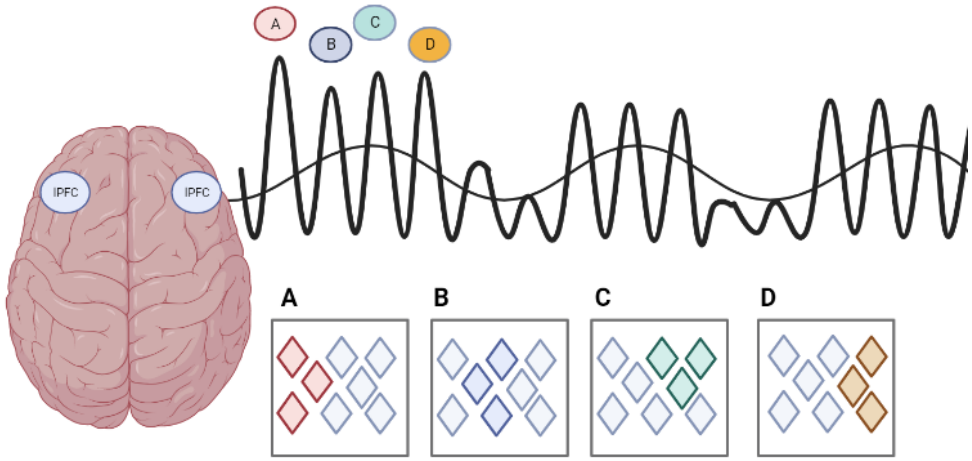

Figure 3. Graphical representation of theta-gamma coupling adapted from Turi Z, Alekseichuk I, Paulus W (2018). The figure shows that gamma activity holds distinct mental representations activated by specific neuronal assemblies nested and organized at specific phases across the theta cycle. The nesting of gamma along the theta frequency is reflective of theta-gamma coupling. The mental representation of a letter is associated with a unique activation pattern of neuronal assemblies (colorful diamonds), resulting in a gamma oscillation. Theta, with its own unique assembly, controls the synchronized pattern of gamma oscillations to maintain the letter presentations in sequence. Heightened TGC is therefore reflective of higher integration of distinct neuronal assemblies.

There has been empirical support for TGC in the N-back task at frontal lateral sites that correspond to lateral PFC regions. Rajji and colleagues (2017) found that TGC at frontal-lateral sites was significantly higher during trials that required the ordering of information compared to trials that did not (i.e., higher on targets and lures in comparison to non-targets). This study supported the idea that TGC reflects a process initiated by the need to maintain the sequential ordering of information. TGC has also been studied for those with various psychiatric conditions, including Schizophrenia and Alzheimer's Disease (for review, Yakubov et al., 2022). These studies have found that TGC at frontal-lateral sites is decreased in those diagnosed with Schizophrenia, Alzheimer's Disease, and mild cognitive impairment compared to healthy controls (Barr et al., 2017; Brooks et al., 2021; Goodman et al., 2018). These conditions are also well-known to correspond with decreases in dlPFC recruitment during working memory tasks

(Guo et al., 2019; Kumar et al., 2017). Importantly, consistent with the role of the dlFPC in exerting top-down control to support working memory (see Figure 1), some work has supported that TGC is increased during high load conditions in comparison to low load (e.g., 0-back) (Barr et al., 2017; Rajji et al., 2017). These findings imply that TGC is sensitive to the neural process that needs to be performed (i.e., the need to maintain the ordering of information). Therefore, given the critical role of the dlPFC as necessary for the control processes involved in working memory, TGC at frontal lateral sites may reflect the instantiation of that process to support the maintenance and ordering of information in mind. Thus, TGC may serve as a promising tool to characterize this neural process for those with elevated levels of worry.

1.6 Dopamine as a Modulator of the Link between Worry and Working Memory

Critically, dopamine (DA) signaling in the PFC is needed to stabilize and maintain mental representations (Braver et al., 2007; Braver & Cohen, 2000; Curtis & D'Esposito, 2003; D'Esposito, 2007), and therefore influences working memory function. Through the mesolimbic and mesocortical pathways, dopamine innervates the PFC and has far-reaching actions on brain regions and neuronal communication involved in working memory and anxiety (Haber, 2010). Despite the critical role of dopamine in working memory, understanding how dopamine modulates anxiety's impact on cognitive performance and brain function remains a gap in the current anxiety literature. Below I briefly review dopamine's critical role in PFC-dependent function and its potential utility for illuminating worry-related working memory dysfunction.

Seminal studies in primates were the first to identify a role for DA in the PFC in cognitive function and found that dopamine depletion in the dlPFC impairs working memory in rhesus monkeys (Brozoski et al., 1979; Williams & Goldman-Rakic, 1995). We have since come to understand that the relationship between dopamine and working memory follows an inverted-

U curve, such that too much or too little dopamine impairs performance (Arnsten, 2009) – termed the "signal-to-noise" hypothesis. Specifically, DA in the PFC plays a role in sculpting mental representations and maintain task set. Too little dopamine makes it challenging to inhibit distraction, and higher dopamine levels make it difficult to maintain anything in mind (i.e., a suppression effect). Therefore, depending on where individuals lie on the inverted-U at a given time, DA may impair or support PFC-dependent cognitive function.

Support for the inverted-U association comes from work in humans using PET studies. D1 class dopamine receptors are more densely populated in the PFC, in comparison to D2-class receptors which are more densely populated in the striatum (Arnsten & Li, 2005). PET studies have found that reduced D1 receptor binding supports dlPFC activity during working memory tasks (Bäckman et al., 2011). Another study found a U-shaped association between D1 binding and errors on a sorting task, supporting that too little to too much binding, which reflects heightened and reduced dopamine availability, respectively, impairs performance (Takahashi et al., 2008).

Another common way to study dopaminergic activity in the PFC in humans is the catechol-o-methyltransferase (COMT) gene. The COMT gene codes for the COMT enzyme that is responsible for over 60% of DA degradation in the PFC. The gene has gained traction as a proxy for prefrontal dopaminergic tone because it is mostly expressed in the PFC, compared to other brain regions dense in dopaminergic neurons (Matsumoto et al., 2003). The most studied functional single nucleotide polymorphism (SNP) is rs4680. This SNP codes for the ancestral valine (Val) to methionine (Met) substitution at codon 158 ($Val^{158}Met$). Met carriers have less enzyme activity and therefore more DA availability than Val carriers (Tunbridge et al., 2006, 2019).

It is essential to differentiate the utility of COMT as a proxy for tonic dopamine levels (i.e., basal levels) in the PFC instead of a candidate gene for personality traits or psychiatric vulnerability. Considerable caution has been advised when attempting to link genes to psychiatric illnesses due to concerns with publication bias and false positive rates (Duncan & Keller, 2011; Keller, 2014). However, the purpose of using COMT in the present study is to leverage our knowledge of the functional role of the COMT enzyme. It is a non-invasive way to approximate individuals' putative position on the inverted-U association between dopamine and working memory at baseline.

There has been traction for the utility of COMT in this regard. Homozygous Met carriers (more baseline DA) have demonstrated enhanced performance on working memory tasks, including the Wisconsin Card Sorting Test (Egan et al., 2001) and the N-back task (Goldberg et al., 2003) compared to Val carriers. This effect has also been replicated when dopamine levels are manipulated with tolcapone, a COMT inhibitor (Apud et al., 2007; Roussos et al., 2009), such that Val carriers perform better than Met carriers when given tolcapone during working memory tasks. COMT has also been shown to be related to differences in neural efficiency during the completion of working memory tasks. Met carriers demonstrate an advantage by having lower sustained activity in the dlPFC (Egan et al., 2001; Mattay et al., 2003; Meyer-Lindenberg et al., 2006). Similarly, when participants are given amphetamine, which increases dopamine in the PFC, Val carriers show enhanced efficient activity in the PFC and Met carriers do not (Mattay et al., 2003).

Importantly, few studies have examined the interactive effects of COMT and anxiety on working memory performance. Previous literature has found that stress and COMT interact to increase dopamine in the PFC to impact performance. Increases in stress may lead to a phasic

increase in dopamine in the PFC. For Val carriers, this increase might help support working memory, while it may be detrimental to Met carriers. For instance, studies have found that Val carriers evidence enhanced performance on 2-back conditions following an acute stressor (Buckert et al., 2012; Qin et al., 2012). These findings suggest that increases in stress-induced dopamine availability may have differential effects for Met and Val carriers because of their relative differences in dopaminergic tone at baseline.

Our group recently showed that worry also interacts with the COMT gene to influence working memory performance. Preliminary evidence has shown that within-person increases in worry over time are related to impaired performance on 2-back lure trials for Val carriers (Louis et al., 2021). We did not find that having more worry on average (i.e., between people) interacted with COMT to predict working memory performance. These findings may seem contradictory to the aforementioned results with acute stress. Unlike stress, however, acute changes in worry may not increase DA signaling in the PFC. Instead, worry places additional demand on cognitive systems, such as the central executive. We concluded that Val carriers are dually impacted by within-person increases in worry and lower dopamine levels (Louis et al., 2021). Due to dopamine's influence on the ability to gate distraction and stabilize mental representations, it may play a critical modulatory role in the association between worry and working memory.

1.7 Estradiol as a Modulator of the Link between Worry and Working Memory

Dopamine in the PFC is influenced by a variety of factors, including sex hormones. 17β-estradiol ('estradiol'), the major estrogen during reproductive years, influences the abundance of dopamine in the PFC (Xiao et al., 2011) and dopaminergic neurotransmission (Barth et al., 2015). As such, estradiol further modulates dopaminergic action in the PFC. Parsing out the role

of dopamine and estradiol in anxiety is critical to understanding the neurobiology of anxiety-related cognitive dysfunction in female populations.

Numerous studies have found that estradiol facilitates better working memory performance in rats (Bimonte & Denenberg, 1999; Holmes et al., 2002), and that introducing estradiol in the PFC (in comparison to the hippocampus) also improves working memory in rats (Sinopoli et al., 2006). In humans, results follow a similar effect. In a young adult female sample of those not on hormonal contraceptives, one study measured estradiol concentrations via radioimmunoassay and grouped women into low and high estradiol groups. They found that working memory performance was higher for women in the high estradiol group compared to women in the low estradiol group (Hampson & Morley, 2013). Hampson & Morley (2013) also found that only estradiol, and not progesterone, was related to fewer errors. Additional evidence comes from work examining the benefits of hormone replacement therapy (HRT) in postmenopausal women. Those taking estrogen-based HRT (compared to combined administration of estrogen and progesterone and a control) performed better on spatial and verbal working memory tasks (Duff & Hampson, 2000). Another study found that exogenous estradiol (delivered transdermally) improved performance on a variety of PFC-dependent tasks (e.g., the Stroop task, and digit span task), as opposed to those that may rely more heavily on the hippocampus (e.g., delay recall) (Krug et al., 2006). This finding supports another study that found that HRT benefits working memory performance (Keenan et al., 2001). Collectively, these studies provide evidence that estradiol concentrations throughout the lifespan influence working memory performance.

Estradiol influences working memory partially via its modulatory actions on dopamine (Barth et al., 2015; Shansky et al., 2004; Xiao & Becker, 1994). Pertinent to this study, estradiol

interacts with COMT specifically, by down-regulating COMT enzyme activity and increasing dopamine availability in the PFC (Xiao & Becker, 1994). Therefore, the effect of COMT could be modulated by varying levels of estradiol across the menstrual cycle (see Figure 4). In a direct test of this, Jacobs and D'Esposito (2011) examined whether the effect of dopamine (measured via the COMT gene and enzyme) was modulated by within-person changes in estradiol. They found that at low estradiol levels, Met carriers demonstrated higher accuracy on 2-back trials of the N-back compared to Val carriers – consistent with the inverted U hypothesis. However, when estradiol was high, this effect was reversed such that Val carriers performed better than Met carriers (see Figure 4). The same finding was replicated in a separate sample (N=74) of young adult females using the same task (Louis et al., unpublished data). These effects support estradiol's modulatory role in dopamine levels in the PFC and how it impacts working memory performance. These effects were also specified to moderate levels of task difficulty, suggesting that stress due to task difficulty may also moderate the effect of COMT (see Figure 4).

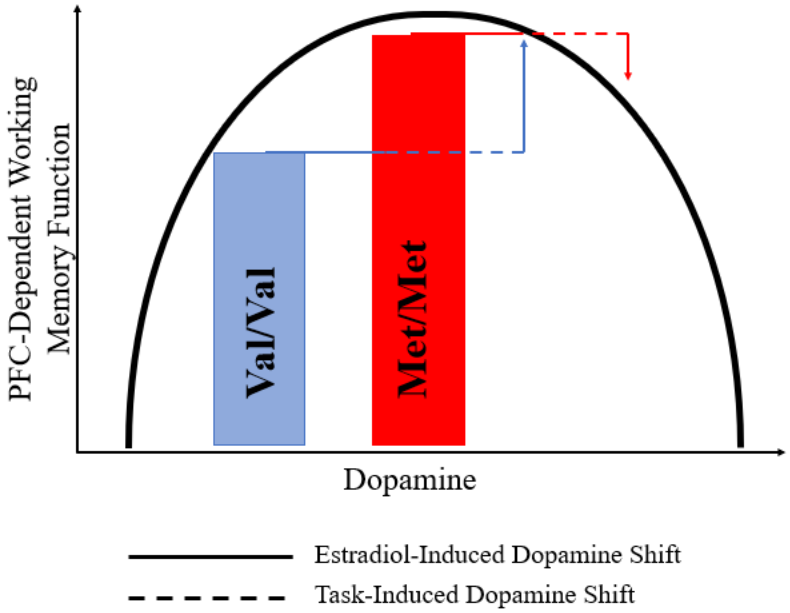

Figure 4. Graphical depiction of the inverted-U association between dopamine and the PFC-dependent function. Val/Val carriers have more COMT enzyme activity, reducing DA availability in the PFC. In contrast, Met carriers have relatively less enzyme activity and more DA availability in the PFC. As such, Met/Met carriers are hypothesized to be at the top of the inverted-U at baseline. However, DA availability is malleable and can be influenced by sex hormones and cognitive demand. Adapted from Jacobs & D'Esposito (2011).

Finally, in a recent study, Gloe et al. (2021) found that worry and estradiol interacted to predict working memory performance on lure trials. They found that higher average levels of estradiol across the menstrual cycle was associated with reduced accuracy on lure trials for those with high average levels of worry. They found no effects of within-person worry and estradiol on performance. These findings provided preliminary evidence that average levels of worry and estradiol influence working memory performance. Given estradiol's effect on tonic dopaminergic tone, examining whether within-person changes in estradiol impact the association between worry and working memory on a neural level will be critical. Although Gloe and colleagues did not within-person effects on behavior, it may be present at the neural level.

1.8 The Current Study

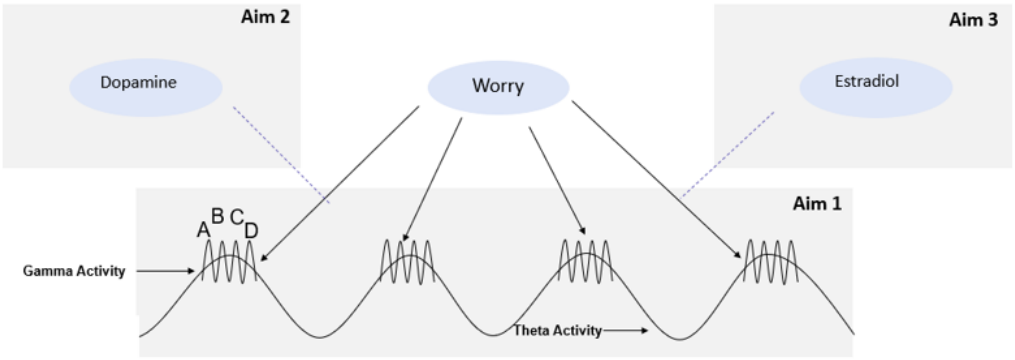

Figure 5. Graphical Illustration of Main Aims. Aim 1 examines whether worry (within- and between- persons) is associated with TGC. Aim 2 examines whether dopamine influences the association. Aim 3 examines the modulatory role of estradiol.

The existing literature suggests that worry is associated with poor working memory performance and altered activity in the dlFPC. The current study therefore examined the association between worry and TGC at frontal-lateral sites on the N-back task. Based on previous literature, I hypothesized two directions for the association between worry and TGC. First, I hypothesized that worry would be associated with reduced TGC due to prior studies that have found this effect for those with psychiatric conditions. Such a finding would indicate that worriers experience difficulties with lPFC neuronal integration and reduced activity at lPFC regions (i.e., *hypoactivation hypothesis)*. Alternatively, worry may be associated with hyperactivation in the dlPFC (e.g., increased TGC). Such a finding would indicate that worriers may enhance effort to maintain favorable performance, which would be aligned with ACT (i.e., *processing inefficiency hypothesis*). The current study will examine both within-person and between-person differences in worry as studies have found effects for both (Gloe et al., 2021; Louis et al., 2021; Zainal & Newman, 2020), and ACT predicts that trait and state worry are likely to impair working memory. Similarly, as ACT proposes, I expected the association

between worry and TGC to be present for high average worriers who also experiences a within-person increase in worry (ie., those high on between- and within- person worry).

Second, I used the COMT gene as a proxy for tonic dopamine to examine whether it moderated the association between worry and TGC. No studies have directly tested whether dopamine modulates TGC, however several lines of evidence suggest that it may be influential. TGC has been linked to conditions known to be affected by changes in dopaminergic pathways, such as Schizophrenia. Using an animal model, Lohani et al (2019) proposed that dopamine excitability in the ventral tegmental area (VTA; which innervates the PFC) can enhance TGC strength. Further, dopamine may aid in selecting relevant information that should be maintained (Benchenane et al., 2011). Pertinent to this study, within-person increases in worry interacted with COMT allele group to predict working memory performance, such that for Val carriers, higher levels of worry predicted worse performance on the N-back task. Therefore, I expected there would be an interaction between COMT and within-person changes in worry to predict TGC, such that association would be present for Val carriers. More basal dopamine may be protective by allowing for the maintenance of information in mind. Therefore, irrespective of whether the association between worry and TGC follows a suppression or processing inefficiency effect, I expect the association to be stronger for Val carriers.

Lastly, I aim to examine whether estradiol levels across the menstrual cycle (within-person changes) moderate the association between worry and TGC. Given that estradiol tends to increase neural efficiency and support working memory function, I predict that the association between worry and TGC will be enhanced at low estradiol states. Notably, however, Gloe et al. (2021), did not find that within-person changes in estradiol moderated the association between worry and working memory. I predicted that these effects might be evident at the neural level. It

is also possible that the effects will be null and consistent with Gloe and colleagues' findings. Relatedly, considering basal dopamine levels may be essential for elucidating estradiol's effects. To address this, exploratory analysis will examine whether worry, COMT, and estradiol interact to predict behavior and TGC. This exploratory analysis will attempt to bridge all three aims to work toward a comprehensive understanding of the interactive effects of worry, dopamine, and estradiol on TGC and behavioral performance.

2. METHODS

2.1 Participants

Participants were recruited from central Michigan and the surrounding area as part of a larger investigation reported elsewhere (Gloe et al., 2021; Guevara et al., 2023). Participants had to be between the ages of 18-25, could not be diagnosed with a severe mental health condition (e.g., schizophrenia or bipolar disorder), be on psychotropic medication, or have been diagnosed with conditions that could affect neuroendocrine function or be on hormonal contraception. A total of 139 individuals were genotyped for the COMT Val158/Met (rs4680) polymorphism. Of these, 136 had complete data. One participant served as a leverage point (see Data Analysis plan) and was therefore removed from the analyses. This resulted in a sample of 135 participants (M = 20.66, SD = 1.60). One participant identified as non-binary, and 134 participants identified as women. The sample mostly consisted of individuals who identified as White (63%), followed by individuals who identified as Black (25%), Asian (8%) and those who identified as more than one race (4%). Most of the sample consisted of those who completed partial college (56%), however there were also many who had a college level education (31%), completed a high school level of education (12%), and one person who had a graduate level education (1%). For income levels, 48% of the sample reported an annual household income of $50,000 or less, while 52% of the sample reported an annual household income > $50,000. Most of the sample consisted of students who were enrolled as full or part-time (78%) and most endorsed that they were financially supported by someone else in the past year (73%).

2.2 Measures

Penn State Worry Questionnaire (PSWQ; Meyer, 1990). The PSWQ is a 16-item questionnaire that measures levels of worry. The measure was anchored to the day of

competition and responded on a Likert scale from 1 ("Not at all Typical of Me") to 5 ("Very Typical of Me"). The possible range on the questionnaire is 16-80. Items include "My worries overwhelm me" and "I worry all the time."

N-Back. Working memory was measured with the verbal N-back task (Jacobs & D'Esposito, 2011; Kirchner, 1958). For each trial, letters were presented sequentially for 1000 milliseconds (ms). Participants were tasked with responding to each letter by identifying whether the letter was presented *n* trials back. The task consisted of three conditions – 0-, 2-, and 3-back load. The N-back consisted of 320 trials (0-back – 160; 2-back – 80; 3-back – 80). For the 0-back load condition, participants were asked to identify the letter "X" as a "target" (left button press) when it appeared on the screen and respond to any other letters as non-targets (right button press). On 2- and 3-back conditions, memory load was manipulated by asking participants to respond to a letter based on whether the letter presented *n*- trials prior. For instance, on a 2-back load condition, a "target" (i.e., the correct response) is a letter that was presented two trials prior, while a "non-target" (i.e., incorrect response) would be a letter that was not presented two trials back. Furthermore, 2- and 3-back conditions included lure trials. Lure trials add an additional "load' complexity, as they require participants to not only remember the sequence of letters that were presented prior, but also require them to inhibit a prepotent response to seeing a previously presented letter.

Estradiol. As part of the larger investigation, participants provided daily assays of 1.8 mL of saliva using the passive drool method across the full length of their menstrual cycle within 30 minutes of waking. Participants were asked to keep completed samples in their own personal freezer. During in-person lab visits, participants provided their saliva samples which were then

transferred to a -80F degree freezer. All samples were sent to Salimetrics LLC (State College, PA) to assay estradiol levels.

COMT Extraction. On a separate occasion, one saliva sample for each participant was shipped to CD Genomics (Shirley, NY) to extract COMT Val158/Met (rs4680) polymorphisms using SNaPshot Multiplex System for SNP Genotyping. Of the 139, 74 participants were homozygous allele carriers. As stated above, one participant was removed due to being a leverage point in our analyses. Therefore, the final sample consisted of 33 Met/Met and 40 Val/Val carriers The observed genotype frequencies of all the participants were in Hardy-Weinberg equilibrium (χ^2= .54, df = 1, *n.s*), indicating no significant difference from the expected frequencies.

2.3 Psychophysiological data recording, reduction, and analysis

Continuous electroencephalographic activity was recorded using the Active Two Biosemi system (BioSemi, Amsterdam, The Netherlands). Data was collected using 64 Ag-AgCl electrodes placed in a stretch-lycra cap in accordance with the 10/20 system. In addition, electrodes were placed on the left and right mastoids. Electrooculogram (EOG) activity from eye movements and blinks was recorded at FP1 and three additional electrodes placed on the sides of the right and left eyes, as well as one additional electrode below the left eye. All signals were digitized at 512 Hz, using the ActiView software (BioSemi) during data collection. Offline data reduction was performed using BrainVision Analyzer 2 (BrainProducts, Gilching, Germany). Scalp recordings were re-referenced to the numeric mean of the left and right mastoids. Additionally, all signals were band-pass filtered with cutoffs of 0.1 and 80 Hz (12 dB/oct rolloff). Ocular artifacts were then corrected using the method developed by Gratton, Coles, and Donchin (1983). Stimulus-locked data were segmented into individual epochs beginning 200ms

prior to the response and 1000 ms post-response. Trials were rejected using a computer-based algorithm defined by the following criteria: a voltage step exceeding 50 μV between contiguous sampling points, a voltage difference of more than 300 μV within a trial, activity that exceeds +/- 200 μV, or activity less than 0.5 μV within a trial.

2.4 Theta-Gamma Coupling Calculation

Much of the research on TGC in the N-back task has focused on low gamma (30-50 Hz) (Barr et al., 2017; Brooks et al., 2020; Goodman et al., 2018; Rajji et al., 2017). However, other studies have noted that high gamma can also be phase-locked to theta across various working memory tasks (Alekseichuk et al., 2016; Canolty et al., 2006; Edwards et al., 2005). Functional differences between theta-low gamma and theta-high gamma coupling have not been well characterized on the N-back task (but see Papaioannou et al., 2022; Yang & Huang, 2018). High gamma band activity is modulated by working memory load at lateral sites (Carver et al., 2018; Roux et al., 2012). Some work suggests that low and high gamma's phase locking with theta may reflect a similar sequential ordering function for working memory (Alekseichuk et al., 2016). Therefore, we examined coupling with theta across two gamma ranges (described below).

Computation of a time frequency based TGC was completed in MATLAB using the methods reported in Munia and Aviyente (2019). TGC was computed for each trial type (i.e., targets, non-targets, and lures) for low gamma (30-50 Hz) and high gamma (50-80 Hz). Theta was characterized as activity between 4-8 Hz. Electrodes were selected a priori across 10 fronto-lateral sites: AF3/4, F1/2, F3/4, F5/6, F7/8 as done in previous studies based on the importance of lateral activity for working memory (Barr et al., 2017; Rajji et al., 2017). I also computed TGC for two control sites, P4/5, in which I expected less TGC activity. Time was segmented to capture the post-stimulus response on correct trials across two segments – the first half of the

time segment (0-500 ms post-stimulus) and the second half of the segment (500-100 ms). This was done because prior research suggests that timing may be an important feature to consider for TGC, as the earlier part of the segment may be when TGC is critical for performance on the N-back task (Rajji et al., 2017). It has not been tested whether there are significant differences in TGC in the first and second half of the time range post-stimulus on the N-back task. Therefore, I computed them separately. Past research suggests that the segment length could affect the PAC metric's computation (i.e., smaller time segments may affect the signal-to-noise ratio). However, I computed TGC averaged across trials (instead of across time) and performed surrogate testing (described below) that ensured the validity of our TGC metric (Aru et al., 2015). Therefore, TGC was computed for each trial type across two gamma ranges (low, and high) and two time ranges (0-500 ms and 500-1000 ms).

There are three broad steps to the computation of the TGC signal, as outlined by Aru et al. (2015): (1) applying a transform to extract the amplitude and phase signal; (2) quantifying the association between amplitude and phase across the time series; (3) significance testing to ensure the validity of the TGC signal.

To extract the signal, within each trial type and electrode, the envelope of the high amplitude signal and the phase of the low amplitude is extracted from the average activity in each electrode. To do this, the Reduced Interference Rihaczek (RID-Rihaczek) time-frequency distribution was used to extract the components of gamma amplitude and theta phase (Aviyente et al., 2017). The RID- Rihaczek offers advantages over the commonly used Hilbert Transform because it is more robust against bandpass filtering (Munia & Aviyente, 2019a).

A time-frequency based mean vector length (tf-MVL) was computed to quantify TGC (Canolty et al., 2006; Munia & Aviyente, 2019b). To do this, a complex number is calculated by

combining the phase and amplitude across each time point on an analytic signal. The complex value is a vector on a polar plane (measured in radians or degrees to represent specific phases). Coupling exists when the magnitude of a vector is higher at a specific phase, indicating higher amplitude strength at specific locations across the phase time series. Computing the mean vector length provides a value that corresponds to the average length of vectors across specific phases – which quantifies the PAC. When no coupling is present, the data points would be sporadically placed across the polar plane, resulting in a short mean vector length. Stronger coupling results in a higher value (i.e., longer vector length). Notably, the MVL can be biased by amplitude, such that it can result in inflated PAC values due to a higher amplitude (Hülsemann et al., 2019). A solution to this has been to normalize the MVL value which results in numbers from 0 to 1 (Özkurt & Schnitzler, 2011). The normalized tf-MVL is computed as follows:

$$normalized\ tf-MVL = \frac{1}{\sqrt{T}} \frac{|\sum_{t=1}^{T} A_{fa}(t) e^{j\Phi_{fp}(t)}|}{\sqrt{\sum_{t=1}^{T} A_{fa}(t)^2}}$$

Where T is the total number of data points, $A_{fa}(t)$ is the amplitude component and $\Phi_{fp}(t)$ is the phase component at data point *t.*

Finally, to further ensure the validity of the PAC signal, significance testing of the tf-MVL was performed by generating surrogate datasets using a block-swapping approach following the procedures in Aru et al. (2015). To do this, a surrogate time series are creased by spitting the envelope of the high amplitude (i.e., gamma) at random locations across the time series and swapping them. This is done to disrupt the temporal synchronization of the amplitude and phase, while all other parts of the time series remain the same. Using the newly generated swapped data, an MVL value is computed with the phase of the original low frequency oscillation (i.e., theta). This was done 100 times. The observed tf-MVL was then compared to the

surrogate data and was deemed significant only if it was significantly larger than 95% of the surrogate values.

After the computation of the TGC signal, I examined the coupling strength across sites in the full sample (N=135). Multi-level modeling was used to examine whether TGC across frontal sites significantly differed from TGC at control sites (i.e., P4/5). The tf-MVL value was the outcome with electrode as a predictor, while controlling for load and time range as main effects. I then conducted a pairwise post-hoc analysis, comparing each a priori site to the control sites. This resulted in 20 comparisons. To be conservative, I adopted a Bonferroni correction, resulting in a threshold p-value of .0025. I found that AF3/4, F5/6, F7/F8 were significantly higher than P4 and P5 (all *p's* > .0001). However, F1/F2 showed significantly less coupling than P4 and P5 ($p < .0001$). Finally, F3/4 were not significantly different than P4 and P5 ($p > .2$). The results were consistent for Load 2 and 3 (see Figure 6a and 6b). Therefore, for the remaining analyses, I only used TGC for frontal lateral sites - AF3/4, F5/6, F7/F8 (Figure 6c).

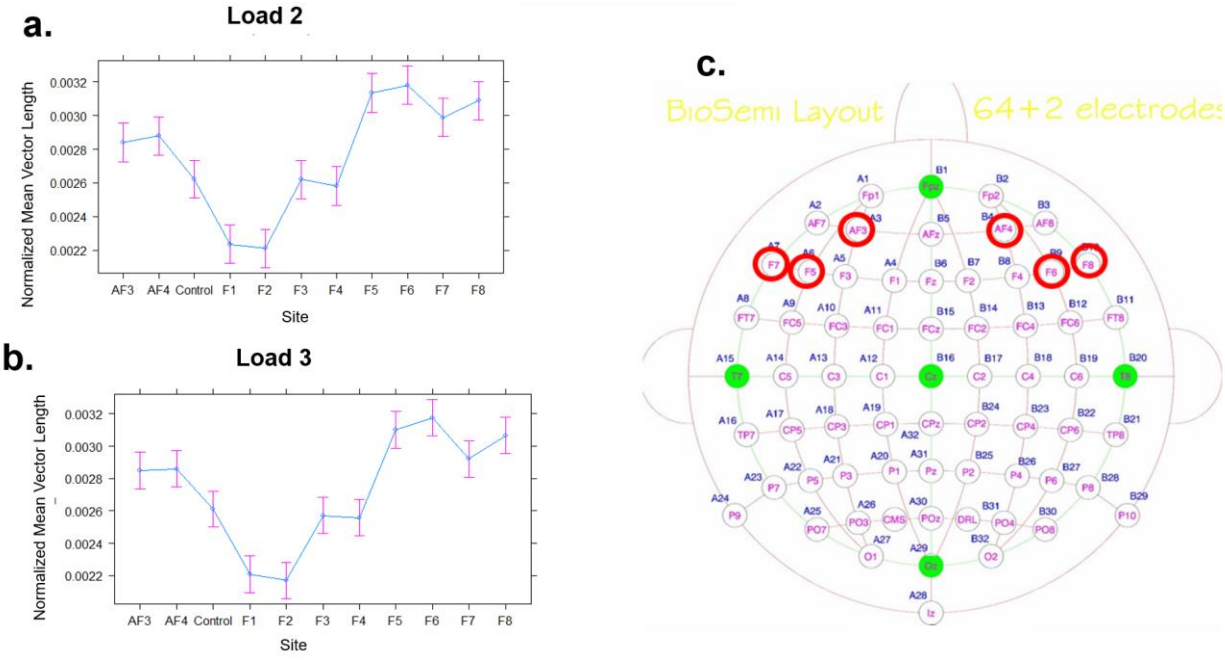

Figure 6. Site Specification for the TGC Analyses. **1a.** Average TGC Across Sites and Trial Type for Load 2. The results show that AF3/4, F5/6, F7/8 show significantly more coupling than

Figure 6 (cont'd)

sites selected as the control. **1b.** Average TGC Across Sites and Trial Type for Load 3. The results show that AF3/4, F5/6, F7/8 show significantly more coupling than control sites. **1c.** Plot showing the sites used for the subsequent analyses, including AF3/4, F5/6, and F7/8. Control sites are the averaged activity at sites P4/5.

2.5 Procedure

All interested participants completed a phone screening to determine eligibility for the study. After the phone screening, participants came into the lab to complete an initial intake visit. The intake visit gave participants their overall responsibilities during the study, including how to complete and store their saliva samples and instructions for completing daily questionnaires. Participants were asked to complete their saliva sample assays within 30 minutes after waking and complete daily questionnaires in the evening between 5-10 PM. Throughout the length of their 35-day participation, participants were also asked to complete in-person lab visits, which were scheduled using phase projection methods (described in Gloe et al., 2021). During in-person lab visits, participants were asked to complete computerized cognitive tasks, including the N-back), and the Flanker task (not completed in the analyses, while concurrent EEG was recorded. Participants also completed O- and R-span tasks without EEG as part of the larger investigation. Participants were compensated $280 for complete data collection and prorated compensation amounts were dispersed based on the amount of missing data.

2.6 Data Analysis Plan

All analyses for the main aims of the study were conducted using the "lme4" package (Bates et al., 2007) in R Version 3.5.1 to estimate effects from multi-level models. A series of models were run for each aim. Cook's distance was computed for each model to examine leverage points, and one participant was removed due to having a Cook's distance greater than .5. I also graphed residuals to examine normality. The first aim was to examine whether worry

predicted TGC. For this model I examined worry (within- and between-centered) as predictors of TGC. To examine within-person effects, I computed a mean for each participant and subtracted the mean from in-person lab visit observations. This allowed us to examine within-person differences from participants' own mean. To examine between-persons effects, a mean was computed for each participant. This was then used to compute an overall mean (i.e., mean of means). This allowed me to examine relative differences between people, on average, during their in-person lab visit days. A cross-classified model was conducted to account for shared variance in participants and electrodes. That is, the model estimated a random intercept for both participants and electrodes. I examined whether worry predicted TGC low gamma and high gamma on load 2 and 3. This resulted in four models for the first aim. Two-way interactions were probed using the Johnson-Neyman approach (Preacher et al., 2006). This allowed me to examine effects of interest across the range of the moderator, instead of restricting it to +/- 1 SD of the mean.

Aim 1 Model (N=135):

$$TGC = \gamma_{00} + \gamma_{10}(Worry_{ij}) + \gamma_{01}(Worry_{0j}) + \gamma_{10}(Worry_{ij}) * \gamma_{01}(Worry_{0j}) + \gamma_{01}(EEG\ Visit_{0j}) + u_{ij}(Electrode) + u_{0j}(Partcipant) + r_{ij}$$

For the second aim, I examined whether COMT moderated the association between worry and TGC. I maintained the within- and between- interaction effects of worry and added COMT as an effects coded-predictor. Significant interactions were probed using simple slopes analysis examining the effect of worry on lure trials at 2- and 3-back for Met and Val carriers separately.

Aim 2 Model (N=73):

$$TGC = \gamma_{00} + \gamma_{10}(Worry_{ij}) + \gamma_{01}(Worry_{0j}) + \gamma_{01}(COMT_{0j}) + \gamma_{10}(Worry_{ij}) * \gamma_{01}(Worry_{0j}) + \gamma_{01}(COMT_{0j}) * \gamma_{10}(Worry_{ij}) + \gamma_{01}(COMT_{oo}) * \gamma_{01}(Worry_{0j}) + \gamma_{01}(COMT_{0j}) * \gamma_{10}(Worry_{ij}) * \gamma_{01}(Worry_{0j}) + \gamma_{01}(EEG\ Visit_{0j}) + u_{ij}(Electrode) + u_{0j}(Partcipant) + r_{ij}$$

For the third and final aim, I examined whether estradiol moderated the association between worry and TGC. I maintained the within- and between- interaction effects of worry and within-person centered estradiol to examine as a continuous predictor. Significant interactions were probed using the Johnson-Neyman approach, examining the worry-TGC association across the range of within-person estradiol values. For ease of interpretation of the exploratory analysis that combines all predictors, I maintained the same sample sizes for Aim 2 and 3 (N=74). However, a supplementary analysis was conducted to examine whether the effects for Aim 3 change when leveraging the full sample (N=135).

Aim 3 Model (N=73):

$$TGC = \gamma_{00} + \gamma_{10}(Worry_{ij}) + \gamma_{01}(Worry_{0j}) + \gamma_{10}(Etstradiol_{ij}) + \gamma_{10}(Worry_{ij}) * \gamma_{01}(Worry_{0j}) + \gamma_{10}(Etstradiol_{ij}) * \gamma_{10}(Worry_{ij}) + \gamma_{10}(Etstradiol_{ij}) * \gamma_{01}(Worry_{0j}) + \gamma_{10}(Etstradiol_{ij}) * \gamma_{10}(Worry_{ij}) * \gamma_{01}(Worry_{0j}) + \gamma_{01}(EEG\ Visit) + u_{ij}(Site) + u_{0j}(Partcipant) + r_{ij}$$

2.7 Power Analysis

A post-hoc sensitivity analysis was completed to examine the size of the effect I could detect with this sample size. Using G Power, the alpha probability level was set to .05 and a power probability was set to .8 to determine the expected effect size of a between-within

interaction at 80% power. The sample size was set to 73, number of groups was 2 (Met/Val), and the number of repeated measurements was set to 24 (6 electrode observations across 4 visits).

I estimated different sets of sensitivity-based analyses based on between-within interactions and within-within interactions for each dependent variable. Average correlations across repeated measurements were as follows for 2-back TGC low and high gamma and 3-back TGC low and high gamma, respectively *r*'s = .38, .41, .33, .35.

I used a conversion to estimate the *f* value provided by G Power to eta squared (η^2). The results of the power analyses revealed that for the full sample (N=135), we were powered to detect small between-within interactions for 2-back TGC low gamma a (η^2 = 0.0042) and TGC-high gamma (η^2 =.004), as well as 3-back TGC-low gamma (η^2 =.0046) and high gamma (η^2 = .0044). For a subset of the sample (N=73), I was also powered to detect a small between-within interaction for two back TGC-low gamma (η^2 =.0079) and TGC high gamma (η^2_p = .0076), as well as three back TGC low gamma (η^2_p =.0086) and TGC high gamma (η^2_p = .0083). Therefore, I proceeded with the analyses with the ability to detect small effects given the sample size.

3. RESULTS

3.1 Examining TGC Across Time, Trial Types and Gamma Ranges

Analyses for TGC across time and trial type are presented in the Appendix. Overall, there was more coupling on target and lure trials compared to non-targets. In addition, although there was less coupling in the first half compared to the second half, the first half revealed more distinct effects of trial type. This is likely because the second half of the trial may be influenced by response selection. Finally, the results were similar across TGC-low and TGC-high gamma. Therefore, I proceeded with the final analyses with TGC in the first half for low and high gamma on correct lure trials, where we saw increased TGC on 2- and 3-back trials across the selected electrodes (see Figure 7). Lure trials were our condition of interest as previous studies have found that performance on lure trials is associated with worry (Fales et al., 2008; Gloe et al., 2021; Louis et al., 2021), as well as dopamine and estradiol (Jacobs & D'Esposito, 2011; Louis et al., unpublished data). The enhanced coupling on lure trials compared to non-targets supported that lures influence TGC strength.

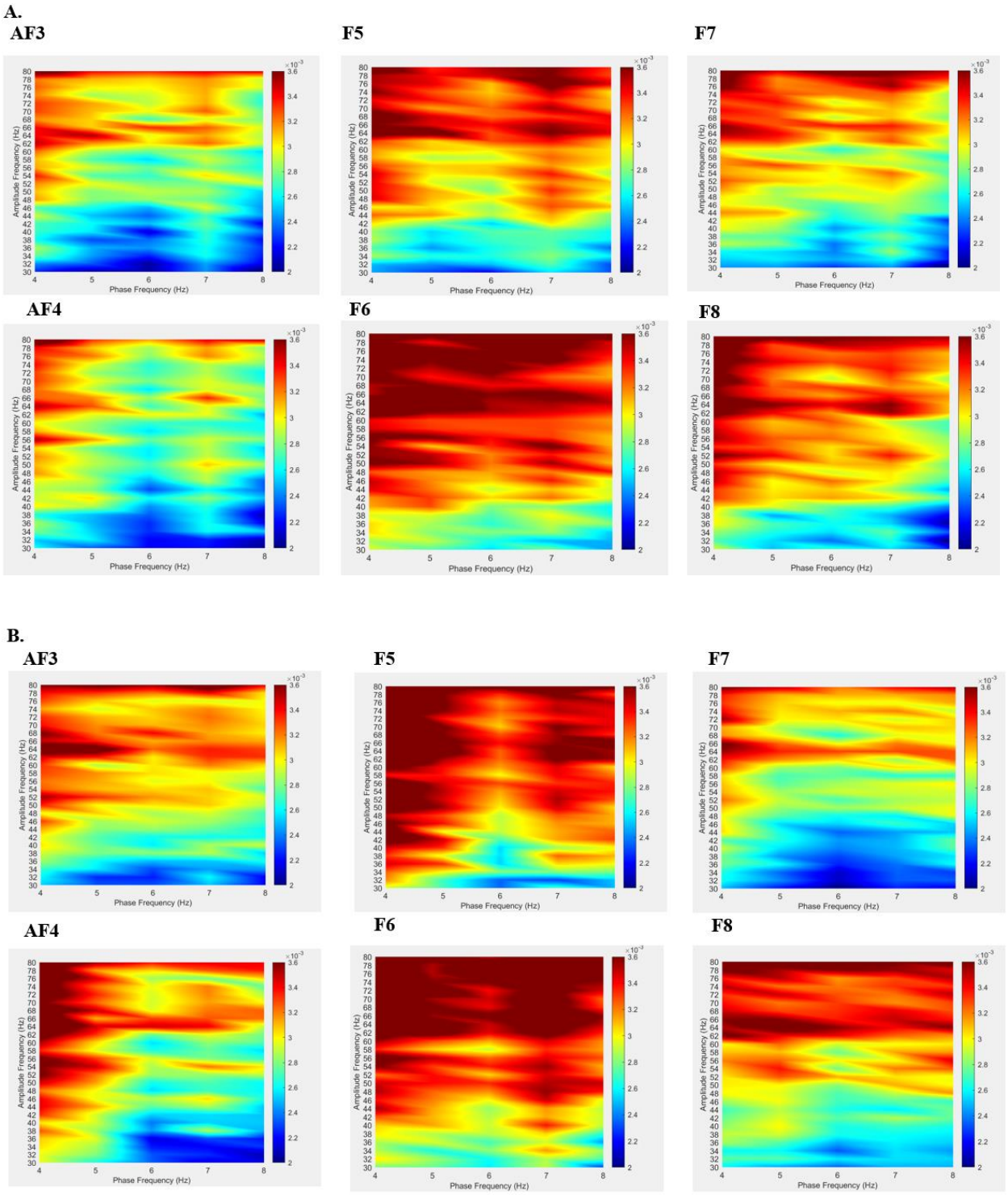

Figure 7. Comodulogram Plots for theta-gamma phase amplitude coupling for each electrode used in the final analyses. Theta phase (4-8 Hz) is on the x-axis and gamma amplitude (30-80 Hz) is on the y-axis. **A.** Theta-Gamma comodulogram plots for each electrode on 2-back lure trials. **B.** Theta-Gamma comodulogram plots for each electrode on 3-back lure trials.

3.2. Descriptive Statistics

Table 1 reports the descriptive statistics for predictors and dependent variables.

Table 1. Summary of Predictor and Dependent Variables for the full sample (N=135).

Variable	Mean	SD	Observed Range
PSWQ	41.64	15.41	16-80[1]
Estradiol (pg/mL)	1.47	.74	.10- 5.14
TGC-low gamma 2-back Lures	.0026	.0022	0 - .014
TGC-low gamma 3-back Lures	.0028	.0023	0-.015
TGC-high gamma 2-back Lures	.003	.002	.00064 - .016
TGC-high gamma 3-back Lures	.003	.002	.000057-.017

Note. PSWQ = Penn State Worry Questionnaire; pg/mL = picograms per milliliter

3.3 Aim 1 Results

For the first aim, I hypothesized two plausible directions for the association between worry and TGC. First, previous literature has found that those with psychiatric conditions evidenced reduced TGC on correct trials. Alternatively, worry may be associated with higher TGC which would be consistent with ACT.

3.3.1 Two-back Lure trials

There was a significant interaction between average worry and within-person worry (η^2_p = .003) (see Table 2). The interaction was probed using a Johnson-Neyman approach (see Figure 8). Aligned with ACT, within-person increases in worry related to less coupling for individuals with higher average worry scores (Average PSWQ > 50.39). On the other hand, within-person

[1] 7% (n=10) of participants were above the clinical cutoff score for the PSWQ (Average scores greater than or equal to 60)

increases in worry related to more TGC for individuals with low average worry scores across the menstrual cycle (Average PSWQ < 33.17).

Table 2. Estimates for multi-level model of PSWQ on TGC-low gamma for 2-back lure trials. EEG Visit was not a significant predictor in the model (p = .21).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	2.67×10^{-3}	$1.11\ 10^{-4}$	30.02	24.07	< .0001
PSWQ (within-centered)	1.86×10^{-6}	$4.72\ 10^{-6}$	2435	.39	.69
PSWQ (between-centered)	-1.03×10^{-5}	7.33×10^{-6}	13.35	-1.40	.16
PSWQ (within) x PSWQ between	$\mathbf{-1.36x\ 10^{-6}}$	$\mathbf{4.39 \times 10^{-7}}$	**2436**	**-3.10**	**.001**
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	1.01×10^{-6}	1.0×10^{-4}			
Intercept for Electrode	1.92×10^{-8}	1.3×10^{-4}			
Residual	3.86×10^{-6}	1.9×10^{-3}			

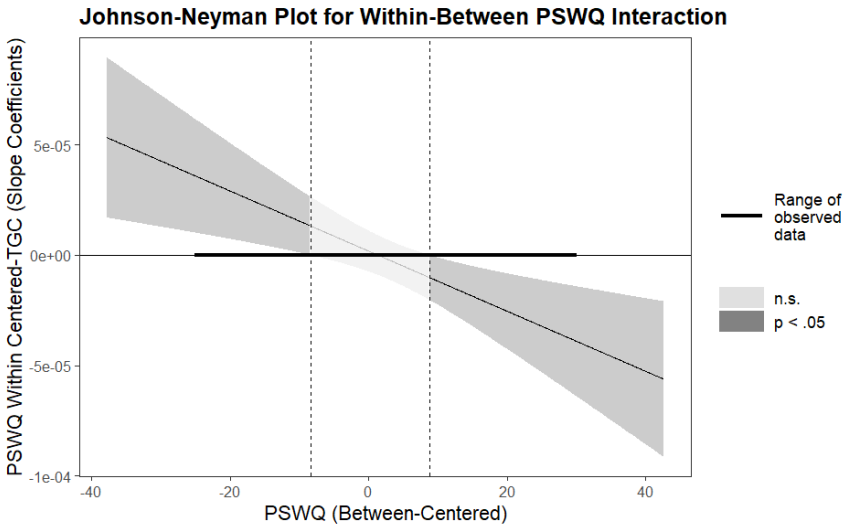

Figure 8. PSWQ Between-Within Interaction Predicting Theta-Gamma Coupling (TGC-low gamma). The effect demonstrates then when average levels of worry are low, within-person increases in worry predict more coupling. On the other hand, when average levels of worry are high, within-person increases in worry predict less coupling.

The results for TGC-high gamma were nearly identical to those of TGC-low gamma (see Table 3). There was a significant interaction between within- and between-centered worry. Within-person increases in worry was associated with reduced TGC for individuals who worry

more on average (Average PSWQ > 50.11). Conversely, within-person increases in worry were associated with higher TGC for individuals who worry less on average (Average PSWQ < 32.31). In summary, for individuals who worry more on average, a within-person increase in worry is associated with reduced TGC on two-back lure trials; whereas for individuals who worry less on average, a within-person increase in worry is associated with higher TGC (see Figure 9).

Table 3. Estimates for multi-level model of PSWQ on TGC-high gamma for 2-back lure trials. EEG visit was not a significant predictor in the model (p = .19).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	3.14×10^{-3}	1.25×10^{-4}	27.65	25.09	< .0001
PSWQ (within-centered)	1.51×10^{-6}	4.99×10^{-6}	2435	.303	.76
PSWQ (between-centered)	-1.22×10^{-5}	8.05×10^{-5}	13. 41	-1.52	.13
PSWQ (within) x PSWQ between	$\mathbf{-1.41 \times 10^{-6}}$	$\mathbf{4.64 \times 10^{-7}}$	**2436**	**-3.05**	**.002**
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	1.2×10^{-6}	1.10×10^{-4}			
Intercept for Electrode	1.80×10^{-8}	1.34×10^{-5}			
Residual	4.12×10^{-6}	2.03×10^{-3}			

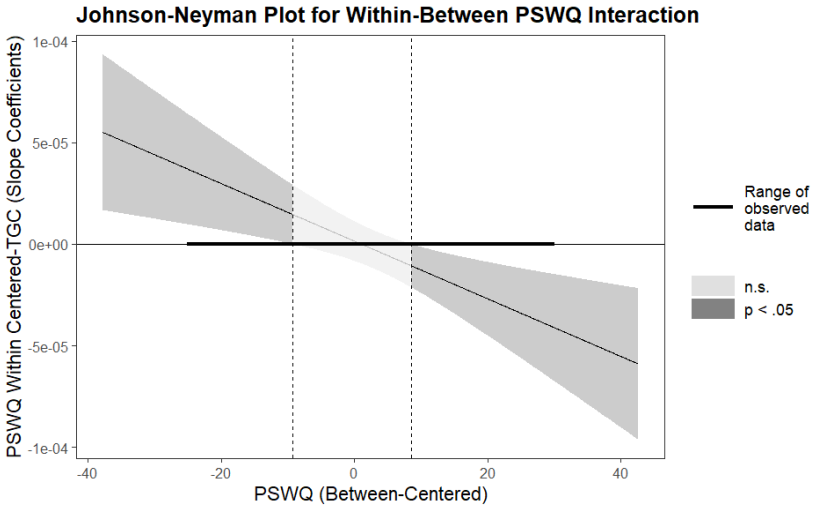

Figure 9 . PSWQ Between-Within Interaction Predicting Theta-Gamma Coupling (TGC-high gamma). The effect demonstrates then when average levels of worry are low, more worry predicts more coupling. On the other hand, when average levels of worry are high, more worry predicts less coupling.

3.3.2 Three-Back Lure Trials

Within-person increases in worry predicted more coupling on 3-back lure trials. The positive association was consistent across TGC-low gamma (p = .001, η^2_p = .008) and TGC-high gamma (p = .002, η^2_p = .002). Importantly, however, there was no interaction with average levels of worry (see Tables 4 and 5).

Table 4. Estimates for multi-level model of PSWQ on TGC-low gamma for 3-back lure trials. EEG was a significant predictor in the model ($p < .001$).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	2.76×10^{-3}	1.15×10^{-4}	2780	24.13	< .0001
PSWQ (within-centered)	$\mathbf{1.60 \times 10^{-5}}$	$\mathbf{4.89 \times 10^{-6}}$	**2422**	**3.27**	**.001**
PSWQ (between-centered)	-1.02×10^{-5}	7.49×10^{-6}	137	-1.36	.17
PSWQ (within) x PSWQ between	-2.57×10^{-7}	4.59×10^{-7}	2423	-.56	.57
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	1.03×10^{-6}	1.01×10^{-3}			
Intercept for Electrode	2.16×10^{-8}	1.47×10^{-4}			
Residual	4.19×10^{-6}	2.04×10^{-3}			

Table 5. Estimates for multi-level model of PSWQ on TGC-high gamma for 3-back lure trials. EEG was a significant predictor in the model ($p < .001$).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	3.27×10^{-3}	1.21×10^{-4}	31.24	27.02	< .0001
PSWQ (within-centered)	$\mathbf{1{,}61 \times 10^{-5}}$	$\mathbf{5.28 \times 10^{-6}}$	**2421**	**3.05**	**.002**
PSWQ (between-centered)	-1.29×10^{-5}	8.09×10^{-6}	136.4	-1.60	.11
PSWQ (within) x PSWQ between	-3.37×10^{-7}	4.95×10^{-7}	2422	-.68	.50
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	1.20×10^{-6}	1.08×10^{-3}			
Intercept for Electrode	2.12×10^{-8}	1.46×10^{-4}			
Residual	4.88×10^{-6}	2.21×10^{-3}			

3.4 Aim 2 Results

I hypothesized that there would be a significant interaction between worry and COMT to predict TGC, such that the association would be present for Val carriers.

3.4.1. Two-Back Lure Trials

The significant interaction between within- and between-person centered worry remained (p = .002). Consistent with hypotheses, there was a significant within-person worry x COMT interaction (p = .04, η^2_p = .003) (see Table 6). Simple slope analyses revealed that within-person increases in worry predicted more coupling for Val carriers (p <.0001), but not for Met carriers (p = .34) (see Figure 10).

Table 6. Estimates for multilevel model examining the effects of PSWQ within- and between-centered and COMT on TGC-low gamma on 2-back lure trials. EEG was not a significant predictor in the model (p = .31).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	2.61×10^{-3}	1.34×10^{-4}	40.52	19.42	< .0001
PSWQ (within-centered)	$\mathbf{2.12 \times 10^{-5}}$	$\mathbf{6.71 \times 10^{-6}}$	**1327**	**3.16**	**.002**
PSWQ (between-centered)	-5.29×10^{-6}	9.87×10^{-6}	68.95	.055	.59
COMT	-4.51×10^{-5}	1.26×10^{-4}	67.75	.36	.72
PSWQ (within) x PSWQ (between)	$\mathbf{-1.72 \times 10^{-6}}$	$\mathbf{5.81 \times 10^{-7}}$	**1327**	**-2.95**	**.003**
PSWQ (within) x COMT	$\mathbf{-1.37 \times 10^{-5}}$	$\mathbf{6.68 \times 10^{-6}}$	**1326**	**-2.05**	**.04**
PSWQ (between) x COMT	7.31×10^{-6}	9.87×10^{-6}	68.89	.74	.46
PSWQ (within) x PSWQ (between) x COMT	-5.08×10^{-7}	5.83×10^{-7}	1328	-.87	.38
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	9.45×10^{-7}	9.72×10^{-4}			
Intercept for Electrode	1.28×10^{-8}	1.13×10^{-5}			
Residual	3.51×10^{-6}	1.87×10^{-3}			

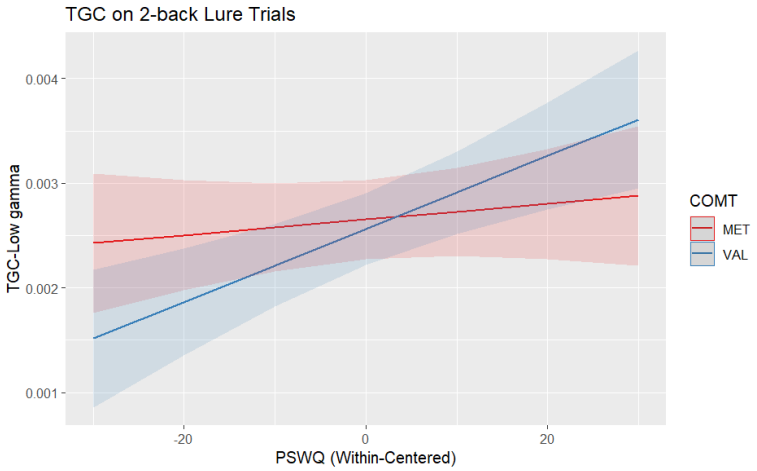

Figure 10. PSWQ (within-centered) and TGC-low gamma revealing that increases in worry for Val carriers predicts more TGC while there was no effect for Met carriers.

The results were similar for 2-back TGC-high gamma (see Table 7). The within-between interaction remained (p = .005). The within-worry x COMT interaction was marginal (p = .08, η^2_p = .002). Simple slope analyses revealed that within-person increases in worry predicted more coupling for Val carriers (p < .001) but not for Met carriers (p = .43).

Table 7. Estimates for multilevel model examining the effects of PSWQ within- and between-centered and COMT on TGC-high gamma on 2-back lure trials. EEG was not a significant predictor in the model (p = .18).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	3.12×10^{-3}	1.53×10^{-4}	41.51	20.38	< .0001
PSWQ (within-centered)	$\mathbf{1.94 \times 10^{-5}}$	$\mathbf{7.25 \times 10^{-6}}$	**1327**	**2.67**	**.008**
PSWQ (between-centered)	-7.32×10^{-6}	1.11×10^{-5}	69.35	-.66	.51
COMT	7.12×10^{-5}	1.42×10^{-4}	68.19	.350	.62
PSWQ (within) x PSWQ (between)	$\mathbf{-1.73 \times 10^{-6}}$	$\mathbf{6.29 \times 10^{-7}}$	**1327**	**-2.76**	**.005**
PSWQ (within) x COMT	$\mathbf{-1.27 \times 10^{-5}}$	$\mathbf{7.22 \times 10^{-6}}$	**1326**	**-1.77**	**.08**
PSWQ (between) x COMT	8.48×10^{-6}	1.11×10^{-5}	69.29	.76	.44
PSWQ (within) x PSWQ (between) x COMT	-4.61×10^{-7}	6.30×10^{-7}	1328	-.73	.46
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	1.23×10^{-6}	1.11×10^{-4}			
Intercept for Electrode	1.80×10^{-8}	1.34×10^{-5}			
Residual	4.11×10^{-6}	2.03×10^{-3}			

3.4.2 Three-Back Lure Trials

As seen in Tables 8 and 9, the main effect of within-person worry remained across TGC-low and high gamma. No other effects reached significance (p's > .13).

Table 8. Estimates for multilevel model examining the effects of PSWQ within- and between-centered and their effect on TGC-low gamma on lure trials on load 3. EEG was a significant predictor in the model (p = .04).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	2.70×10^{-3}	1.32×10^{-4}	42.71	20.43	< .0001
PSWQ (within-centered)	$\mathbf{2.84 \times 10^{-5}}$	$\mathbf{7.22 \times 10^{-6}}$	**1312**	**3.93**	**< .0001**
PSWQ (between-centered)	-5.64×10^{-7}	9.99×10^{-6}	70.18	-.06	.95
COMT	-1.03×10^{-4}	1.28×10^{-4}	68.60	-.80	.42
PSWQ (within) x PSWQ (between)	-9.47×10^{-7}	6.28×10^{-7}	1312	-1.51	.13
PSWQ (within) x COMT	6.28×10^{-6}	7.18×10^{-6}	1311	.88	.38
PSWQ (between) x COMT	3.60×10^{-7}	9.99×10^{-6}	70.06	.04	.97
PSWQ (within) x PSWQ (between) x COMT	-3.80×10^{-7}	6.30×10^{-7}	1313	-.60	.55
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	9.35×10^{-7}	9.67×10^{-4}			
Intercept for Electrode	6.36×10^{-9}	7.98×10^{-5}			
Residual	4.10×10^{-5}	2.03×10^{-3}			

Table 9. Estimates for multilevel model examining the effects of PSWQ within- and between-centered and COMT on TGC-low gamma on 3-back lure trials. EEG was a significant predictor in the model (p < .01).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	3.23×10^{-3}	1.50×10^{-4}	43.60	21.55	< .0001
PSWQ (within-centered)	$\mathbf{2.73 \times 10^{-5}}$	$\mathbf{7.87 \times 10^{-6}}$	**1312**	**3.46**	**.0005**
PSWQ (between-centered)	-2.74×10^{-6}	1.13×10^{-5}	70.00	-.24	.80
COMT	-8.97×10^{-5}	1.44×10^{-4}	68.47	-.62	.54
PSWQ (within) x PSWQ (between)	-8.38×10^{-7}	6.85×10^{-7}	1312	-1.22	.22
PSWQ (within) x COMT	1.28×10^{-5}	7.83×10^{-6}	1311	1.63	.10
PSWQ (between) x COMT	1.38×10^{-6}	1.13×10^{-5}	69.88	.12	.90
PSWQ (within) x PSWQ (between) x COMT	-5.86×10^{-7}	6.87×10^{-7}	1313	-.85	.39
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	1.21×10^{-6}	1.10×10^{-2}			
Intercept for Electrode	9.53×10^{-9}	9.76×10^{-5}			

Table 9 (cont'd)

Residual	4.87×10^{-6}	2.21×10^{-3}			

3.5 Aim 3 Results

I hypothesized that the association between worry and TGC may be present when estradiol is low.

3.5.1 Two-Back Lure Trials

There continued to be an interaction between within-between worry (p = .003). However, worry did not interact with estradiol to predict TGC across low and high gamma (see Tables 10 and 11).

Table 10. Estimates for multilevel model examining the effect of PSWQ within- and between-centered and estradiol (within-centered) on TGC-low gamma on 2-back lure trials. EEG was not a significant predictor in the model (p = .41).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	2.60×10^{-3}	1.33×10^{-4}	40.20	19.60	< .0001
PSWQ (within-centered)	**2.27×10^{-5}**	**6.93×10^{-6}**	**1344**	**3.27**	**.001**
PSWQ (between-centered)	-6.47×10^{-6}	9.65×10^{-6}	71.70	-.67	.50
Estradiol (within-centered)	-3.57×10^{-5}	1.25×10^{-4}	1327	-.285	.78
PSWQ (within) x PSWQ (between)	**-1.96×10^{-6}**	**5.52×10^{-7}**	**1326**	**-3.55**	**.003**
PSWQ (within) x estradiol (within)	-7.09×10^{-6}	2.07×10^{-5}	1368	-.34	.73
PSWQ (between) x estradiol (within)	6.60×10^{-7}	1.02×10^{-5}	1330	.07	.94
PSWQ (within) x PSWQ (between) x estradiol (within)	6.73×10^{-7}	1.74×10^{-6}	1357	.39	.70
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	9.26×10^{-7}	9.6×10^{-4}			
Intercept for Electrode	1.27×10^{-8}	1.13×10^{-4}			
Residual	3.54×10^{-6}	1.88×10^{-3}			

Table 11. Estimates for multilevel model examining the effects of PSWQ within- and between-centered and estradiol (within-centered) on TGC-high gamma on 2-back lure trials. EEG was not a significant predictor in the model (p = .41).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	3.10×10^{-3}	1.51×10^{-4}	41.24	20.56	< .0001
PSWQ (within-centered)	$\mathbf{2.04 \times 10^{-5}}$	$\mathbf{7.49 \times 10^{-6}}$	**1343**	**2.72**	**.006**
PSWQ (between-centered)	-8.56×10^{-6}	1.09×10^{-5}	72.13	-.79	.43
Estradiol (within-centered)	-1.21×10^{-5}	1.35×10^{-4}	1327	-.089	.93
PSWQ (within) x PSWQ (between)	$\mathbf{-1.95 \times 10^{-6}}$	$\mathbf{5.96 \times 10^{-7}}$	**1326**	**-3.28**	**.001**
PSWQ (within) x estradiol (within)	-3.29×10^{-6}	2.25×10^{-5}	1377	-.15	.88
PSWQ (between) x estradiol (within)	1.85×10^{-6}	1.10×10^{-5}	1330	.19	.87
PSWQ (within) x PSWQ (between) x estradiol (within)	6.91×10^{-7}	1.89×10^{-6}	1369	.37	.71
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	1.20×10^{-6}	1.10×10^{3}			
Intercept for Electrode	1.79×10^{-8}	1.34×10^{-4}			
Residual	4.13×10^{-6}	2.03×10^{-3}			

3.5.2 Three-Back Lure Trials

The main effect of within-person increases in worry remained across TGC-low and TGC-high gamma. However, no other effects reached significance[2].

Table 12. Estimates for multilevel model examining the effect of PSWQ within- and between-centered and estradiol (within-centered) on TGC-low gamma on 3-back lure trials. EEG was a significant predictor in the model (p = .01).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	2.72×10^{-3}	1.30×10^{-4}	42.40	20.86	< .0001
PSWQ (within-centered)	$\mathbf{2.44 \times 10^{-5}}$	$\mathbf{7.43 \times 10^{-6}}$	**1330**	**3.29**	**.001**
PSWQ (between-centered)	-3.81×10^{-7}	9.73×10^{-6}	73.13	-.04	.97
Estradiol (within-centered)	1.19×10^{-4}	1.35×10^{-4}	1312	.88	.38
PSWQ (within) x PSWQ (between)	-1.07×10^{-6}	5.94×10^{-7}	1311	-1.80	.07
PSWQ (within) x estradiol (within)	4.18×10^{-5}	2.21×10^{-5}	1331	1.89	.06
PSWQ (between) x estradiol (within)	7.12×10^{-7}	1.10×10^{-5}	1315	.65	52
PSWQ (within) x PSWQ (between) x estradiol (within)	6.43×10^{-7}	1.86×10^{-6}	1316	.35	.72
Random Effects	**Variance**	**Standard Deviation**	--	--	--

[2] Although Table 10 and 11 reveal marginal interactions with worry and estradiol, the effects did not survive when we leveraged the full data set (N=135). Therefore, the marginal interaction was not discussed or probed.

Table 12 (cont'd)

Intercept for Participant	9.06×10^{-7}	9.52×10^{-4}			
Intercept for Electrode	6.40×10^{-9}	8.00×10^{-5}			
Residual	4.09×10^{-6}	2.02×10^{-3}			

Table 13. Estimates for multilevel model examining the effect of PSWQ within- and between-centered and estradiol (within-centered) on TGC-low gamma on 3-back lure trials. EEG was a significant predictor in the model ($p = .06$).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	3.25×10^{-3}	1.47×10^{-4}	43.22	22.02	< .0001
PSWQ (within-centered)	$\mathbf{2.25 \times 10^{-5}}$	$\mathbf{8.10 \times 10^{-6}}$	**1329**	**2.78**	**.006**
PSWQ (between-centered)	-2.43×10^{-6}	1.09×10^{-5}	72.87	-.22	.82
Estradiol (within-centered)	1.39×10^{-4}	1.48×10^{-4}	1312	.93	.35
PSWQ (within) x PSWQ (between)	-1.02×10^{-6}	6.47×10^{-7}	131	-1.58	.12
PSWQ (within) x estradiol (within)	4.58×10^{-5}	2.41×10^{-5}	1322	1.90	.06
PSWQ (between) x estradiol (within)	1.23×10^{-5}	1.20×10^{-5}	1315	1.03	.30
PSWQ (within) x PSWQ (between) x estradiol (within)	1.74×10^{-6}	2.03×10^{-6}	1329	.86	.39
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	1.17×10^{-6}	1.08×10^{3}			
Intercept for Electrode	9.69×10^{-9}	9.79×10^{-5}			
Residual	4.86×10^{-6}	2.20×10^{-3}			

3.6 Exploratory Analyses: Full Models Examining Worry, COMT and Estradiol on Behavior and TGC

Separate investigations examining the interactive effects of worry, COMT, and estradiol have revealed evidence for their independent and interactive influence on lure performance. These previous analyses have begun illuminating for whom and when worry's association with reduced working memory performance is enhanced. Based on previous studies and the current study, what remains unclear is whether COMT and estradiol combined moderate associations between worry and 2-back lure performance or neural activity. Given that estradiol down-regulates COMT enzyme activity, it is also important to test their combined modulatory influence. Indeed, previous

findings have shown that estradiol is associated with improved lure performance for Val carriers and less favorable performance for Met carriers (Jacobs & D'Esposito, 2011; Louis et al., unpublished data).

Our previous and current studies have revealed that Val carriers who experience acute increases in worry evidence reduced performance (Louis et al., 2021) and enhanced coupling on correct lure trials. We did not find an interactive effect with COMT and average worry on performance, nor did we examine a COMT x worry x estradiol interaction (Louis et al., 2021). On the other hand, those who experience high worry and have higher estradiol concentrations on average, may be at higher risk for working memory impairments (Gloe et al., 2021). While Gloe and colleagues speculate that dopamine may be a key mechanism involved in these effects, it has yet to be empirically tested.

Therefore, I conducted four exploratory models to examine a within-person worry x within-person estradiol x COMT interaction on 2-back lure (1) accuracy and (2) TGC, and between-person worry x between-person estradiol x COMT interaction on 2-back lure (3) accuracy and (4) TGC. For the first two sets of analyses, I predicted that within-person increases in worry would be associated with reduced accuracy and enhanced TGC on correct trials for Val carriers when estradiol is low. If supported, these results would further strengthen the hypothesis that basal dopamine is a significant moderator in the association between state worry (within-person changes) and working memory. I will also test a model to examine if the three-way interaction is moderated by between-person worry, given the present findings with TGC. The predictions for models 3 and 4 were less precise. Our previous analyses did not find that COMT moderated the association between average estradiol and performance (Louis et al., unpublished data). Further, Gloe and colleagues found that high amounts of progesterone also predict worse accuracy for high

worriers. Therefore, it is possible that the association between average worry and estradiol is not moderated by basal dopamine. Such a finding would indicate that the COMT gene may not be sensitive to between-person differences in worry and estradiol across the menstrual cycle.

3.7 Exploratory Models 1 and 2: Testing whether COMT and estradiol moderates within-person effects of worry and estradiol on 2-back lure performance and TGC

My results were partially consistent with hypotheses, as a marginal three-way interaction between COMT x within-person worry x estradiol emerged (p = .07) (see Figure 11). The results revealed that as estradiol levels decreased, the association between worry and accuracy became more negative for Val carriers (i.e., enhanced negative association when estradiol was low) (see Figure 10). Lower-order interactions also supported what we have found in previous studies (see Table 12). There was a main effect of COMT (p = .04), such that Val carriers (M = .73, SE = .03) were less accurate than Met carriers (M = .80, SE = .03). There was also a significant COMT x within-person worry interaction (p = .03), such that the association was present for Val carriers (b = -.004, p = .004), but not Met carriers (p = .99). A significant COMT x estradiol interaction emerged (p = .006), revealing a positive association between estradiol and accuracy for Val carriers (b = .04, p = .06), and a negative association for Met carriers (b = -.06, p = .04). Importantly, another analysis was conducted to test whether the results of the three-way interaction on accuracy were further moderated by between-person worry. In this model, all significant effects remained and the three-way between worry, COMT, and estradiol remained marginal (p = .08). No effects with between-worry reached significance (all p's > .12).

Table 14. Estimates for multilevel model examining the effects of PSWQ within-centered, estradiol within-centered and COMT on 2-back lure accuracy. EEG Visit was a not a significant predictor in the model (p = .38).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	.64	.03	121.15	23.92	< .001
PSWQ (within-centered)	**-.004**	**.001**	**170.53**	**-2.9**	**.004**
COMT	**.07**	**.03**	**70.37**	**2.04**	**.04**
Estradiol (within-centered)	.04	.02	164.08	1.916	.05
PSWQ (within) x Estradiol (within)	.005	.004	203.64	1.44	.15
PSWQ (within) x COMT	**.004**	**.001**	**166.61**	**2.16**	**.03**
Estradiol (within) x COMT	**-.10**	**.04**	**163.81**	**-2.78**	**.006**
PSWQ (within) x Estradiol (within) x COMT	-.01	.005	199.08	-1.79	.07
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	.02	.13			
Residual	.01	.11			

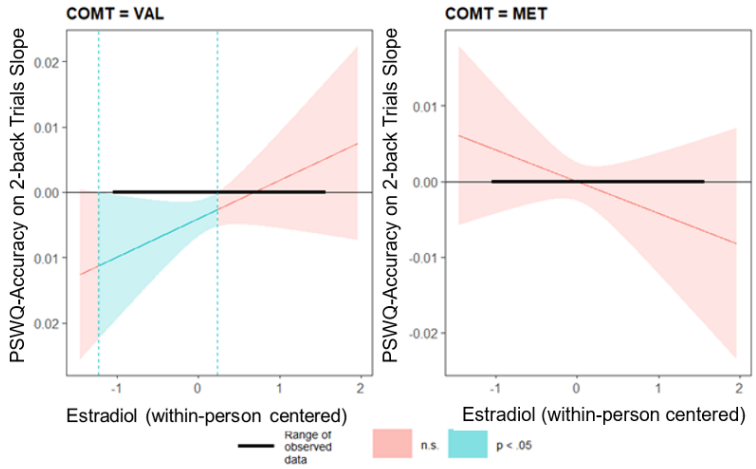

Figure 11. Johnson-Neyman plot for the trending interaction between worry, COMT, and estradiol. The plot demonstrates that at lower levels of estradiol, the negative association between PSWQ and accuracy is enhanced for Val carriers, while there is no significant effect for Met carriers.

Next, we examined a model for TGC, hypothesizing that more worry would predict enhanced coupling for Val carriers during high estradiol states. Interestingly, there was a trending COMT x worry x estradiol interaction (p = .07). Johnson-Neyman analyses revealed that as

estradiol levels increased, the association between within-person worry and TGC increased in Val carriers. However, the findings seemed to follow a U-shape, and the region of significance was narrow (see Figure 10). Similarly, I also examined whether the three-way interaction was further moderated by between-person worry. While the within-between worry interaction remained, no other effects reached significance. Therefore between-person worry was entered as a covariate in the final model (see Table 13).

Table 15. Estimates for multilevel model examining the effects of PSWQ within-centered, estradiol within-centered and COMT on 2-back TGC on correct trials. Between-person worry was included as a covariate.

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	2.6×10^{-3}	1.35×10^{-4}	41.05	19.33	< .0001
PSWQ (within-centered)	$\mathbf{1.28 \times 10^{-5}}$	$\mathbf{6.51 \times 10^{-6}}$	**1354**	**1.97**	**.04**
COMT	4.09×10^{-5}	1.27×10^{-4}	68.48	.322	.75
Estradiol (within-centered).	5.67×10^{-5}	1.33×10^{-4}	1339	.43	.67
PSWQ (between-centered)	-6.35×10^{-6}	9.78×10^{-6}	70.35	-.65	.52
PSWQ (within) x Estradiol (within)	-2.03×10^{-5}	1.99×10^{-5}	1323	-1.02	.31
PSWQ (within) x COMT	$\mathbf{-1.50 \times 10^{-5}}$	$\mathbf{6.48 \times 10^{-6}}$	**1350**	**-1.52**	**.02**
Estradiol (within) x COMT	1.63×10^{-4}	1.32×10^{-4}	1327	1.24	.21
PSWQ (within) x Estradiol (within) x COMT	$\mathbf{-3.5 \times 10^{-5}}$	$\mathbf{1.97 \times 10^{-6}}$	**1337**	**-1.77**	**.07**
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	9.56×10^{-7}	$9.79 \times 10\text{-}^{4}$			
Intercept for Electrode	1.27×10^{-8}	$1.13 \times 10\text{-}^{4}$			
Residual	3.54×10^{-6}	1.88×10^{-3}			

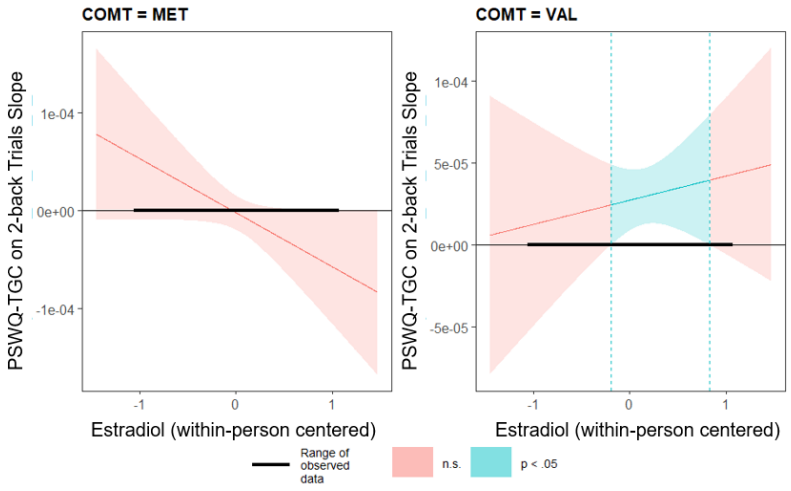

Figure 12. Johnson-Neyman plot for the trending interaction between worry, COMT, and estradiol on 2-back lure TGC. The plot demonstrates that at lower levels of estradiol the positive association between PSWQ and TGC is enhanced for Val carriers, while there is no effect for Met carriers.

3.8 Exploratory Models 3 and 4: Testing whether COMT moderates between-person effects of worry and estradiol on 2-back lure performance and TGC

Results for accuracy and TGC are reported in Tables 13 and 14, respectively. Similar to above, the model examining TGC controlled for within-person worry. Neither model revealed evidence for a combined modulatory role of between-worry, between-estradiol and COMT (*p*'s > .27).

Table 16. Estimates for multilevel model examining the effects of PSWQ within-centered, estradiol within-centered and COMT on 2-back lure accuracy. EEG Visit was a significant predictor in the model ($p < .001$).

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	.64	.03	111.53	25.10	.000*
PSWQ (between-centered)	-.002	.002	67.60	-.89	.44
COMT	**.07**	**.03**	**78.40**	**-.76**	**.03**
Estradiol (between-centered).	-.03	.04	78.40	-.76	.44
PSWQ (between) x Estradiol (between)	**-.006**	**.002**	**74.38**	**-2.28**	**.03**
PSWQ (between) x COMT	-.0008	.002	64.71	-.28	.77
Estradiol (between) x COMT	.07	.07	68.25	1.09	.27

Table 16 (cont'd)

PSWQ (between) x Estradiol (between) x COMT	.008	.007	66.08	1.10	.27
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	.02	.12			
Residual	.01	.12			

Table 17. Estimates for multilevel model examining the effects of PSWQ between-centered, estradiol between-centered and COMT on 2-back lure accuracy. Within-person worry was included as a covariate.

Fixed Effects	**Estimate**	**SE**	***df***	***t***	***p***
Intercept	2.67×10^{-3}	1.44×10^{-4}	44.17	18.47	< .0001
PSWQ (within-centered)	$\mathbf{1.32 \times 10^{-5}}$	$\mathbf{6.19 \times 10^{-6}}$	**1329**	**2.13**	**.03**
COMT	1.11×10^{-4}	1.37×10^{-4}	63.03	.81	.42
Estradiol (between-centered).	3.71×10^{-4}	2.74×10^{-4}	64.92	1.36	.18
PSWQ (between-centered)	-2.34×10^{-6}	1.15×10^{-6}	64.11	-.02	.98
PSWQ (between) x Estradiol (between)	3.06×10^{-5}	2.99×10^{-5}	63.76	1.02	.31
PSWQ (between) x COMT	-1.24×10^{-5}	1.15×10^{-5}	64.08	1.08	.29
Estradiol (between) x COMT	2.52×10^{-4}	2.74×10^{-4}	64.97	.92	.36
PSWQ (between) x Estradiol (between) x COMT	1.31×10^{-5}	2.99×10^{-5}	63.75	.44	.66
Random Effects	**Variance**	**Standard Deviation**	--	--	--
Intercept for Participant	9.53×10^{-7}	9.77×10^{-4}			
Intercept for Electrode	1.26×10^{-8}	1.12×10^{-4}			
Residual	3.54×10^{-6}	1.88×10^{-3}			

4. DISCUSSION

The current study had three aims converging on questions about how worry and working memory function are associated. I examined (1) the association between worry and working memory-related TGC; and then tested whether (2) tonic dopamine (as measured by COMT) and (3) estradiol levels across the menstrual cycle moderated their association. In line with ACT, I found: (1) for those with high average levels of worry, within-person increases in worry predicted reduced TGC, while for those with low average levels of worry, within-person increases in worry predicted enhanced TGC on 2-back lure trials; (2) within-person changes in worry interacted with the COMT genotype on 2-back lure trials, revealing that for Val carriers, more worry predicted enhanced TGC; (3) no effects for estradiol. Our findings demonstrate that TGC is influenced by within- and between-person changes in worry and PFC dopaminergic tone.

4.1 The Utility of TGC for Characterizing Working Memory Dysfunction in Worry

Our findings provide support for both the processing inefficiency and suppression hypotheses, with the critical moderator being average worry levels. Within-person increases in worry over time were associated with increased TGC strength on correct trials for those who worry less on average. The reverse was true for those who worry more on average, such that increases in worry over time were associated with reduced TGC on correct trials. Our findings converge on an interesting theory that TGC may be a neural correlate of how *adaptation* occurs for worriers when presented with more worry than they are used to. Increases in worry for low chronic worriers may motivate enhanced effort at lateral sites and therefore enhanced TGC strength, but there may be a particular threshold of cognitive demand that reverses this effect (see Figure 11). The findings for low worriers are in line with ACT's predictions. ACT proposes that increases in state worry may result in individuals aiming to reduce its deleterious effects by

exuding more effort, perhaps reflected as enhanced neural activity (Eysenck et al., 2007, 2022). Low chronic worriers may attempt to compensate for the distracting effects of worry when state worry increases, resulting in enhanced TGC strength on correct lure trials. On the other hand, for those with high levels of worry on average, state worry may lead to cognitive overload and therefore, reduced TGC strength. Previous studies have found that those with clinical anxiety demonstrate reduced lPFC activity (Balderston et al., 2017), weakened activity of the PFC during stress (Arnsten et al., 2015), and reduced TGC at lateral sites in psychiatric conditions (Barr et al., 2017; Goodman et al., 2018).

Notably, on 3-back lure trials, there was no interaction between within and between worry on TGC. Although within-person increases in worry predicted more coupling across gamma ranges, it did not interact with between-centered worry. This further suggests, aligning with the abovementioned theory, that when task demands are high, high average worriers may be less reliant on TGC and instead recruit other resources to perform well (Silton et al., 2011). For those with high average worry, because the lPFC is taxed, increases in worry may lead to the need to suppress lPFC activity to employ compensatory strategies that do not rely on the dlPFC (see Figure 13). Indeed, there was no between-within worry interaction to predict behavior. It would be fruitful for studies to assess changes in interchannel phase coupling (i.e., connectivity between two electrodes) to explore whether a potential compensatory strategy is reorganizing frontal-parietal network connectivity, which is implicated in top-down control. Finally, TGC may have less utility as a biomarker, and instead aid in understanding neural function in the context of worry.

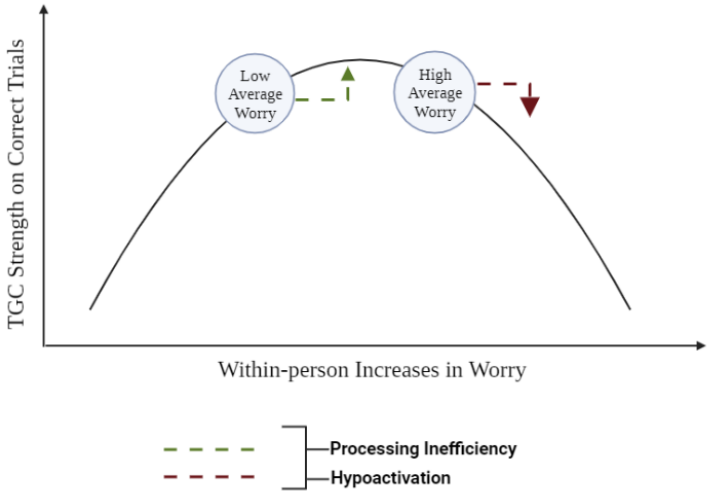

Figure 13. Hypothesized model for how within-person changes in worry influence TGC on two-back lure trials. The findings suggest that the association between worry and TGC is moderated by the average degree of worry one experiences. Worry may increase TGC to compensate for increased task demands. However, for those who experience more worry on average, within-person changes lead to reduced TGC. Reduced TGC at lateral sites may be needed to employ other compensatory strategies.

4.2 Examining the Interactive Role of Dopamine and Estradiol in the Association between Worry and TGC

I also found that within-person increases in worry predicted enhanced coupling on 2-back lure trials for Val carriers. Consistent with ACT, Val carriers may attempt to compensate for worry, and implement enhanced effort (i.e., increased activity in the lPFC) to perform well on the N-back (Elton et al., 2017; Jacobs & D'Esposito, 2011). In addition, the exploratory analyses revealed a protective role for estradiol levels across the menstrual cycle. The negative association between worry and accuracy was present for Val carriers when estradiol was low. On the other hand, the positive association between worry and TGC was present when estradiol was high. It may be surprising that heightened estradiol did not dampen this effect for Val carriers (i.e., no association between worry and TGC when estradiol is high). Our findings instead imply that

estradiol may support the process of employing enhanced effort when worry is higher than one's own average.

Lohani and colleagues (2019) suggest that dopamine neurons in the mesocortical pathway may influence the selection of information to be maintained in working memory. It could be that those with less dopamine may be in a less optimal state to efficiently select the information to be stored in working memory efficiently. When worry levels are relatively higher, it may be difficult for this to be maintained and therefore, Val carriers may overextend effort (evidenced by increased TGC) when faced with more worry than they are used to in to aid in the organization and maintenance of information. Heightened estradiol does not seem to alleviate this effort but may help support this process.

Striatal dopaminergic function may be another plausible mechanism that may explain the interactive effects of within-person worry and dopamine on working memory. Striatal dopamine has been implicated in effort deployment on tasks, due to its sensitivity to motivation. Cools (2015) suggests that striatal dopaminergic activity is important for aiding with the cost-benefit analysis of effort. Higher levels of striatal dopamine may motivate the destabilization of task goals because it is too effortful. Based on the dual state theory of dopamine (Durstewitz & Seamans, 2008), Val carriers have lower tonic dopamine levels (i.e., low D1 state), and higher levels of striatal dopamine (i.e., high D2 state). Therefore, for Val carriers, within-person increases in worry may serve as a motivation to increase goal-stabilization, and estradiol may further support this process resulting in higher TGC.

Importantly, although within-person changes in estradiol did not interact with worry to predict TGC, a clearer role for estradiol emerged when also accounting for COMT in hypothesized directions. Within-person worry, COMT, and estradiol also interacted to predict

behavior. For those with lower levels of dopamine, higher estradiol levels were associated with enhanced TGC and lower estradiol levels with less favorable performance. The findings reveal a protective role for estradiol in the context of worry– specifically for Val carriers. Perhaps, acute increases in estradiol aid those with lower dopamine levels when they experience worry. Our fundings reveal that dopamine is a critical mechanism involved in the acute effects of worry on TGC and working memory performance – and increased estradiol can help overcome the taxing effects of worry by supporting the effort employed by the dlPFC.

My exploratory analyses for between-centered worry did not provide convincing results for the moderating role of COMT. Further, although Gloe and colleagues found that between-person worry and estradiol interacted to influence lure performance, no effect was found for TGC in the exploratory analyses. Previous research and the present study imply that COMT is useful for understanding how acute changes in estrogen, stress, cognitive load, and worry may impact performance. However, COMT may be a less helpful proxy for understanding between-person effects. Higher estradiol levels during the length of the menstrual cycle, may not exert between-person effects on dopaminergic tone. Therefore, other ways of examining dopaminergic action (e.g., PET) may offer insight into how average estradiol levels may be involved in the association between worry and working memory.

4.3 Limitations

This study allowed me to leverage within- and between-levels of worry to assess how it may affect working memory function. However, future work would benefit from assessing whether those with clinical levels of chronic worry differ from those with less worry. Results from this analysis suggest that those with high average worry may have differences in TGC across the cycle. Notably the mean PSWQ scores this sample was low (~40), and therefore, I did

not have a sizable number of participants who had high levels of average worry (n=23) to be able to conduct meaningful between groups analyses (e.g., high vs low average worriers). It would be useful for studies to either collect data with more female participants across the range of worry scores or conduct between-groups analyses (worry < 40; worry > 50), to test between groups differences in TGC.

Second, while this study examined TGC across low and high gamma ranges, the high gamma range was selected based on visual inspection of the data. The literature often does not converge on what should be considered low or high gamma. Given this, there may not be an upper limit of 80 Hz for high gamma, and future research might benefit from examining higher gamma ranges. Further, the findings were similar across gamma ranges. Therefore, the distinction of TGC-low and high gamma on the N-back task requires future investigation.

4.4 Future Directions

Future studies would benefit from pursuing several additional avenues to elucidate the role of TGC in worriers. It would be fruitful for studies to examine network-based analyses using EEG methods. Phase synchrony and inter-channel PAC are two additional methods that could inform how worriers adapt to increasing load. Phase synchrony occurs when the same frequency rhythm is phase-locked across electrodes. Previous studies have found that worry may lead to reductions in phase synchrony within prefrontal sites that results in worse performance on a basic speeded response task (Moran et al., 2015). In addition, network analyses may provide insight into how worriers may be compensating on tasks. For instance, Silton and colleagues have proposed that worriers may demonstrate enhanced activity in the anterior cingulate cortex (ACC) when dlPFC is taxed (Silton et al., 2010). There is substantial evidence that theta at frontal midline sites is impacted by anxiety (Cavanagh & Shackman, 2015). Unlike faster frequency

rhythms, slower rhythms, such as theta, can evidence long range synchronization (Canolty et al., 2007), and therefore well suited as a control mechanism that may alter neural connectivity between regions (Sauseng et al., 2010). It may be fruitful to examine theta phase synchrony particularly between fontal midline theta and lateral sites to examine whether interchannel neural communication differs across high and low worriers. In summary, future studies should consider how worry affects neural networks. Dopamine and estradiol should continue to be considered as modulators of these effects, given their importance in working memory, and the results of the current study.

Considering these findings in a treatment context, future studies should examine how TGC may be altered depending on within-person changes in worry. Therefore, in addition to stratifying data collection between high and low worriers, studies should consider inducing worry within these groups to examine TGC change. Many studies have attempted to train working memory to improve function. One promising study found that working memory training using an updating task improves performance and reduces susceptibility to repetitive negative thinking (which includes worries) (Roberts et al., 2021). Therefore, examining whether TGC changes with working memory training would be a fruitful avenue to pursue. Our results also highlight the need to study chronic and state worry that should be pursued in future research.

In addition, future studies could greatly contribute to the field by measuring the COMT enzyme and estradiol concentrations. Assaying for COMT enzyme activity may provide a clearer understanding of how amounts of dopamine in the PFC and estradiol concentrations contribute to neural processing and may interact with worry to do so. A previous study examining the same N-back task in a female sample indeed found that it can provide additional explanatory value in this regard (Jacobs & D'Esposito, 2011). Future work should seek to explore these complex

interactions across various female life stages (e.g., pregnancy and menopause) or for those with medical conditions that alter endocrine function (e.g., polycystic ovarian syndrome; PCOS), due to drastic differences in estradiol concentrations observed within these contexts.

4.5 Conclusion

The advantage of using EEG-based neural methods is that they allow for a temporally precise understanding of neural correlates involved in cognitive processing. The findings outlined above highlight worry's influence on holding mental representations in mind – a needed process for many daily functions, such as maintaining goals and planning (Cools, 2015). Stabilizing mental representations under dynamic external and internal conditions is effortful and demanding, and our findings highlight that worry adds an additional "load" that alters one's ability to keep information in mind. Our results converge on the notion that the experience of worry may influence adaptations to increased mental demands. Worry may play a volitional role in motivating enhanced effort in high-demanding contexts (leading to inefficiency) or avoidance of mental demands. That is, worry plays a pivotal role in influencing whether individuals approach or avoid increased mental demands.

The findings also reveal that neurotransmission and endocrine factors influence worry's impact on cognition. Mental representations in the lateral PFC are highly influenced by dopamine and estrogen states. For those with less baseline dopamine in the PFC, high estrogen states help support goal stabilization and increase tolerance to stress. Indeed, our findings highlight that for those who may be more susceptible to distraction (i.e., those with less basal dopamine), estrogen may help increase mental stabilization during times of increased cognitive demands. The findings point to a supportive role of estrogen, specifically for those more susceptible to distraction.

Finally, the current results may provide clarity on how worry interrupts or facilitates processes conducive to goal attainment via sustained mental representations. Specifically, worry, as an internal interference, seems to be an important factor in the trade-off between the decision to overcome or avoid cognitive demand. Illuminating the contexts that influence this decision has implications for understanding how worry affects strategies to attain goals that require effortful top-down control and sustained mental representations. The promise of understanding dopamine and estradiol states in the association between worry and cognition is that they may offer insight into what can be termed the "mental demand approach-avoidance tradeoff" due to their role in the neural computation of motivation value and the cost of effort deployment (Ambrase et al., 2021; Braver et al., 2014; Cools, 2015).

In sum, few studies have specified the neurocognitive processes that are influenced by worry. I aimed to address this gap by examining how worry influences a neural mechanism involved in the sequential ordering of information in mind in a female sample. The advantages of this study are twofold – (1) leveraging longitudinal data to model acute and chronic worry levels; and (2) incorporating known endogenous modulators of working memory, namely dopamine and estradiol, to clarify neural mechanisms involved in the impact of worry on cognitive function. The findings reveal that the effect of acute worry on working memory-linked neural processing is dependent on the degree of worry one experiences on average. Higher worry levels may motivate enhanced effort by increasing neural coordination as a compensatory strategy, but excessive amounts of worry may dampen the use of this mechanism. Second, this study suggests that menstrual cycle dependent changes in estradiol levels and dopamine influence the association between acute worry and working memory. Specifically, higher levels of estradiol help strengthen neural coordination for those with lower levels of dopamine at baseline –

indicating that estradiol aids in the maintenance and ordering of information in mind during times of acute worry. The current study highlights that the ways in which worry impacts cognition is nuanced and emphasizes the utility of comprehensive models that consider various experiences of worry over time as well as complex interactions between genetic and hormonal factors. Taking such an approach would not only aid in our understanding of worry and working memory, but also encourage more precise models for those who are most impacted by worry.

REFERENCES

Alekseichuk, I., Turi, Z., de Lara, G. A., Antal, A., & Paulus, W. (2016). Spatial working memory in humans depends on theta and high gamma synchronization in the prefrontal cortex. *Current Biology*, *26*(12), 1513–1521.

Altemus, M., Sarvaiya, N., & Neill Epperson, C. (2014). Sex differences in anxiety and depression clinical perspectives. *Frontiers in Neuroendocrinology*, *35*(3), 320–330. https://doi.org/10.1016/j.yfrne.2014.05.004

Ambrase, A., Lewis, C. A., Barth, C., & Derntl, B. (2021). Influence of ovarian hormones on value-based decision-making systems: Contribution to sexual dimorphisms in mental disorders. *Frontiers in Neuroendocrinology*, *60*, 100873. https://doi.org/10.1016/j.yfrne.2020.100873

Apud, J. A., Mattay, V., Chen, J., Kolachana, B. S., Callicott, J. H., Rasetti, R., Alce, G., Iudicello, J. E., Akbar, N., Egan, M. F., Goldberg, T. E., & Weinberger, D. R. (2007). Tolcapone Improves Cognition and Cortical Information Processing in Normal Human Subjects. *Neuropsychopharmacology*, *32*(5), Article 5. https://doi.org/10.1038/sj.npp.1301227

Arnsten, A. F., & Li, B.-M. (2005). Neurobiology of executive functions: Catecholamine influences on prefrontal cortical functions. *Biological Psychiatry*, *57*(11), 1377–1384.

Arnsten, A. F. T. (2015). Stress weakens prefrontal networks: Molecular insults to higher cognition. *Nature Neuroscience*, *18*(10), 1376–1385. https://doi.org/10.1038/nn.4087

Arnsten, A. F. T., Raskind, M. A., Taylor, F. B., & Connor, D. F. (2015). The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder. *Neurobiology of Stress*, *1*, 89–99. https://doi.org/10.1016/j.ynstr.2014.10.002

Aru, J., Aru, J., Priesemann, V., Wibral, M., Lana, L., Pipa, G., Singer, W., & Vicente, R. (2015). Untangling cross-frequency coupling in neuroscience. *Current Opinion in Neurobiology*, *31*, 51–61. https://doi.org/10.1016/j.conb.2014.08.002

Aviyente, S., Tootell, A., & Bernat, E. M. (2017). Time-frequency phase-synchrony approaches with ERPs. *International Journal of Psychophysiology*, *111*, 88–97.

Axmacher, N., Henseler, M. M., Jensen, O., Weinreich, I., Elger, C. E., & Fell, J. (2010). Cross-frequency coupling supports multi-item working memory in the human hippocampus. *Proceedings of the National Academy of Sciences*, *107*(7), 3228–3233.

Bäckman, L., Karlsson, S., Fischer, H., Karlsson, P., Brehmer, Y., Rieckmann, A., MacDonald, S. W. S., Farde, L., & Nyberg, L. (2011). Dopamine D1 receptors and age differences in brain activation during working memory. *Neurobiology of Aging*, *32*(10), 1849–1856. https://doi.org/10.1016/j.neurobiolaging.2009.10.018

Baddeley, A. (2000). The episodic buffer: A new component of working memory? *Trends in Cognitive Sciences*, *4*(11), 417–423. https://doi.org/10.1016/S1364-6613(00)01538-2

Baddeley, A. (2012). Working Memory: Theories, Models, and Controversies. *Annual Review of Psychology*, *63*(1), 1–29. https://doi.org/10.1146/annurev-psych-120710-100422

Baddeley, A. D., & Hitch, G. (1974). Working Memory. In G. H. Bower (Ed.), *Psychology of Learning and Motivation* (Vol. 8, pp. 47–89). Academic Press. https://doi.org/10.1016/S0079-7421(08)60452-1

Baddeley, A. D., & Logie, R. H. (1999). *Working memory: The multiple-component model.*

Balderston, N. L., Vytal, K. E., O'Connell, K., Torrisi, S., Letkiewicz, A., Ernst, M., & Grillon, C. (2017). Anxiety Patients Show Reduced Working Memory Related dlPFC Activation During Safety and Threat. *Depression & Anxiety (1091-4269)*, *34*(1), 25–36. https://doi.org/10.1002/da.22518

Barbey, A. K., Koenigs, M., & Grafman, J. (2013). Dorsolateral prefrontal contributions to human working memory. *Cortex*, *49*(5), 1195–1205. https://doi.org/10.1016/j.cortex.2012.05.022

Barker, H., Munro, J., Orlov, N., Morgenroth, E., Moser, J., Eysenck, M. W., & Allen, P. (2018). Worry is associated with inefficient functional activity and connectivity in prefrontal and cingulate cortices during emotional interference. *Brain and Behavior*, *8*(12), e01137.

Barr, M. S., Rajji, T. K., Zomorrodi, R., Radhu, N., George, T. P., Blumberger, D. M., & Daskalakis, Z. J. (2017). Impaired theta-gamma coupling during working memory performance in schizophrenia. *Schizophrenia Research*, *189*, 104–110.

Barth, C., Villringer, A., & Sacher, J. (2015). Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. *Frontiers in Neuroscience*, *9*, 37.

Bates, D., Sarkar, D., Bates, M. D., & Matrix, L. (2007). The lme4 package. *R Package Version*, *2*(1), 74.

Baxter, A. J., Vos, T., Scott, K. M., Ferrari, A. J., & Whiteford, H. A. (2014). The global burden of anxiety disorders in 2010. *Psychological Medicine*, *44*(11), 2363–2374.

Beery, A. K., & Zucker, I. (2011). Sex bias in neuroscience and biomedical research. *Neuroscience & Biobehavioral Reviews*, *35*(3), 565–572.

Benchenane, K., Tiesinga, P. H., & Battaglia, F. P. (2011). Oscillations in the prefrontal cortex: A gateway to memory and attention. *Current Opinion in Neurobiology*, *21*(3), 475–485. https://doi.org/10.1016/j.conb.2011.01.004

Berggren, N., & Derakshan, N. (2013). Attentional control deficits in trait anxiety: Why you see them and why you don't. *Biological Psychology*, *92*(3), 440–446. https://doi.org/10.1016/j.biopsycho.2012.03.007

Bijsterbosch, J., Smith, S., Forster, S., John, O. P., & Bishop, S. J. (2014). Resting state correlates of subdimensions of anxious affect. *Journal of Cognitive Neuroscience*, *26*(4), 914–926.

Bimonte, H. A., & Denenberg, V. H. (1999). Estradiol facilitates performance as working memory load increases. *Psychoneuroendocrinology*, *24*(2), 161–173. https://doi.org/10.1016/S0306-4530(98)00068-7

Braver, T. S. (2012). The variable nature of cognitive control: A dual mechanisms framework. *Trends in Cognitive Sciences*, *16*(2), 106–113. https://doi.org/10.1016/j.tics.2011.12.010

Braver, T. S., & Cohen, J. D. (2000). On the control of control: The role of dopamine in regulating prefrontal function and working memory. *Control of Cognitive Processes: Attention and Performance XVIII*, 713–737.

Braver, T. S., Gray, J. R., & Burgess, G. C. (2007). Explaining the many varieties of working memory variation: Dual mechanisms of cognitive control. *Variation in Working Memory*, *75*, 106.

Braver, T. S., Krug, M. K., Chiew, K. S., Kool, W., Westbrook, J. A., Clement, N. J., Adcock, R. A., Barch, D. M., Botvinick, M. M., Carver, C. S., Cools, R., Custers, R., Dickinson, A., Dweck, C. S., Fishbach, A., Gollwitzer, P. M., Hess, T. M., Isaacowitz, D. M., Mather, M., … Somerville, L. H. (2014). Mechanisms of motivation–cognition interaction: Challenges and opportunities. *Cognitive, Affective & Behavioral Neuroscience, 14*(2), 443–472. https://doi.org/10.3758/s13415-014-0300-0

Brooks, H., Goodman, M. S., Bowie, C. R., Zomorrodi, R., Blumberger, D. M., Butters, M. A., Daskalakis, Z. J., Fischer, C. E., Flint, A., Herrmann, N., Kumar, S., Mah, L., Mulsant, B. H., Pollock, B. G., Voineskos, A. N., & Rajji, T. K. (2020). Theta–gamma coupling and ordering information: A stable brain–behavior relationship across cognitive tasks and clinical conditions. *Neuropsychopharmacology*, *45*(12), Article 12. https://doi.org/10.1038/s41386-020-0759-z

Brooks, H., Mirjalili, M., Wang, W., Kumar, S., Goodman, M. S., Zomorrodi, R., Blumberger, D. M., Bowie, C. R., Daskalakis, Z. J., Fischer, C. E., Flint, A. J., Herrmann, N., Lanctôt, K. L., Mah, L., Mulsant, B. H., Pollock, B. G., Voineskos, A. N., & Rajji, T. K. (2021). Assessing the Longitudinal Relationship between Theta-Gamma Coupling and Working Memory Performance in Older Adults. *Cerebral Cortex (New York, NY)*, *32*(8), 1653–1667. https://doi.org/10.1093/cercor/bhab295

Brozoski, T. J., Brown, R. M., Rosvold, H. E., & Goldman, P. S. (1979). Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science*, *205*(4409), 929–932.

Buckert, M., Kudielka, B. M., Reuter, M., & Fiebach, C. J. (2012). The COMT Val158Met polymorphism modulates working memory performance under acute stress. *Psychoneuroendocrinology*, *37*(11), 1810–1821. https://doi.org/10.1016/j.psyneuen.2012.03.014

Canolty, R., Soltani, M., Dalal, S., Edwards, E., Dronkers, N., Nagarajan, S., Kirsch, H., Barbaro, N., & Knight, R. (2007). Spatiotemporal dynamics of word processing in the human brain. *Frontiers in Neuroscience*, *1*. https://www.frontiersin.org/articles/10.3389/neuro.01.1.1.014.2007

Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., Berger, M. S., Barbaro, N. M., & Knight, R. T. (2006). High gamma power is phase-locked to theta oscillations in human neocortex. *Science*, *313*(5793), 1626–1628.

Canolty, R. T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends in Cognitive Sciences*, *14*(11), 506–515.

Carver, F. W., Rubinstein, D. Y., Gerlich, A. H., Fradkin, S. I., Holroyd, T., & Coppola, R. (2018). Prefrontal high gamma during a magnetoencephalographic working memory task. *Human Brain Mapping*, *40*(6), 1774–1785. https://doi.org/10.1002/hbm.24489

Cavanagh, J. F., & Shackman, A. J. (2015). Frontal midline theta reflects anxiety and cognitive control: Meta-analytic evidence. *Journal of Physiology-Paris*, *109*(1), 3–15. https://doi.org/10.1016/j.jphysparis.2014.04.003

Chai, W. J., Abd Hamid, A. I., & Abdullah, J. M. (2018). Working Memory From the Psychological and Neurosciences Perspectives: A Review. *Frontiers in Psychology*, *9*. https://doi.org/10.3389/fpsyg.2018.00401

Cools, R. (2015). The cost of dopamine for dynamic cognitive control. *Current Opinion in Behavioral Sciences*, *4*, 152–159. https://doi.org/10.1016/j.cobeha.2015.05.007

Correa-de-Araujo, R. (2006). Serious gaps: How the lack of sex/gender-based research impairs health. *Journal of Women's Health, 15*(10), 1116–1122.

Crowe, S. F., Matthews, C., & Walkenhorst, E. (2007). Relationship between worry, anxiety and thought suppression and the components of working memory in a non-clinical sample. *Australian Psychologist, 42*(3), 170–177.

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences, 7*(9), 415–423.

D'Esposito, M. (2007). From cognitive to neural models of working memory. *Philosophical Transactions of the Royal Society B: Biological Sciences, 362*(1481), 761–772.

D'Esposito, M., Detre, J. A., Alsop, D. C., Shin, R. K., Atlas, S., & Grossman, M. (1995). The neural basis of the central executive system of working memory. *Nature, 378*(6554), Article 6554. https://doi.org/10.1038/378279a0

D'Esposito, M., & Postle, B. R. (2015a). The Cognitive Neuroscience of Working Memory. *Annual Review of Psychology, 66*(1), 115–142. https://doi.org/10.1146/annurev-psych-010814-015031

D'Esposito, M., & Postle, B. R. (2015b). THE COGNITIVE NEUROSCIENCE OF WORKING MEMORY. *Annual Review of Psychology, 66*, 115–142. https://doi.org/10.1146/annurev-psych-010814-015031

Diamond, D. M. (2005). Cognitive, Endocrine and Mechanistic Perspectives on Non-Linear Relationships between Arousal and Brain Function. *Nonlinearity in Biology, Toxicology, Medicine, 3*(1), nonlin.003.01.001. https://doi.org/10.2201/nonlin.003.01.001

Duff, S. J., & Hampson, E. (2000). A Beneficial Effect of Estrogen on Working Memory in Postmenopausal Women Taking Hormone Replacement Therapy. *Hormones and Behavior, 38*(4), 262–276. https://doi.org/10.1006/hbeh.2000.1625

Duncan, L. E., & Keller, M. C. (2011). A Critical Review of the First 10 Years of Candidate Gene-by-Environment Interaction Research in Psychiatry. *American Journal of Psychiatry, 168*(10), 1041–1049. https://doi.org/10.1176/appi.ajp.2011.11020191

Durstewitz, D., & Seamans, J. K. (2008). The Dual-State Theory of Prefrontal Cortex Dopamine Function with Relevance to Catechol-O-Methyltransferase Genotypes and Schizophrenia. *Biological Psychiatry, 64*(9), 739–749. https://doi.org/10.1016/j.biopsych.2008.05.015

Edwards, E., Soltani, M., Deouell, L. Y., Berger, M. S., & Knight, R. T. (2005). High Gamma Activity in Response to Deviant Auditory Stimuli Recorded Directly From Human

Cortex. *Journal of Neurophysiology*, *94*(6), 4269–4280. https://doi.org/10.1152/jn.00324.2005

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., Goldman, D., & Weinberger, D. R. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences*, *98*(12), 6917–6922.

Elton, A., Smith, C. T., Parrish, M. H., & Boettiger, C. A. (2017). COMT Val158Met Polymorphism Exerts Sex-Dependent Effects on fMRI Measures of Brain Function. *Frontiers in Human Neuroscience*, *11*. https://www.frontiersin.org/articles/10.3389/fnhum.2017.00578

Eysenck, M. W., & Derakshan, N. (2011). New perspectives in attentional control theory. *Personality and Individual Differences*, *50*(7), 955–960. https://doi.org/10.1016/j.paid.2010.08.019

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: Attentional control theory. *Emotion*, *7*(2), 336.

Eysenck, M. W., Moser, J. S., Derakshan, N., Hepsomali, P., & Allen, P. (2022). A neurocognitive account of attentional control theory: How does trait anxiety affect the brain's attentional networks? *Cognition and Emotion*, *0*(0), 1–18. https://doi.org/10.1080/02699931.2022.2159936

Fales, C. L., Barch, D. M., Burgess, G. C., Schaefer, A., Mennin, D. S., Gray, J. R., & Braver, T. S. (2008). Anxiety and cognitive efficiency: Differential modulation of transient and sustained neural activity during a working memory task. *Cognitive, Affective, & Behavioral Neuroscience*, *8*(3), 239–253.

Feurer, C., Jimmy, J., Chang, F., Langenecker, S. A., Phan, K. L., Ajilore, O., & Klumpp, H. (2021). Resting state functional connectivity correlates of rumination and worry in internalizing psychopathologies. *Depression & Anxiety (1091-4269)*, *38*(5), 488–497. https://doi.org/10.1002/da.23142

Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences*, *9*(10), 474–480. https://doi.org/10.1016/j.tics.2005.08.011

Gloe, L. M., Kashy, D. A., Jacobs, E. G., Klump, K. L., & Moser, J. S. (2021). Examining the role of ovarian hormones in the association between worry and working memory across the menstrual cycle. *Psychoneuroendocrinology*, *131*, 105285. https://doi.org/10.1016/j.psyneuen.2021.105285

Goldberg, T. E., Egan, M. F., Gscheidle, T., Coppola, R., Weickert, T., Kolachana, B. S., Goldman, D., & Weinberger, D. R. (2003). Executive Subprocesses in Working Memory: Relationship to Catechol-O-methyltransferase Val158Met Genotype and Schizophrenia. *Archives of General Psychiatry*, *60*(9), 889–896. https://doi.org/10.1001/archpsyc.60.9.889

Goldman-Rakic, P. S. (1988). Topography of cognition: Parallel distributed networks in primate association cortex. *Annual Review of Neuroscience*, *11*(1), 137–156.

Goodman, M. S., Kumar, S., Zomorrodi, R., Ghazala, Z., Cheam, A. S. M., Barr, M. S., Daskalakis, Z. J., Blumberger, D. M., Fischer, C., Flint, A., Mah, L., Herrmann, N., Bowie, C. R., Mulsant, B. H., & Rajji, T. K. (2018). Theta-Gamma Coupling and Working Memory in Alzheimer's Dementia and Mild Cognitive Impairment. *Frontiers in Aging Neuroscience*, *10*. https://www.frontiersin.org/articles/10.3389/fnagi.2018.00101

Gray, J. A. (1984). The Neuropsychology of Anxiety. In K. Pawlik (Ed.), *Fortschritte der Experimentalpsychologie: Hamburger Mittagsvorlesungen 1983* (pp. 52–71). Springer. https://doi.org/10.1007/978-3-642-69631-2_5

Guo, J. Y., Ragland, J. D., & Carter, C. S. (2019). Memory and cognition in schizophrenia. *Molecular Psychiatry*, *24*(5), Article 5. https://doi.org/10.1038/s41380-018-0231-1

Gustavson, D. E., & Miyake, A. (2016a). Trait worry is associated with difficulties in working memory updating. *Cognition and Emotion*, *30*(7), 1289–1303.

Gustavson, D. E., & Miyake, A. (2016b). Trait worry is associated with difficulties in working memory updating. *Cognition and Emotion*, *30*(7), 1289–1303.

Hallion, L. S., Ruscio, A. M., & Jha, A. P. (2014). Fractionating the role of executive control in control over worry: A preliminary investigation. *Behaviour Research and Therapy*, *54*, 1–6. https://doi.org/10.1016/j.brat.2013.12.002

Hallion, L. S., Tolin, D. F., Assaf, M., Goethe, J., & Diefenbach, G. J. (2017). Cognitive Control in Generalized Anxiety Disorder: Relation of Inhibition Impairments to Worry and Anxiety Severity. *Cognitive Therapy and Research*, *41*(4), 610–618. https://doi.org/10.1007/s10608-017-9832-2

Hampson, E., & Morley, E. E. (2013). Estradiol concentrations and working memory performance in women of reproductive age. *Psychoneuroendocrinology*, *38*(12), 2897–2904.

Hayes, S., Hirsch, C., & Mathews, A. (2008). Restriction of working memory capacity during worry. *Journal of Abnormal Psychology, 117*(3), 712–717. https://doi.org/10.1037/a0012908

Held, J., Vîslă, A., Zinbarg, R. E., Wolfer, C., & Flückiger, C. (2020). How do worry and clinical status impact working memory performance? An experimental investigation. *BMC Psychiatry, 20*(1), 317. https://doi.org/10.1186/s12888-020-02694-x

Heller, W., Nitschke, J. B., Etienne, M. A., & Miller, G. A. (1997). Patterns of regional brain activity differentiate types of anxiety. *Journal of Abnormal Psychology, 106*(3), 376.

Holmes, M. M., Wide, J. K., & Galea, L. A. (2002). Low levels of estradiol facilitate, whereas high levels of estradiol impair, working memory performance on the radial arm maze. *Behavioral Neuroscience, 116*(5), 928.

Hülsemann, M. J., Naumann, E., & Rasch, B. (2019). Quantification of Phase-Amplitude Coupling in Neuronal Oscillations: Comparison of Phase-Locking Value, Mean Vector Length, Modulation Index, and Generalized-Linear-Modeling-Cross-Frequency-Coupling. *Frontiers in Neuroscience, 13*. https://doi.org/10.3389/fnins.2019.00573

Jacobs, E., & D'Esposito, M. (2011). Estrogen shapes dopamine-dependent cognitive processes: Implications for women's health. *Journal of Neuroscience, 31*(14), 5286–5293.

Jaeggi, S. M., Buschkuehl, M., Perrig, W. J., & Meier, B. (2010). The concurrent validity of the N-back task as a working memory measure. *Memory, 18*(4), 394–412. https://doi.org/10.1080/09658211003702171

Kane, M., Conway, A., Miura, T., & Colflesh, G. (2007). Working memory, attention control, and the N-back task: A question of construct validity. *Journal of Experimental Psychology. Learning, Memory, and Cognition, 33*, 615–622. https://doi.org/10.1037/0278-7393.33.3.615

Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychonomic Bulletin & Review, 9*(4), 637–671. https://doi.org/10.3758/BF03196323

Keenan, P. A., Ezzat, W. H., Ginsburg, K., & Moore, G. J. (2001). Prefrontal cortex as the site of estrogen's effect on cognition. *Psychoneuroendocrinology, 26*(6), 577–590. https://doi.org/10.1016/S0306-4530(01)00013-0

Keller, M. C. (2014). Gene × Environment Interaction Studies Have Not Properly Controlled for Potential Confounders: The Problem and the (Simple) Solution. *Biological Psychiatry, 75*(1), 18–24. https://doi.org/10.1016/j.biopsych.2013.09.006

Kessler, R. C., Petukhova, M., Sampson, N. A., Zaslavsky, A. M., & Wittchen, H.-U. (2012). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *International Journal of Methods in Psychiatric Research*, *21*(3), 169–184. https://doi.org/10.1002/mpr.1359

Kirchner, W. K. (1958). Age differences in short-term retention of rapidly changing information. *Journal of Experimental Psychology*, *55*(4), 352–358. http://dx.doi.org/10.1037/h0043688

Konnopka, A., & König, H. (2019). Economic Burden of Anxiety Disorders: A Systematic Review and Meta-Analysis. *PharmacoEconomics*, 1–13.

Krug, R., Born, J., & Rasch, B. (2006). A 3-day estrogen treatment improves prefrontal cortex-dependent cognitive function in postmenopausal women. *Psychoneuroendocrinology*, *31*(8), 965–975. https://doi.org/10.1016/j.psyneuen.2006.05.007

Kumar, S., Zomorrodi, R., Ghazala, Z., Goodman, M. S., Blumberger, D. M., Cheam, A., Fischer, C., Daskalakis, Z. J., Mulsant, B. H., Pollock, B. G., & Rajji, T. K. (2017). Extent of Dorsolateral Prefrontal Cortex Plasticity and Its Association With Working Memory in Patients With Alzheimer Disease. *JAMA Psychiatry*, *74*(12), 1266–1274. https://doi.org/10.1001/jamapsychiatry.2017.3292

Leigh, E., & Hirsch, C. R. (2011). Worry in imagery and verbal form: Effect on residual working memory capacity. *Behaviour Research and Therapy*, *49*(2), 99–105. https://doi.org/10.1016/j.brat.2010.11.005

Li, S. H., & Graham, B. M. (2017). Why are women so vulnerable to anxiety, trauma-related and stress-related disorders? The potential role of sex hormones. *The Lancet Psychiatry*, *4*(1), 73–82. https://doi.org/10.1016/S2215-0366(16)30358-3

Lisman, J. E., & Jensen, O. (2013). The theta-gamma neural code. *Neuron*, *77*(6), 1002–1016.

Louis, C. C., D'Esposito, M., & Moser, J. S. (2021). Investigating interactive effects of worry and the catechol-o-methyltransferase gene (COMT) on working memory performance. *Cognitive, Affective, & Behavioral Neuroscience*, *21*(6), 1153–1163.

Marciniak, M., Lage, M. J., Landbloom, R. P., Dunayevich, E., & Bowman, L. (2004). Medical and productivity costs of anxiety disorders: Case control study. *Depression and Anxiety*, *19*(2), 112–120.

Matsumoto, M., Weickert, C. S., Akil, M., Lipska, B. K., Hyde, T. M., Herman, M. M., Kleinman, J. E., & Weinberger, D. R. (2003). Catechol O-methyltransferase mRNA

expression in human and rat brain: Evidence for a role in cortical neuronal function. *Neuroscience*, *116*(1), 127–137. https://doi.org/10.1016/S0306-4522(02)00556-0

Mattay, V. S., Goldberg, T. E., Fera, F., Hariri, A. R., Tessitore, A., Egan, M. F., Kolachana, B., Callicott, J. H., & Weinberger, D. R. (2003). Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proceedings of the National Academy of Sciences*, *100*(10), 6186–6191. https://doi.org/10.1073/pnas.0931309100

McCarthy, M. M., Arnold, A. P., Ball, G. F., Blaustein, J. D., & De Vries, G. J. (2012). Sex differences in the brain: The not so inconvenient truth. *Journal of Neuroscience*, *32*(7), 2241–2247.

McEwen, B., Akama, K., Alves, S., Brake, W. G., Bulloch, K., Lee, S., Li, C., Yuen, G., & Milner, T. A. (2001). Tracking the estrogen receptor in neurons: Implications for estrogen-induced synapse formation. *Proceedings of the National Academy of Sciences*, *98*(13), 7093–7100.

McEwen, B. S. (2010). Stress, sex and neural adaptation to a changing environment: Mechanisms of neuronal remodeling. *Annals of the New York Academy of Sciences*, *1204*(Suppl), E38–E59. https://doi.org/10.1111/j.1749-6632.2010.05568.x

Meyer-Lindenberg, A., Nichols, T., Callicott, J. H., Ding, J., Kolachana, B., Buckholtz, J., Mattay, V. S., Egan, M., & Weinberger, D. R. (2006). Impact of complex genetic variation in COMT on human brain function. *Molecular Psychiatry*, *11*(9), Article 9. https://doi.org/10.1038/sj.mp.4001860

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*(1), 167–202.

Miyake, A., & Friedman, N. P. (2012). The Nature and Organization of Individual Differences in Executive Functions: Four General Conclusions. *Current Directions in Psychological Science*, *21*(1), 8–14. https://doi.org/10.1177/0963721411429458

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. *Cognitive Psychology*, *41*(1), 49–100. https://doi.org/10.1006/cogp.1999.0734

Mogg, K., & Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behaviour Research and Therapy*, *36*(9), 809–848. https://doi.org/10.1016/S0005-7967(98)00063-1

Mohlman, J., Eldreth, D. A., Price, R. B., Staples, A. M., & Hanson, C. (2017). Prefrontal-limbic connectivity during worry in older adults with generalized anxiety disorder. *Aging & Mental Health*, *21*(4), 426–438.

Moran, T. P. (2016). Anxiety and working memory capacity: A meta-analysis and narrative review. *Psychological Bulletin*, *142*(8), 831.

Moran, T. P., Bernat, E. M., Aviyente, S., Schroder, H. S., & Moser, J. S. (2015). Sending mixed signals: Worry is associated with enhanced initial error processing but reduced call for subsequent cognitive control. *Social Cognitive and Affective Neuroscience*, *10*(11), 1548–1556.

Munia, T. T. K., & Aviyente, S. (2019a). Comparison of Wavelet and RID-Rihaczek Based Methods for Phase-Amplitude Coupling. *IEEE Signal Processing Letters*, *26*(12), 1897–1901.

Munia, T. T. K., & Aviyente, S. (2019b). Time-Frequency Based Phase-Amplitude Coupling Measure For Neuronal Oscillations. *Scientific Reports*, *9*(1), Article 1. https://doi.org/10.1038/s41598-019-48870-2

Nitschke, J. B., Heller, W., Imig, J. C., McDonald, R. P., & Miller, G. A. (2001). Distinguishing Dimensions of Anxiety and Depression. *Cognitive Therapy and Research*, *25*(1), 1–22. https://doi.org/10.1023/A:1026485530405

Norman, D. A., & Shallice, T. (1986). *Attention to action: Willed and automatic control of behavior*. Springer.

Özkurt, T. E., & Schnitzler, A. (2011). A critical note on the definition of phase–amplitude cross-frequency coupling. *Journal of Neuroscience Methods*, *201*(2), 438–443. https://doi.org/10.1016/j.jneumeth.2011.08.014

Papaioannou, O., Crespo, L. P., Clark, K., Ogbuagu, N. N., Alliende, L. M., Silverstein, S. M., & Erickson, M. A. (2022). Is Cortical Theta-Gamma Phase-Amplitude Coupling Memory-Specific? *Brain Sciences*, *12*(9), 1131. https://doi.org/10.3390/brainsci12091131

Parekh, A., Fadiran, E. O., Uhl, K., & Throckmorton, D. C. (2011). Adverse effects in women: Implications for drug development and regulatory policies. *Expert Review of Clinical Pharmacology*, *4*(4), 453–466.

Park, J.-I., Kim, G.-W., Jeong, G.-W., Chung, G. H., & Yang, J.-C. (2016). Brain Activation Patterns Associated with the Effects of Emotional Distracters during Working Memory Maintenance in Patients with Generalized Anxiety Disorder. *Psychiatry Investigation*, *13*(1), 152–156. https://doi.org/10.4306/pi.2016.13.1.152

Price, R. B., & Mohlman, J. (2007). Inhibitory control and symptom severity in late life generalized anxiety disorder. *Behaviour Research and Therapy*, *45*(11), 2628–2639. https://doi.org/10.1016/j.brat.2007.06.007

Qin, S., Cousijn, H., Rijpkema, M., Luo, J., Franke, B., Hermans, E., & Fernández, G. (2012). The effect of moderate acute psychological stress on working memory-related neural activity is modulated by a genetic variation in catecholaminergic function in humans. *Frontiers in Integrative Neuroscience*, *6*. https://www.frontiersin.org/articles/10.3389/fnint.2012.00016

Rajji, T. K., Zomorrodi, R., Barr, M. S., Blumberger, D. M., Mulsant, B. H., & Daskalakis, Z. J. (2017). Ordering Information in Working Memory and Modulation of Gamma by Theta Oscillations in Humans. *Cerebral Cortex*, *27*(2), 1482–1490. https://doi.org/10.1093/cercor/bhv326

Redick, T. S., & Lindsey, D. R. B. (2013). Complex span and n-back measures of working memory: A meta-analysis. *Psychonomic Bulletin & Review*, *20*(6), 1102–1113. https://doi.org/10.3758/s13423-013-0453-9

RepovŠ, G., & Baddeley, A. (2006). The multi-component model of working memory: Explorations in experimental cognitive psychology. *Neuroscience*, *139*(1), 5–21. https://doi.org/10.1016/j.neuroscience.2005.12.061

Roberts, H., Mostazir, M., Moberly, N. J., Watkins, E. R., & Adlam, A.-L. (2021). Working memory updating training reduces state repetitive negative thinking: Proof-of-concept for a novel cognitive control training. *Behaviour Research and Therapy*, *142*, 103871. https://doi.org/10.1016/j.brat.2021.103871

Rosa-Alcázar, Á., Olivares-Olivares, P. J., Martínez-Esparza, I. C., Parada-Navas, J. L., Rosa-Alcázar, A. I., & Olivares-Rodríguez, J. (2020). Cognitive flexibility and response inhibition in patients with Obsessive-Compulsive Disorder and Generalized Anxiety Disorder. *International Journal of Clinical and Health Psychology*, *20*(1), 20–28. https://doi.org/10.1016/j.ijchp.2019.07.006

Roussos, P., Giakoumaki, S. G., & Bitsios, P. (2009). Tolcapone Effects on Gating, Working Memory, and Mood Interact with the Synonymous Catechol-O-methyltransferase rs4818C/G Polymorphism. *Biological Psychiatry*, *66*(11), 997–1004. https://doi.org/10.1016/j.biopsych.2009.07.008

Roux, F., & Uhlhaas, P. J. (2014). Working memory and neural oscillations: Alpha–gamma versus theta–gamma codes for distinct WM information? *Trends in Cognitive Sciences*, *18*(1), 16–25.

Roux, F., Wibral, M., Mohr, H. M., Singer, W., & Uhlhaas, P. J. (2012). Gamma-Band Activity in Human Prefrontal Cortex Codes for the Number of Relevant Items Maintained in Working Memory. *Journal of Neuroscience*, *32*(36), 12411–12420. https://doi.org/10.1523/JNEUROSCI.0421-12.2012

Sari, B. A., Koster, E. H., & Derakshan, N. (2017). The effects of active worrying on working memory capacity. *Cognition and Emotion*, *31*(5), 995–1003.

Sauseng, P., Griesmayr, B., Freunberger, R., & Klimesch, W. (2010). Control mechanisms in working memory: A possible function of EEG theta oscillations. *Neuroscience & Biobehavioral Reviews*, *34*(7), 1015–1022. https://doi.org/10.1016/j.neubiorev.2009.12.006

Sauseng, P., Peylo, C., Biel, A. L., Friedrich, E. V. C., & Romberg-Taylor, C. (2019). Does cross-frequency phase coupling of oscillatory brain activity contribute to a better understanding of visual working memory? *British Journal of Psychology*, *110*(2), 245–255. https://doi.org/10.1111/bjop.12340

Schmiedek, F., Lövdén, M., & Lindenberger, U. (2014). A task is a task is a task: Putting complex span, n-back, and other working memory indicators in psychometric context. *Frontiers in Psychology*, *5*. https://www.frontiersin.org/articles/10.3389/fpsyg.2014.01475

Shackman, A. J., Sarinopoulos, I., Maxwell, J. S., Pizzagalli, D. A., Lavric, A., & Davidson, R. J. (2006). Anxiety selectively disrupts visuospatial working memory. *Emotion*, *6*(1), 40.

Shansky, R. M., Glavis-Bloom, C., Lerman, D., McRae, P., Benson, C., Miller, K., Cosand, L., Horvath, T. L., & Arnsten, A. F. T. (2004). Estrogen mediates sex differences in stress-induced prefrontal cortex dysfunction. *Molecular Psychiatry*, *9*(5), Article 5. https://doi.org/10.1038/sj.mp.4001435

Shansky, R. M., & Lipps, J. (2013). Stress-induced cognitive dysfunction: Hormone-neurotransmitter interactions in the prefrontal cortex. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00123

Silton, R. L., Heller, W., Engels, A. S., Towers, D. N., Spielberg, J. M., Edgar, J. C., Sass, S. M., Stewart, J. L., Sutton, B. P., Banich, M. T., & Miller, G. A. (2011). Depression and Anxious Apprehension Distinguish Frontocingulate Cortical Activity during Top-Down Attentional Control. *Journal of Abnormal Psychology*, *120*(2), 272–285. https://doi.org/10.1037/a0023204

Silton, R. L., Heller, W., Towers, D. N., Engels, A. S., Spielberg, J. M., Edgar, J. C., Sass, S. M., Stewart, J. L., Sutton, B. P., Banich, M. T., & Miller, G. A. (2010). The time course of activity in dorsolateral prefrontal cortex and anterior cingulate cortex during top-down

attentional control. *NeuroImage*, *50*(3), 1292–1302. https://doi.org/10.1016/j.neuroimage.2009.12.061

Sinopoli, K. J., Floresco, S. B., & Galea, L. A. M. (2006). Systemic and local administration of estradiol into the prefrontal cortex or hippocampus differentially alters working memory. *Neurobiology of Learning and Memory*, *86*(3), 293–304. https://doi.org/10.1016/j.nlm.2006.04.003

Snyder, H. R., Silton, R. L., Hankin, B. L., Smolker, H. R., Kaiser, R. H., Banich, M. T., Miller, G. A., & Heller, W. (2022). The dimensional structure of internalizing psychopathology: Relation to diagnostic categories. *Clinical Psychological Science*, 21677026221119484.

Stefanopoulou, E., Hirsch, C. R., Hayes, S., Adlam, A., & Coker, S. (2014). Are attentional control resources reduced by worry in generalized anxiety disorder? *Journal of Abnormal Psychology, 123*(2), 330.

Takahashi, H., Kato, M., Takano, H., Arakawa, R., Okumura, M., Otsuka, T., Kodaka, F., Hayashi, M., Okubo, Y., Ito, H., & Suhara, T. (2008). Differential Contributions of Prefrontal and Hippocampal Dopamine D1 and D2 Receptors in Human Cognitive Functions. *Journal of Neuroscience*, *28*(46), 12032–12038. https://doi.org/10.1523/JNEUROSCI.3446-08.2008

Tallon-Baudry, C., & Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in Cognitive Sciences*, *3*(4), 151–162. https://doi.org/10.1016/S1364-6613(99)01299-1

Taylor, C. M., Pritschet, L., & Jacobs, E. G. (2021). The scientific body of knowledge – Whose body does it serve? A spotlight on oral contraceptives and women's health factors in neuroimaging. *Frontiers in Neuroendocrinology*, *60*, 100874. https://doi.org/10.1016/j.yfrne.2020.100874

Tunbridge, E. M., Harrison, P. J., & Weinberger, D. R. (2006). Catechol-o-Methyltransferase, Cognition, and Psychosis: Val158Met and Beyond. *Biological Psychiatry*, *60*(2), 141–151. https://doi.org/10.1016/j.biopsych.2005.10.024

Tunbridge, E. M., Narajos, M., Harrison, C. H., Beresford, C., Cipriani, A., & Harrison, P. J. (2019). Which Dopamine Polymorphisms Are Functional? Systematic Review and Meta-analysis of COMT, DAT, DBH, DDC, DRD1–5, MAOA, MAOB, TH, VMAT1, and VMAT2. *Biological Psychiatry*, *86*(8), 608–620. https://doi.org/10.1016/j.biopsych.2019.05.014

Warren, S. L., Crocker, L. D., Spielberg, J. M., Engels, A. S., Banich, M. T., Sutton, B. P., Miller, G. A., & Heller, W. (2013). Cortical organization of inhibition-related functions

and modulation by psychopathology. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00271

Williams, G. V., & Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine Dl receptors in prefrontal cortex. *Nature*, *376*(6541), 572–575.

Williams, P. G., Rau, H. K., Suchy, Y., Thorgusen, S. R., & Smith, T. W. (2017). On the validity of self-report assessment of cognitive abilities: Attentional control scale associations with cognitive performance, emotional adjustment, and personality. *Psychological Assessment*, *29*(5), 519.

Xiao, L., & Becker, J. B. (1994). Quantitative microdialysis determination of extracellular striatal dopamine concentration in male and female rats: Effects of estrous cycle and gonadectomy. *Neuroscience Letters*, *180*(2), 155–158. https://doi.org/10.1016/0304-3940(94)90510-X

Xiao, Z., Wang, J., Zhang, M., Li, H., Tang, Y., Wang, Y., Fan, Q., & Fromson, J. A. (2011). Error-related negativity abnormalities in generalized anxiety disorder and obsessive–compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(1), 265–272. https://doi.org/10.1016/j.pnpbp.2010.11.022

Yang, C.-Y., & Huang, C.-K. (2018). Working-memory evaluation based on EEG signals during n-back tasks. *Journal of Integrative Neuroscience*, *17*(3–4), 695–707. https://doi.org/10.3233/JIN-180096

Zainal, N. H., & Newman, M. G. (2020). Within-person increase in pathological worry predicts future depletion of unique executive functioning domains. *Psychological Medicine*, 1–11.

APPENDIX

Studies that have investigated TGC on the N-back have mostly focused on low gamma ranges (30-50 Hz) in the early time segment under the presumption that this is when having the correct ordering of stimuli is critical. However, this has yet to be empirically tested. I therefore conducted a series of multilevel models to examine whether there were differences in theta-low gamma and theta-high gamma across trial type (targets, non-targets, lures) and time range (first half and second half) on the N-back. To test this, I tested a model with trial type (targets, non-targets, lures) and time range (first half, second half) as effects-coded within-subjects factors. Session was entered as an effects-coded predictor to control for the effect of time. A conservative Bonferroni correction was applied to the pairwise comparisons when breaking down effects (.05/24 = .002).

TGC-low gamma on 2-back trials

For 2-back the results revelated a significant effect of trial type ($p < .0001$), time range ($p < .0001$), and trial type x time range ($p = .006$). The effect of trial type revealed that overall, there was significantly more coupling on targets than non-targets ($p < .0001$) and lures ($p < .0001$). In addition, there was more coupling in the second half than the first half ($p < .0001$).

The time range x trial type interaction was probed by examining the effect of trial type in the first and second half. In the first half, there was significantly more coupling on target trials in comparison to non-targets ($p < .0001$), and lures ($p = .03$). There was also more coupling on lures in comparison to non-targets ($p < .0001$). In the second half, there was more coupling on targets trials than lures ($p < .0001$) and non-targets ($p < .0001$). However, non-targets were not significantly different from lures in the second half ($p = .80$).

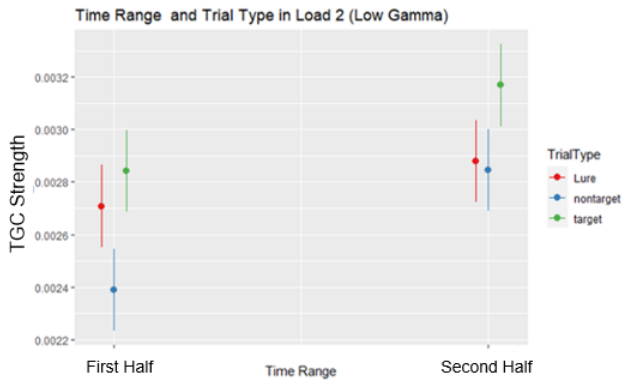

Figure 14. Trial Type x Time range interaction on TGC-low gamma on 2-back TGC.

TGC-low gamma on 3-back trials

For 3-back, there was a main effect of trial type ($p < .0001$), time range ($p < .0001$) and a trial type x time range interaction ($p < .0001$). There was more coupling on targets and lures in comparison to in comparison non-targets (p's < .0001). Targets and lures were not significantly different from each other ($p = .8$). The trial time x time range interaction was examined by investigating the effect of trial type in the first and second half of the time range. The results revealed that in the first half of the time range, there was less coupling on non-targets than targets and lures (p's < .0001). Lures and targets were not significantly different from each other ($p = .16$). In the second half, targets had significantly more coupling than non-targets ($p < .0001$), but not lures ($p < .60$). The difference between lures and non-targets did not survive the correction for multiple comparisons ($p = .01$).

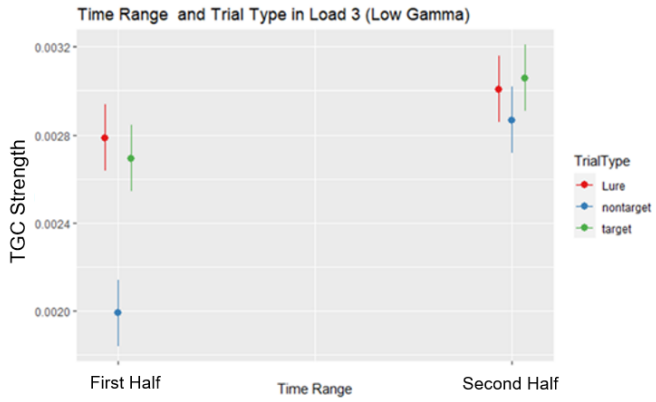

Figure 15. Trial Type x Time range interaction on TGC-low gamma for 3-back TGC.

TGC-high gamma on 2-back trials

For 2-back, similar results of trial type, time range, and trial type x time range emerged (*p*'s < .006). In the first half, there was a significant difference between targets and non-targets (*p* < .0001), but not targets and lures (*p* < .64). Lures had more coupling than not-targets (*p* < .001). In the second half, targets showed significantly more coupling than lures and non-targets (*p*'s < .0001). Non-targets and lures were not significantly different from each other (*p* = .88).

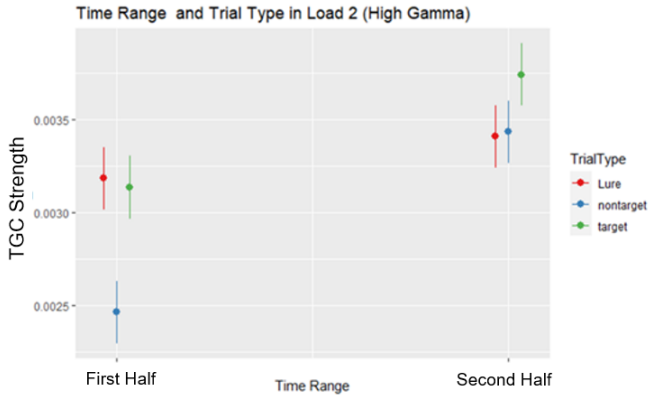

Figure 16. Trial Type x Time range interaction for TGC-high gamma for 2-back TGC.

TGC-high gamma on 3-back trials

For 3-back, similarly, there was a significant effect of trial type ($p < .0001$), time range ($p < .0001$), and a trial type x time range interaction ($p < .0001$). The interaction revealed that in the first half of the time segment, non-targets had significantly less coupling than lures ($p < .001$) and targets ($p < .001$), like what was noted above. In the first half of the time range, lures and targets were also significantly different from each other, with lures having more coupling that targets ($p < .001$). In the second half of the time segment, non-targets did not significantly differ from targets ($p = .02$) or lures ($p = .29$). In addition, targets and lures were not significantly different from each other ($p = .45$)

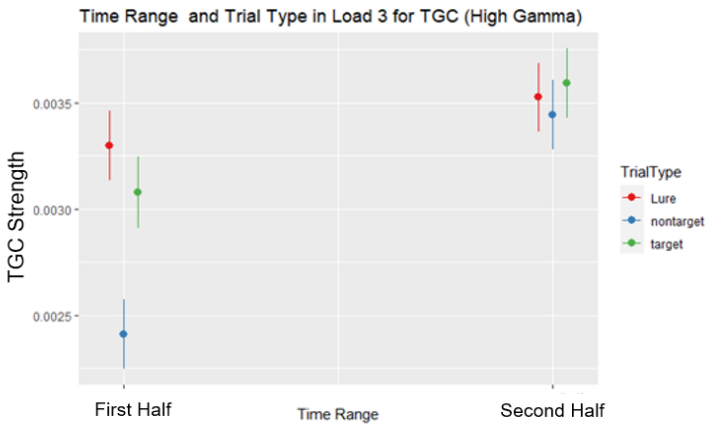

Figure 17. Trial Type x Time range interaction for TGC-high gamma for 3-back TGC.