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Working memory is critical to daily functioning and is a core deficit in numerous disorders. Dopaminergic genes and stress influence working memory, and environmental factors such as stress affect dopamine signaling. Despite this evidence, prior research has not examined the interaction of additive dopaminergic genetic variation and stress to predict working memory. The present study used an augmented dopaminergic additive multilocus genetic profile score (MLPS), and an objective stress-induction, the negative evaluative Trier Social Stress Test, to predict working memory on two complex span tasks (operation span and symmetry span) in *N*=88 healthy adults. Both tasks were completed twice, once in the context of a non-stressful interview (Session 1), and again in the context of either the negative evaluative Trier Social Stress Test or a non-stressful control protocol (Session 2). We predicted an interaction such that participants with lower MLPSs would benefit from stress whereas those with higher MLPSs would be impaired. Four of the planned variants exhibited sufficient genotyping quality for use in the MLPS. Our results did not support hypotheses and are discussed in relation to experimental design, the coding and conceptualization of the MLPS, and potential genotyping errors. However, we observed low agreement between complex span tasks, and exploratory analyses indicated an MLPS x Stress interaction on operation span performance. Our study aimed to extend a novel additive dopaminergic profile score to working memory capacity and examine the moderating effect of stress. Our results do not support the predicted role of this MLPS, stress, or their interaction.

INFLUENCE OF ADDITIVE DOPAMINERGIC GENETIC VARIATION AND ACUTE STRESS ON WORKING MEMORY

by

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CHAPTER I

INTRODUCTION

Working memory is a core component of higher-order cognition and is implicated in adaptive functioning and intellectual achievement (Alloway & Alloway, 2010; Engle, 2002). Heritability estimates suggest moderate to substantial contribution of additive genetic (and non-shared (unique) environmental factors (Ando et al., 2001; Vogler et al., 2014). Basic animal and human research supports that central dopamine facilitates working memory processes (for a review, see Seamans & Yang, 2004); thus, candidate gene investigations of working memory to-date have often studied individual dopaminergic genetic variants (e.g., Brehmer et al., 2009; Wiłkość et al., 2010). In addition environmental influences such as acute stress are thought to play a substantial role in working memory function, (Schoofs, Preuß, & Wolf, 2008; Yuen et al., 2009) and acute stress leads to an efflux of brain dopamine (Abercrombie, Keefe, DiFrischia, & Zigmond, 1989; Nagano-Saito et al., 2013). Taken together, this suggests a model in which some individuals' working memory performance will respond differently to stress than others', a moderating role for stress on dopaminergic genetic variants' influence on working memory performance. Despite this, limited research examines whether the influence of dopaminergic genetic factors on working memory varies as a function of stress. In examining such a question, a recently developed approach to candidate gene research, the multilocus genetic risk profile score (MLPS), permits investigation of the

collective effects of multiple variants, which better fulfill theoretical assumptions of behavioral genetic research than do single variants. Despite the characterization of a dopaminergic MLPS, no research has yet investigated its influence on working memory. The present study addresses these gaps by examining the role of a dopaminergic MLPS in interaction with lab-induced stress to predict working memory in healthy adults.

What is Working Memory?

Working memory reflects the ability to use attention to maintain and manipulate information in a flexible, accessible state (Engle, 2002). For example, working memory processes support tasks such as holding in mind a new telephone number in a distracting situation, or recalling steps for a recipe while searching for the ingredients. This significant aspect of higher-order cognition is a critical predictor of constructs such as academic attainment (Alloway & Alloway, 2010) and fluid intelligence (Engle, Tuholski, Laughlin, & Conway, 1999). Additionally, working memory deficits are prominent in numerous psychiatric disorders such as major depressive disorder (Landrø, Stiles, & Sletvold, 2001) and schizophrenia (Barch, Sheline, Csernansky, & Snyder, 2003) making it a potential target for clinical interventions.

Stress and Working Memory

Prior research has investigated the role of acute stress on working memory given the influence of stress on other aspects of cognition such as learning (Joëls, Pu, Wiegert, Oitzl, & Krugers, 2006) and memory (Roozendaal, McEwen, & Chattarji, 2009). Many studies of acute stress and working memory have utilized controlled, lab-based forms of stress such as the Trier Social Stress Test (TSST, involving giving a speech to an

audience) and the cold-pressor task, involving holding one's hand in ice water. Research on the relationship between acute stress and working memory is mixed. Several studies suggest that acute stress impairs working memory. For example, the acute stress induction, the TSST, predicting poorer n-back (Schoofs et al., 2008) and reading span (Luethi, Meier, & Sandi, 2009) task performance relative to a non-stressful control condition. Furthermore, a cold-pressor stress induction was associated with impairments in backwards digit-span and operation span working memory tasks relative to a non-stressful control condition (Schoofs, Wolf, & Smeets, 2009). Other studies suggest an enhancing, or at least mixed, influence of acute stress on working memory. In response to a forced-swim stress test, rats showed elevated working memory (Yuen et al., 2009). Moreover, in response to a cold-pressor task, human participants responded more quickly (though with increased mistakes) than participants in a non-stressful control condition to more cognitively demanding trials in a Sternberg item recognition task, a test of working memory (Duncko, Johnson, Merikangas, & Grillon, 2009).

Despite these apparently conflicting results, evidence that arousal level and working memory performance are related in a non-linear fashion (i.e., a Yerkes-Dodson relationship) may help reconcile these results. The Yerkes-Dodson curve of arousal suggests that arousal facilitates performance on challenging tasks, but beyond a certain point of arousal, performance will decline, as in the form of an inverted U-curve (Cools & D'Esposito, 2011; Yerkes & Dodson, 1908). The potential implication is that moderate stressors may boost working memory performance whereas more severe stressors degrade working memory performance. Similarly, even within a single objective severity

level of stress, less stress-sensitive individuals may experience enhancements in working memory whereas more stress-sensitive individuals experience decrements. For example, individuals with low trait anxiety performed worse than individuals with high trait anxiety under no stress, but under a stressor (i.e., video game competition), the opposite pattern emerged: Individuals with high trait anxiety (suggesting greater stress-sensitivity) experienced reduced working memory capacity on a reading span task (Sorg & Whitney, 1992). Thus, in the present study, we considered both individual and contextual (stress-related) differences in working memory.

Role of Dopamine in Working Memory

Role of prefrontal dopamine.

Three main dopaminergic pathways innervate the brain (for a review, see Malenka, Nestler, & Hyman, 2009). The nigrostriatal dopamine pathway begins in the substantia nigra and projects to the basal ganglia. The mesolimbic dopamine pathways begins in the ventral tegmental area and projects to the striatum. The mesocortical dopamine pathways begins in the ventral tegmental area and projects primarily to the medial prefrontal cortex (PFC; Bannon, Michelhaugh, Wang, & Sacchetti, 2001). Of these three, the mesocortical pathway has been well-studied in relation to working memory. In this pathway, prefrontal dopamine assists in the manipulation of information over temporal gaps (Fuster, 1973) whereas lesions to the PFC are associated with deficits in working memory (Winocur, 1992). Furthermore, prefrontal dopamine is necessary for adequate working memory function. In rhesus monkeys, regional depletion of PFC dopamine, but not other neurotransmitters, resulted in severe impairment in working

memory, whereas dopamine agonists reversed this impairment (Brozoski, Brown, Rosvold, & Goldman, 1979).

Critically, however, evidence indicates that the effect of prefrontal dopamine on working memory follows a curvilinear rather than a linear relationship, in which moderate levels are optimal and both the lowest and highest levels are suboptimal, in the form of an inverted U-curve. For instance, pharmacological studies using selective dopamine agonists and antagonists have shown that the effects of these drugs can vary widely depending on basal dopamine levels. Young monkeys with normal basal dopamine levels and aged monkeys, used as a model of naturally-occurring dopamine depletion, demonstrated a differential effect in response to manipulation of Dopamine Receptor-1 (D1), a receptor involved in augmenting dopamine activity in the PFC (Williams & Goldman-Rakic, 1995). The D1 receptor antagonist impaired working memory in young but not older (dopamine depleted) monkeys, whereas a D1 receptor partial agonist improved performance in aged (dopamine depleted) monkeys but not young monkeys (Arnsten, Cai, Murphy, & Goldman-Rakic, 1994).

Genetic evidence similarly highlights the role of individual differences in predicting working memory. The Catechol-o-Methyltransferase gene (*COMT*) encodes an enzymatic protein product that degrades dopamine; its effects are particularly salient in the PFC given the relative lack of dopamine transporter, another source of dopamine removal, in this brain region (Morón, Brockington, Wise, Rocha, & Hope, 2002; Sesack, Hawrylak, Matus, Guido, & Levey, 1998). In one functional single nucleotide substitution in the *COMT* gene with Met and Val alleles variants, relative to individuals

with the Met allele, Val allele homozygotes have greater expression of *COMT* and thus, lower basal levels of dopamine. As expected, among adults, carriers of the Met allele (i.e., those who would have higher basal dopamine levels) have been shown to perform better in working memory tasks (Meyer-Lindenberg et al., 2005). However, poorer performance by Val allele homozygotes is improved by a dopamine agonist known to boost dopamine levels, dextroamphetamine, whereas this drug paradoxically impairs working memory for Met allele carriers, who may thus have "optimal" basal levels (Mattay et al., 2003). Taken together, these studies suggest that dopamine modulates working memory: Either insufficient or excessive dopamine disrupts working memory performance, whereas a moderate amount of dopamine appears to correspond to optimal working memory functioning. In the present study, we sought to examine this inverted U-curve relationship of dopamine to working memory through a continuous measure of dopaminergic genetic markers. Additionally, we considered both prefrontal and striatal dopaminergic influences on working memory.

Role of striatal dopamine.

Although *prefrontal* dopamine has received ample study in relation to working memory, striatal dopamine in the basal ganglia may play a distinct role in working memory. Specifically, one theory suggests that dopamine in the basal ganglia plays a role in cognitive flexibility through a "gating" role in updating working memory: Phasic dopamine release in response to novel or rewarding stimuli may allow new information to update working memory through frontostriatal pathways (for review see Frank, Loughry, & O'Reilly, 2001). In support of this theory, greater fMRI-measured

frontostriatal activity (specifically in the dorsolateral and ventrolateral prefrontal cortices and bilateral striatum) was found during a working memory task, with unique activation in the caudate nuclei (located in the dorsal striatum) in trials requiring updating and manipulation, versus only retrieval (Lewis, Dove, Robbins, Barker, & Owen, 2004). Furthermore, in healthy humans, greater striatal dopamine synthesis, as measured by Positron Emission Tomography (PET), an imaging technique that use a radioactive tracer to measure neurotransmitter release and receptor binding (Patel, Lee, Alexoff, Dewey, & Schiffer, 2008), was correlated with enhanced working memory capacity (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008) and was predictive of PFC activity during a working memory task (Landau, Lal, O'Neil, Baker, & Jagust, 2009). Further, studies of individual genetic markers of striatal dopamine signaling have suggested that striatal dopamine influences working memory (Rodriguez-Jimenez et al., 2007; Stelzel, Basten, Montag, Reuter, & Fiebach, 2009). Thus, prefrontal and striatal dopamine appear to work synergistically and affect working memory similarly.

Similar to prefrontal dopamine, striatal dopamine follows a Yerkes-Dodson inverted-U relationship with working memory: Relative to moderate striatal dopamine signaling, insufficient or excessive striatal dopamine is detrimental to working memory. For example, administration of bromocriptine, an agonist of the D_2 receptor (primarily expressed in the striatum), to healthy individuals improved both working memory performance and frontostriatal connectivity (measured using fMRI) in participants with low baseline working memory; by contrast, this impaired both working memory and

frontostriatal connectivity in participants with high baseline working memory (Cools, Sheridan, Jacobs, & D'Esposito, 2007).

Taken together, these studies suggest that working memory may be dependent on frontostriatal connectivity, that is, a joint relationship between the PFC and the striatum. This suggests that genetic polymorphisms with predominantly striatal influence ought to influence working memory despite the prior conception of primarily prefrontal mediation of working memory.

Dopamine and Stress

As demonstrated by animal research, acute stress leads to an efflux of brain dopamine in the striatum, nucleus accumbens, and the PFC (Abercrombie et al., 1989; Imperato, Puglisi-Allegra, Casolini, & Angelucci, 1991). Evidence from both rodent and human studies points to stress induced dopamine efflux and suggests this relationship may be independent of the action of stress-responsive hormones, the corticosteroids. Restraint stress in rats, but not corticosterone agonists, leads to an increase in dopamine in the PFC (Imperato et al., 1991). Furthermore, in healthy human participants, the Montréal Imaging Stress Task—a psychosocial stress induction modified for neuroimaging contexts—induced PFC dopamine release measured by Positron Emission Tomography. This pattern of dopamine efflux was not significantly predicted by cortisol reactivity (Lataster et al., 2011; Nagano-Saito et al., 2013) suggesting a similar pattern of dopamine release in response to acute stress in rodents and humans (barring Type II error).

Given the roles of dopamine and stress in predicting working memory, examining potential interactions between acute stress and dopamine is critical to understanding working memory. Such research is likely to improve our understanding of working memory functioning and inform future interventions leveraging environmental contexts tailored on genetic markers to optimize working memory performance in both clinical and healthy populations.

Furthermore, prior research does not provide definitive guidance regarding whether stress influences working memory change within person (i.e., idiographic measurement; Brehmer et al., 2009), differences between groups (i.e., nomothetic measurement; Zilles et al., 2012) or perhaps both. Thus we consider both idiographic and nomothetic measurement in the present study.

Genetics and Working Memory

Twin studies and Genome Wide Association Studies (GWAS) have estimated the heritability of working memory between 43 to 49% (Ando et al., 2001) and found a substantial role of unique environmental factors (51 to 57 %; Ando et al., 2001). These estimates suggest substantial heritability of working memory and emphasize the potential utility of studying genetic contributions to working memory. However, as with most psychological phenomena, working memory is not entirely heritable, implicating unique environmental factors such as stress.

Despite this evidence that both genetics and environmental factors influence working memory performance, researchers have extensively examined dopaminergic genetic variants in relation to working memory, largely under *basal,* rather than *stressful*

conditions. Functional polymorphisms (common genetic variants that affect protein production or functionality) with physiological effects in the PFC (e.g., for dopamine reuptake or receptor binding) have received the most attention. Functional polymorphisms are common genetic variants that affect protein production or functionality. Here, we review literature on seven individual dopaminergic polymorphisms known to affect dopamine functioning including variants on the Dopamine Transporter (*DAT1*) gene, Dopamine Receptor 2 (*DRD2*) gene, Dopamine Receptor 4 (*DRD4*) gene, and the *COMT* gene (Brehmer et al., 2009; Wiłkość et al., 2010; Xu et al., 2007).

DAT1.

The dopamine transporter (*DAT1*) controls the reuptake of extracellular dopamine at or near the synapse. A 40-base pair (bp) variable number tandem repeat (VNTR) genetic variant most commonly occurs in the 9- and 10-repeat alleles. The 10-repeat allele is associated with higher levels of *DAT1* gene expression, resulting in greater dopamine reuptake and less dopamine availability (Heinz et al., 2000). Consistent with the importance of dopamine in working memory function, in a clinical population, 9-repeat carriers showed greater visuospatial working memory performance (Zilles et al., 2012). However, another study found no difference in baseline working memory performance between genotypes but greater training-related gains in visuospatial working memory in 9-repeat versus 10-repeat homozygotes (Brehmer et al., 2009). Last, a sample of 291 healthy adults showed no effect of DAT1 genotype on working memory

performance in an n-back task (Blanchard, Chamberlain, Roiser, Robbins, & Müller, 2011).

DRD2.

DRD2 is primarily expressed in the striatum (Camps, Cortes, Gueye, Probst, & Palacios, 1989) and plays a role in working memory function. Three polymorphisms on the *DRD2* gene are associated with working memory: *DRD2* C957T (rs6277), a *DRD2* 141C insertion/deletion polymorphism ("Ins/Del") in the promoter region (rs1799732), and the *ANKK1* Taq1A polymorphism (rs1800497). T-allele carriers for *DRD2* C957T have increased striatal binding (T/T > T/C > C/C; Hirvonen et al., 2004). Further, in mice (Kellendonk et al., 2006), and humans (Rodriguez-Jimenez et al., 2007; Xu et al., 2007), C allele homozygotes perform poorly relative to T allele carriers in working memory and other executive function tasks. Relative to insertion homozygotes, deletion carriers (deletion/deletion or insertion/deletion) in the *DRD2* 141C polymorphism show reduced transcription and lower expression of inhibitory D_2 receptors (Arinami, Gao, Hamaguchi, & Toru, 1997) and greater striatal reactivity (Forbes et al., 2009). Though not yet directly linked to working memory, insertion homozygotes of the 141C Ins/Del on the *DRD2* gene is linked to schizophrenia (Cordeiro, Siqueira-Roberto, Zung, & Vallada, 2009), which is associated with deficits in executive function (Goldman-Rakic, 1994). Another genetic variant influencing *DRD2*, the Taq1A polymorphism in the *ANKK1* gene nearby DRD2, is thought to affect executive function. A1 allele carriers have a 30-40% reduction in D_2 receptor density in carriers (Ritchie & Noble, 2003) as well as lower cognitive flexibility (Fagundo et al., 2014). Furthermore, evidence suggests utility in considering a

heterozygote genotype (i.e., A1/A2) intermediate to homozygote genotypes (i.e., A1/A1 and A2/A2; Choi & Shin, 2015). Furthermore, in interaction with the *COMT* Val^{158}Met polymorphism, the A2 allele predicted elevated working memory functioning (Stelzel et al., 2009), underscoring the importance of considering both prefrontal (COMT) and striatal (*ANKK1)* dopamine in working memory.

DRD4.

DRD4 receptors are abundant in the PFC (Oak, Oldenhof, & Van Tol, 2000) and likely play an inhibitory role on neuronal firing (Rubinstein et al., 1997). The 7-repeat allele of a 48-bp variable number tandem repeat (VNTR, a type of polymorphism in which individuals differ in the number of times a particular series of bases repeats itself in the DNA sequence, rather than differing in a single nucleotide base) on the *DRD4* gene is associated with reduced postsynaptic inhibition and greater dopamine signaling (Wang et al., 2004). Despite the 7-repeat allele's association with greater dopamine signaling, some studies implicate the 7-repeat allele with poorer working memory (Froehlich et al., 2007) and inefficient prefrontal activity (Herrmann et al., 2007). Further, The T allele of an additional *DRD4* polymorphism, C521T (rs1800955), is associated with less dopaminergic signaling (Okuyama et al., 2000).

COMT.

The Val/Val genotype of the Val^{158}Met polymorphism on the *COMT* gene (rs4680) is associated with quicker catabolism of dopamine whereas the Met allele results in less catabolism and more synaptic dopamine. Copies of the Met variant additively increase level of dopamine availability (Met/Met > Val/Met > Val/Val; Chen et al.,

2004). For example, the Met allele has been associated with enhanced performance on a letter-number sequencing task (Bruder et al., 2005) and on an n-back task (Goldberg et al., 2003) though this is not always the case (Buckert, Kudielka, Reuter, & Fiebach, 2012).

Divergent Findings in Individual Genetic Variant Studies

The individual variant literature clearly implicates dopaminergic genetic variation in working memory, though the direction of its effect appears mixed. Two primary explanations exist for divergent and null findings. First, theory and evidence from behavioral genetics (i.e., twin studies) supports that psychological phenomena tend to be influenced by numerous genetic variants of small effect sizes acting additively, rather than by any one, individual polymorphism (Fisher, 1919; Plomin, Haworth, & Davis, 2009). This suggests utility in using additive and polygenic (i.e., multiple variant) genetic variables over analyses of single polymorphisms. Second, as demonstrated by heritability estimates of working memory (Ando et al., 2001; Vogler et al., 2014), and evidence of environmental influences on cognition (Joëls et al., 2006; Roozendaal et al., 2009; Schoofs et al., 2008), we expect a moderating role of environmental processes. Consistent with this hypothesis, the effect of the *COMT* Met allele, traditionally considered advantageous to cognition, on working memory, varies as a function of acute stress (Buckert et al., 2012). These inverted-U relationships have been demonstrated in both the *COMT* Val^{158}Met polymorphism and D1 receptors with working memory (Cai & Arnsten, 1997). However, prior research has not considered the interaction between acute stress and an additive dopaminergic genetic variation on working memory.

Dopaminergic Multilocus Profile Scores

To address drawbacks of examining individual polymorphisms, a multilocus genetic profile score (MLPS) approach permits leveraging the additive effect of multiple functional polymorphisms. In several cases, these polymorphisms have been chosen a priori and coded in the direction of a putative outcome based on either biological or behavioral evidence (Nikolova, Ferrell, Manuck, & Hariri, 2011; Pearson-Fuhrhop et al., 2014; Vrshek-Schallhorn et al., 2015). This technique allows inclusion of individual polymorphisms that, on their own, may not account for large portions of variance, but additively (based on a priori coding) with other variants, explain significant portions of variance and more closely approximate polygenic assumptions of genetic research on complex human behavior than do individual variants. A further advantage of the MLPS approach is that it provides a dimensional genetic variable, which ought to improve power over dichotomized single-polymorphism variables (Cohen, 1983).

Given the relationship between dopamine and reward (Wise & Rompré, 1989), prior research has focused on using the dopaminergic MLPS to predict reward sensitivity. A dopaminergic MLPS composed of 5 genetic variants reviewed above, coded in the putative direction of greater dopamine functioning, predicted 10.9% of variance in ventral striatal BOLD fMRI activation to a monetary reward task (Nikolova et al., 2011). Similarly, a dopaminergic MLPS—composed of the same 5-polymorphism coded similarly—predicted fMRI activation in the dorsal striatum and insula to monetary reward (Stice, Yokum, Burger, Epstein, & Smolen, 2012). In addition to task-related reactivity in reward-related brain regions, the MLPS approach has been used to predict

reward-related pathology and personality traits. A six-polymorphism MLPS predicted food addiction and food addiction-related behaviors (Davis et al., 2013) and addiction-prone personality traits (Davis & Loxton, 2013). A seven-polymorphism dopaminergic MLPS (an augmented extension of Nikolova et al's MLPS) predicted sensation-seeking and indirectly predicted physiological reactivity to sad mood—a risk indicator for depression (R^2=3.8-5.9%; Sapuram, Vrshek-Schallhorn, Hilt, & Stroud, under revision).

A dopaminergic MLPS has also been employed to predict psychopathology in clinical samples. A five-polymorphism dopaminergic MLPS predicted depressive symptoms in healthy adults and a three-variant MLPS predicted clinical diagnoses of depression (Pearson-Fuhrhop et al., 2014). Last, a four-variant dopaminergic MLPS reflecting higher subcortical dopamine activity predicted lower negative schizophrenia symptoms (Eisenstein et al., 2017; see Table 2 for detailed overview of MLPS studies).

Despite providing insight into reward-related functioning and aspects of psychopathology, to our knowledge, no research has studied the role of the dopaminergic MLPS in working memory or the moderating effect of stress on the relationship between the dopaminergic MLPS and working memory. These relationships are crucial given the importance of dopamine and stress to working memory functioning and the influence of stress on dopamine release.

The Present Study

The goal of this study was to explore the relationship between acute stress and a dopaminergic MLPS on working memory in adults. In brief, healthy adults provided DNA samples and completed computerized working memory measures at two visits one

day apart: a putatively non-stressful interview visit on Session 1, and on Session 2 either a stressful negative evaluative TSST or a putatively non-stressful control protocol. First, examining idiographic change in working memory across two working memory measurements (Session 2 minus Session 1) we predicted a significant dopaminergic MLPS x Stress condition interaction, such that the effect of the dopaminergic MLPS on within-person change in working memory would differ by Session 2 Stress condition (Hypothesis 1; see Figure 1). Specifically, in the control condition, we did not anticipate a significant effect of the dopaminergic MLPS on change in working memory (i.e., 0 slope). By contrast, in the TSST (Stress) condition, we predicted that the dopaminergic MLPS would be negatively associated with change in working memory (i.e., a negative slope): Individuals with lower MLPS scores should improve their performance from the interview to the TSST condition, and participants with higher MLPS scores should decline in performance from the interview to the TSST condition. Second, examining between-group differences in working memory performance as a function of MLPS when isolating Session 2 to examine nomothetic processes, we predicted that (Hypothesis 2; see Figure 2) under control conditions, the MLPS would be positively associated with working memory, whereas in the TSST condition, the MLPS would be negatively associated with working memory.

CHAPTER II

METHOD

Participants

The present study examined healthy young adults aged 18 to 30 (N = 102) within a larger study on genetics, lab-based stress, and stress responding. Participants identified as Black (n=44, 43.1%), White (non-Hispanic; n=39, 38.2%), Hispanic/Latino (n=6, 5.9%), Biracial (n=3, 2.9%), Other (n=3, 2.9%), and Asian/Pacific Islander (n=1, 1%). Participants were recruited through the University of North Carolina at Greensboro undergraduate student population. After undergoing a mass screening, participants currently using hormonal contraceptives, nicotine, corticosteroids, psychoactive medications, stimulant medications, or experiencing a chronic health condition (all contraindications for cortisol testing) were excluded from participation. Furthermore, on arrival to Session 1, due to other aims examining cardiovascular responses to lab-based stress, participants with either a systolic blood pressure above 160 and/or a diastolic blood pressure above 100 (i.e., the diagnostic threshold for hypertension) were excluded. Eight participants with a current depressive episode as determined by a clinical interview at Session 1 did not complete the negative evaluative TSST given that current depression predicts blunted cortisol reactivity in a meta-analysis (Burke, Davis, Otte, & Mohr, 2005). These individuals were diverted to the control condition and excluded from the primary analyses. Additionally, exclusion criteria relevant to cognitive tests included self-

reported head trauma history, uncorrected hearing/visual deficits, learning disabilities, and colorblindness. We excluded participant data from three participants who received a processing score below 67% on the cognitive tasks. The final number of participants following these exclusions was N=88 (stress condition: N=49, control condition: N=39). Participants received course credit or $30 for study completion, and all participants received $5 as an incentive for an additional cognitive task not described here.

Materials

Working memory tasks.

We measured working memory through two short-form versions of complex span tasks: operation span and symmetry span tasks (Oswald, McAbee, Redick, & Hambrick, 2015). Complex span tasks are thought to better capture individual differences in working memory through both processing and recall components, differentiating working memory from short-term memory (Engle et al., 1999). These complex span tasks have had good reliability (α = .71, .69; Oswald et al., 2015), and using two such tasks as opposed to one task has been shown to capture greater working memory related variance (Foster et al., 2015; Oswald et al., 2015).

Instructions for complex span tasks were modified for the present study. Standard instructions warn participants their data will be unusable if participants do not maintain at least 85% accuracy in processing trials and are given warning messages if their accuracy dips below this threshold. Given hypotheses regarding negative evaluative stress, task instructions were modified to prevent complex span tasks from conveying marked negative evaluation (known to induce elevated cortisol secretion associated with stress;

Dickerson & Kemeny, 2004) while still encouraging best performance (per typical neuropsychological testing protocols). Participants were instructed to improve their processing score if it fell below 85% without the threat of the experiment ending but received accuracy feedback after each of the sets (symmetry span: 6 sets, operation span: 6 sets).

Operation span.

In each trial, participants viewed arithmetic equations and judged whether each equation was correct ("processing" phase). After each equation, participants viewed a letter to be recalled later ("storage" phase). At the end of each set of trials, participants recalled the letters they viewed in order. Set sizes ranged from 4 to 6 trials, with two administrations for each set size with a total of 30 processing-storage pairs. To establish a time limit unique to each participant, participants first completed processing practice trials. Trials in the actual experiment were time-limited to 2.5 standard deviations above the mean time for processing-only responses during the practice trials (Oswald et al., 2015).

Symmetry span.

Participants viewed an 8x8 matrix of black and white squares and made judgments as to whether the matrix was symmetrical down the vertical axis ("processing" step). Following the processing step, participants saw a red square positioned in a 4x4 matrix to be recalled at the end of the set ("storage" step). Set sizes were randomized and ranged from 3 to 5 trials with two administrations for each set size for a total of 24 processing-storage pairs. To establish a time limit unique to each participant, participants

first completed processing practice trials. Trials in the actual experiment were time-limited to 2.5 standard deviations above the mean time for processing-only responses during the practice trials (Oswald et al., 2015).

Working memory composite.

Working memory was indexed by "partial-credit score", that is, the number of letters (operation span) or red squares (symmetry span) correctly recalled in each set (Oswald et al., 2015). These partial-credit scores were standardized (i.e. z-scored) for each complex span task and then averaged together to create one working memory composite. If data from only one of the working memory tasks was missing (e.g., due to experimenter error), data from the other task was used to create the composite score (N=2).

Salivary DNA.

In the first session of the study, participants provided saliva samples into sterile, cryogenic, DNAse and RNAse-free vials. Saliva provides identical genotypic information as compared to other tissues such as blood. After collection, saliva samples was stored in a freezer at -80°C. After data collection was completed, genotyping for 7 dopaminergic variants was conducted according to standard practices including polymerase chain reaction and fluorescent detection. For quality control, allele frequencies will be tested for deviations from expected genotype frequencies (i.e. Hardy Weinberg Equilibrium).

Manipulation checks.

Salivary cortisol.

In the present study, salivary cortisol was used as a manipulation check of the TSST. Participants provided saliva samples via passive drool into sterile cryogenic vials 5 times during the second session, 4 of which were planned for use in assessing cortisol reactivity. (One sample was collected five minutes after the baseline sample for the assessment of salivary alpha amylase, which changes more rapidly than does cortisol.) After collection, saliva samples were stored in a freezer at -80°C. After data collection was completed, samples were shipped to Trier, Germany, for duplicate assay by time-resolved fluorescent-detection immunoassay (DELFIA; Dressendorfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992).

Self-report.

Both after Session 1 and after completing the TSST or control protocol during Session 2, participants were asked how challenging or difficult the experience was, to what extent they felt evaluated, and whether the evaluation was positive or negative.

Multilocus profile score.

Augmenting the five-polymorphism MLPS used by Nikolova et al. (2011), we planned to use a seven-polymorphism dopamine MLPS to examine the influence of dopaminergic genetic variation. Across all polymorphisms, each genotype was coded by its putative level of dopamine functioning; we coded "high" dopamine genotypes with a score of 1 and "low" dopamine genotypes with a score of 0. If biological evidence existed for unique heterozygote dopamine transmission phenotype relative to and in between

homozygotes, “intermediate” genotypes were scored as 0.5 (Nikolova et al., 2011). For each participant, scores across all seven polymorphisms were summed to calculate the MLPS. Participants were included if missing up to 1 genotyping call. When an individual was missing a genotype, the MLPS was prorated by calculating the individual’s sum of available risk scores, divided by their maximum possible total score without the missing polymorphism (i.e., 6) to achieve a proportion score, and returned to the scale of the MLPS via multiplication by 7. Due to genotyping errors, six of seven planned polymorphisms were used to calculate the dopamine MLPS. For a full list of polymorphisms and their coding, see Table 1.

Procedure

Participants were quasi-randomly assigned to either the control or TSST condition. That is, participants were blind to their scheduled condition, and the study coordinator did not know the identity of the participants when scheduling. Participants completed two sessions 1 day apart at the same time of the day. All sessions were completed between 1 and 5:30 P.M. to reduce the influence of diurnal variation in cortisol (Dickerson & Kemeny, 2004).

During Session 1 Participants first provided salivary DNA, then as part of a larger study, participants completed an interview about recent life experiences (not utilized in the present analyses) and the depressive episode sections of the Structured Clinical Interview for DSM-IV Disorders, Non-Patient Edition (SCID-I/NP; First, Spitzer, Gibbon, & Williams, 2002). If the interviewer preliminarily diagnosed a current major depressive episode, the participant was placed in the control condition (for Session 2).

These participants were excluded from primary analyses to ensure this decision did not impact results due to violation of pseudo-randomization and given the effects of depression on suppressed cortisol reactivity (Burke et al., 2005). Following the interviews, participants then completed the operation span task followed by the symmetry span task. Finally, participants completed questionnaires rating the degree to which they felt evaluated or challenged.

During Session 2, participants underwent a negative-evaluative Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993; Way & Taylor, 2010) or a non-evaluative control procedure. During the TSST or control, participants provided salivary cortisol collected at 4 time points (baseline: 0, before the TSST: +25 minutes, After the TSST: +40, After debriefing and brief rest: +65), and repeated measures of blood pressure, pulse, and self-reported affect (not examined in the present study). Immediately after the TSST or control protocol, participants self-reported perceived evaluation and challenge/difficulty. Immediately following these manipulation checks, participants again completed the operation span task followed by the symmetry span task.

Trier social stress test (TSST).

Both experimental conditions share several common elements and rely on commonly used protocols (Kirschbaum et al., 1993; Way & Taylor, 2010). In both conditions, participants were told they will be video-recorded and instructed to face the camera. They also had 5 minutes to prepare for a 5-minute speech. Following this, they completed an arithmetic task counting backwards from 2,017 by 13's. If they make a mistake, they were instructed to start back from 2,017 again. In addition, the conditions

had several differences. The negative evaluative TSST represents a modification designed to be overtly negative (Way & Taylor, 2010) compared to the more neutral original TSST (Kirschbaum et al., 1993). In the TSST condition, participants were told that they will be evaluated by two judges (1 male, 1 female confederates). Throughout the speech and arithmetic tasks, confederate judges reminded participants to face the camera and follow a behavioral script during the speech task (see Appendix A) and provided stern feedback during the arithmetic task. Additionally, the speech topic differed by condition: in the TSST, participants spoke about why their peers should select them for a student leadership position whereas in the control condition, participants spoke about tips for living a healthy lifestyle. In the control condition, no confederates were present, their speech topic was less evaluative, and they received neutral, polite feedback from the experimenter, who pretended to prepare for future sessions in the same small room but out of the participants' line of sight during the tasks. In prior work, these experimental conditions produced the expected differences in cortisol reactivity and in perceived global, negative, and positive evaluation (Avery & Vrshek-Schallhorn, 2015).

Analytic Plan

Preliminary genetic analyses.

First, Chi-squared tests examined whether each genetic polymorphism with two alleles was in Hardy-Weinberg Equilibrium. Variants with greater than two alleles (*DRD4* VNTR and *DAT1* VNTR) were not subject to analyses. Significant results indicate deviation from Hardy-Weinberg Equilibrium and may indicate potential for errors in genotyping. Second, Chi-squared tests for dichotomously scored variants

bivariate correlations for continuously scores variants were run to examine whether polymorphisms were associated. We made no a priori hypotheses regarding tests.

Group equivalence and manipulation checks.

To ensure that participant characteristics (i.e., gender, minority status (coded white and non-Hispanic = 0, other = 1) , and MLPS) were randomly distributed across groups, Chi-squared tests were run for dichotomous variables (i.e., gender and minority status), and a one-way ANOVA was run for MLPS, testing whether each participant characteristic differed between the Control and Stress conditions. As a manipulation check of the TSST, a one-way ANOVA examined differences in cortisol reactivity and self-reported perceived evaluation between groups for Session 2. To index cortisol reactivity, we calculated cortisol area under the curve with respect to increase (AUC_I; Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) across 4 time points. Positive AUC_I values indicate greater reactivity from baseline cortisol. Negative AUC_I values indicate an overall negative slope from baseline cortisol which is consistent with the normal diurnal rhythm of cortisol, which declines from waking to bedtime (Adam & Kumari, 2009; Pruessner et al., 1997). We predicted greater cortisol reactivity in the Stress condition.

Practice effects.

To test for the potential of participants improving Session 2 working memory score through familiarity and practice with the complex span tasks, we planned to run a one-sample *t*-test examining whether in the Control condition, working memory change

score significantly deviated from 0. Here, significant deviation from 0 would indicate potential of practice effects.

Primary analyses.

As prior research does not sufficiently inform whether idiographic (i.e., capturing change within person across multiple assessments; Brehmer et al., 2009) or nomothetic (i.e., relative level between individuals; Zilles et al., 2012) approaches are optimal in assessing the role of genetic factors in working memory, we used both approaches and corrected statistically for two tests using False Discovery Rate correction (FDR; Benjamini & Hochberg, 1995) for significant results (i.e. $p<.05$). First, we examined the effect of dopamine and stress on a working memory change score (Hypothesis 1; idiographic) followed by examining the effect of dopamine and stress on working memory Session 2 score (Hypothesis 2; nomothetic). In all analyses, gender (coded females = 0, males = 1) was included as a covariate given differences in stress reactivity between males and females (Uhart, Chong, Oswald, Lin, & Wand, 2006).

To score working memory tasks, a partial-credit raw score was calculated from the sum of correctly recalled elements in each trial as opposed to using an absolute score (i.e., number of sets in which all elements were recalled correctly and in order). We chose this approach given the high correlation between the partial-credit scores and absolute scores ($r>.91$), greater variance provided by using a partial-credit score, and precedence (e.g., Oswald et al., 2015). For each participant, the two partial credit raw scores from each working memory task were standardized. We z-scored Session 1 partial credit raw scores and standardized Session 2 partial credit raw scores with respect to the mean and

standard deviation of Session 1 scores (henceforth called Session 2 score for simplicity) to account for potential differences in means and variability between Session 1 and Session 2. These scores were averaged together to form a working memory composite score per session. To counter practice effects, a working memory change score was calculated by subtracting the Session 1 from Session 2 working memory composite scores. To test Hypothesis 1, in a linear regression using M*plus* (Muthén & Muthén, 2010), this change score was regressed on dopaminergic MLPS, stress condition, and the interaction of dopamine MLPS and stress condition, covarying gender. To test Hypothesis 2, in a second linear regression, the Session 2 score was regressed on dopamine MLPS, stress condition, and the interaction of dopamine MLPS and stress condition, covarying gender.

Planned post-hocs.

We planned to follow all significant MLPS x Stress interactions with simple slopes and regions of significance analyses by examining the influence of the MLPS in each condition separately (Preacher, Curran, & Bauer, 2003).We also planned to follow significant effects of the dopamine MLPS x Stress with sensitivity analyses designed to examine the extent to which each polymorphism contributes to the observed polygenic effect (e.g., Vrshek-Schallhorn et al., 2015). First, an "N-1" analysis tested recalculated versions of the MLPS each with a single polymorphism removed in succession to examine whether any one polymorphism is driving the effect, which would be inconsistent with polygenic, additive theory. Second, regressing the working memory change score/Session 2 score on each individual polymorphism, stress, and the

interaction of that polymorphism with stress provided effect sizes estimating the contributions of individual polymorphism to the overall effect. Critically, polygenic, additive theory suggests that individual polymorphism interaction effects are sufficiently small and unlikely to be statistically significant; thus, we made no hypotheses regarding the significance of these post-hoc tests.

Primary analyses were re-run in the largest racial sub-group in both samples, to rule out the possibility of spurious findings arising from population stratification. Population stratification refers to non-random variation in allele frequencies within a racially/ethnically diverse sample; spurious results can arise due to enrichment of a variant (i.e., stratification) and coincidentally greater levels of the criterion in one subsample. Last, we planned to re-run analyses coding the MLPS with each variant including an intermediate score (i.e., 0.5) for each heterozygote variant given coding discrepancies for heterozygote genotypes in prior studies (Nikolova et al., 2011; Stice et al., 2012) and additive model assumptions that each allele should incrementally contribute to dopamine functioning (Fisher, 1919; Wright, 1921).

Power considerations.

Insufficient work in this area hampers formal power analyses given that there are no polygenic dopaminergic genetic tests in the context of stress. However, the closest related genetic studies provide insights. A five-polymorphism MLPS predicted dopamine-related fMRI outcomes (N = 69; Nikolova et al., 2011). Furthermore, an individual polymorphism (*COMT* Val ^{158}Met) predicted working memory under acute stress (N = 50; Buckert, Kudielka, Reuter, & Fiebach, 2012). Polygenic, additive theory

suggests that the dopaminergic MLPS should capture greater variance than using individual polymorphisms. Thus, the sample size of the present study was expected to be similar to or greater than that of related studies.

CHAPTER III

RESULTS

Preliminary Genetic Analyses

DRD4 C521T failed to amplify during genotyping. Thus, we excluded this variant from analyses. Two further polymorphisms deviated significantly from Hardy-Weinberg Equilibrium (HWE; *DRD2* C957T: χ^2=6.204, *p*=.013; *DRD2* 141C: χ^2=8.078, *p*=.005) indicating the potential for errors in genotyping. The remaining polymorphisms were in HWE ($\chi^2 \leq 0.269$, *p*s≥.600). Prior multilocus profile studies have handled limited deviations from HWE by including deviating variants in initial analyses and re-running results with these variants excluded (e.g., Vrshek-Schallhorn et al., 2015). The analytic plan was altered given these errors in genotyping. Rather than testing a seven-polymorphism MLPS, we instead conducted analyses using a six-polymorphism MLPS excluding only *DRD4* C521T, and separately with a four-polymorphism MLPS excluding *DRD4* C521T and both polymorphisms out of Hardy-Weinberg Equilibrium (*DRD2* C957T and *DRD2* 141C). FDR correction for two tests (six-variant and four-variant) was applied following these procedures. Both MLPSs appeared to be normally distributed (six-variant MLPS *M*=2.704, *SD*=1.099; four-variant MLPS *M*=1.704, *SD*=.935). Bivariate correlations and Chi-squared analyses tested whether polymorphisms were associated and revealed several significant relationships: *COMT* Val158Met and *DRD2*

141C were negatively associated (r=-.247, p=.021), *COMT* Val158Met and *DRD2* C957T were negatively associated (r=-.252, p=.018), *ANNK1* Taq1A and *DRD2* C957T were positively associated (r=.276, p=.009), and *DRD2* 141C and *DRD2* C957T were positively correlated (r=.483, p<.001). No other variant scores were significantly related *(*rs ≤ .209, ps ≥.051*).* Thus, although there were limited correlations of small effect sizes among several variants, the variants included in the MLPS were largely unrelated.

Group Equivalence and Manipulation Checks

A one-way ANOVA suggested no differences in six-variant MLPS ($F_{1,86}$=.000, p=.988) or in four-variant MLPS ($F_{1.87}$=2.447, p=.121) across Stress and Control conditions. Chi-squared tests of independence suggested no differences in gender ($X^2_{1, 88}$= 1.354, p=.245) but significant differences in minority status across conditions ($X^2_{1, 88}$= 3.913, p=.048) such that there were fewer White participants (n=11, 28.2%) than participants of an racial minority (n=28, 71.8%). To ensure that this failure of randomization would not drive results, in addition to planned follow-ups addressing potential population stratification (i.e., re-analyzing significant effects from the full sample in the largest racial/ethnic sub-group), we planned to test whether any significant results persisted controlling for minority status.

A one-way ANOVA supported an expected effect of Stress condition on the extent to which participants felt evaluated during the TSST (F(1,98) = 16.267, p<.001) with participants in the Stress condition (M=3.52, SD=.799) perceiving greater evaluation than participants in the Control condition (M=2.79, SD=.997). Further, cortisol reactivity (i.e., AUC_I) differed as expected between conditions (F(1,97) = 36.530, p<.001):

Participants in the Stress condition showed elevated cortisol AUC_I (*M*=130.608, *SD*=179.873) relative to participants in the Control condition (*M*=-52.700, *SD*=118.352) whose AUC_I values were on average negative, consistent with expected diurnal declines in cortisol level across the day.

Primary Analyses

Four separate multiple regression analyses were run to examine the effect of the Stress x MLPS (six versus four variant) on working memory (change score versus Session 2 score).

Working memory change score.

Full results appear in Table 3. First, in the model examining the regression of the six-variant MLPS, Stress, and their interaction on working memory change, there were no significant main effects of the MLPS, Stress, or the covariate gender (-.108 < *b*s < .036, .204 < *p*s <.963). The MLPS x Stress interaction term approached significance (*b*=.210, SE(*b*)=.116, *p*=.071; see Figure 3). In the four-variant MLPS version of this analysis, there were no significant main effects of the MLPS, Stress, or the covariate gender (-.042 < *b*s < .036, .743 < *p*s <.966). The MLPS x Stress interaction term did not reach significance (*b*=.142, SE(*b*)=.161, *p*=.376).

Session 2 score.

Full results appear in Table 3. In the model examining the regression of the six-variant MLPS, stress, and their interaction on Session 2 score, there were no significant main effects of the MLPS (*b*=-.107, SE(*b*)=.095, *p*=.261), Stress (*b*=.038, SE(*b*)=.146, *p*=.794), or their interaction (*b*=.130, SE(*b*)=.131, *p*=.319; see Figure 4). In the four-

variant MLPS version of this analysis, there were no significant main effects of the MLPS (b=.000, SE(b)=.137, p=.988), Stress (b=.019, SE(b)=.150, p=.897), or their interaction (b=.120, SE(b)=.173, p=.489). Gender emerged as a significant predictor of the Session 2 score with males performing better than females (Gender in six variant model: b=.504, SE(b)=.151, p=.001; Gender in four variant model: b=.512, SE(b)=.150, p=.001). This pattern did not emerge when examining the working memory change score. No re-analyses were conducted to address population stratification, given that the primary planned analyses did not support hypotheses.

Exploratory Analyses

Fully additive MLPS scoring.

Given polygenic, additive model assumptions that each allele will contribute incrementally (Fisher, 1919; Plomin et al., 2009) to affect dopaminergic functioning and given discrepancy in coding in prior dopamine MLPS literature (Nikolova et al., 2011; Stice et al., 2012), we ran an exploratory analysis re-coding the MLPS with heterozygote genotypes coded as intermediate dopamine phenotypes (i.e., 0.5) for each polymorphism. Results were once again consistent with no significant effects of Stress, MLPS, or their interaction, but a consistent effect of Gender on Session 2 score (Gender in six variant model: b=.521, SE(b)=.156, p=.001; Gender in four variant model: b=.502, SE(b)=.155, p=.002).

Task-specific analyses.

See Table 4 for correlations of working memory tasks across sessions. Given expectations that both complex span tasks would additively measure working memory

capacity, no hypotheses were made separately by task. To test whether both tasks were correlated as expected, two bivariate correlations were conducted between the Session 1 operation span and symmetry span partial-credit raw score and separately between Session 2 operation and symmetry span scores. The tasks showed a modest positive correlation in Session 1 (r=.209, p=.048) but were not significantly correlated in Session 2 (r=.075, p=.495). Given the unexpected non-significant correlation between the two tasks in Session 2, further exploratory analyses were conducted to examine potential task related differences by re-running the primary analyses for each complex span task separately.

Operation span.

Full results appear in Table 5. Primary analyses were re-run on operation span change score (two tests: six-variant MLPS and four-variant MLPS) and on Session 2 operation span score (two tests: six-variant MLPS and four-variant MLPS). Across all four tests, there were no significant main effects of MLPS or Stress ($-.228 < b < .007$, $.158 < p < .974$). Gender approached to significance in predicting operation span Session 2 score in the four-variant MLPS model only (b=.363, SE(b) = .220, p=.099) with males performing better than females.

A significant interaction term emerged between Stress and the six-variant MLPS to predict operation span change score (b=.384, SE(b)=.152, p=.012). A simple slopes analysis revealed that the effect of six-variant MLPS on operation span change score differed with respect to Stress condition. In the Control condition, participants with lower MLPSs showed a small but non-significant increase in score at Session 2 relative to

Session 1 whereas participants with higher MLPSs showed a small but non-significant decrease in score at Session 2 relative to Session 1 (b=-.157, SE(b)=.114, p=.172). In the Stress condition, participants showed an increase in Session 2 score relative to Session 1 score. Participants with lower MLPSs showed a slight but non-significant increase in Session 2 score relative to Session 1 score whereas participants with higher MLPSs showed a significant increase in Session 2 score relative to Session 1 score (b=.227, SE(b)=.109, p=.041). Further, a regions of significance analysis indicated that the effect of Stress was significant for participants with an MLPS above 3.93 (See Figures 5 and 6). A single FDR test across all four regression analyses indicated that initially significant results survived correction for multiple testing.

Sensitivity analyses.

Six N-1 sensitivity analyses were run to ensure the MLPS x Stress interaction detected for Operation Span remained significant with any one variant left out (i.e., the effect of the MLPS was not driven by any one variant) and to identify influential variants. These analyses, systematically removing one variant at a time, retained the overall pattern of significance (see Table 6).

Individual variant sensitivity analyses were run to explore the influence of each variant in interaction with Stress to predict operation span change score. Overall, the direction of the interaction for each analysis was consistent with the six-variant MLPS x Stress interaction with the exception of the *COMT* Val158Met x Stress (b=-.762, SE(b)=.527, p=.149; See Figure 7). Descriptively, the strongest effect was the interaction of *ANNK1* Taq1A x Stress (b=1.286, SE(b)=.511, p=0.012; see Table 7).

We then conducted population stratification analyses in Black participants, the largest racial sub-group in the sample (N=38). Results were similar to those of the full sample: The six-variant MLPS x Stress interaction term approached significance in predicting operation span change score (b=.585, SE(b)=.312, p=.070). Given failure in randomization of one participant characteristic (minority status), re-computing the analysis in the full sample and covarying minority status also revealed a similar effect of the six-variant MLPS x Stress interaction term (b=.385, SE(b)=.158, p=.017).

Symmetry span.

Full results appear in Table 8. Analyses were re-run on symmetry span change score (two tests: six-variant MLPS and four-variant MLPS) and on Session 2 symmetry span score (two tests: six-variant MLPS and four-variant MLPS). Across all four tests, no significant effects of the MLPS, Stress, or their interaction emerged (-.086 < b < .287, .138 < p < .879). Gender was a significant predictor of Session 2 symmetry span score in the model with the six-variant MLPS (b=.620, SE(b)=.200, p=.002) and in the model with the four-variant MLPS (b=.617, SE(b)=.200, p=.002). In both tests, males showed higher Session 2 symmetry span scores than females (see Figure 8 for scatterplots).

Practice effects.

To test for practice effects, we ran three, one-sample t-tests examining whether the working memory, operation span, and symmetry span change scores differed significantly from 0 in the Control condition. There was no significant change in working memory overall (t(35)=-.019, p=.985), no significant difference in operation span change

($t(38)=1.043$, $p=.303$), and no significant difference in symmetry span change ($t(38)=-.875$, $p=.387$). Results do not suggest practice effects occurred.

CHAPTER IV

DISCUSSION

The present study aimed to explore the roles of dopaminergic genetic variation and acute stress on working memory. Based on evidence that 1) dopamine has a curvilinear influence on working memory, with optimal performance at moderate levels, and comparatively worse performance at higher and lower levels and that 2) acute stress results in an efflux of dopamine, we hypothesized an interaction: Participants with lower dopamine MLPS's would benefit from acute stress whereas participants with higher dopamine MLPS's would be impaired. The primary results of planned analyses failed to support our hypotheses; we did not find an effect of dopaminergic MLPS interacting with stress to affect working memory change score or Session 2 working memory. Exploratory analyses following unanticipated evidence of weak associations between the two working memory tasks indicated that MLPS x Stress predicted operation span change such that in the stress condition, participants with higher MLPSs showed a greater increase in operation span score at Session 2 relative to Session 1 compared to those with lower MLPSs. Here we discuss potential explanations for this pattern of findings, limitations of the present study, and suggestions for future research.

No Effects of Acute Stress or MLPS on Working Memory Composite Scores

Simple main effects of acute stress and the MLPS were not hypothesized, due to a theoretical model in which stress would enhance some individuals' working memory performance but degrade that of others (an inverted-U conceptualization, Schoofs et al., 2009; Yuen et al., 2009). Thus, the effects of the MLPS would be influenced by stress. Consistent with this view, no simple main effects (i.e., with the interaction included in the model) of stress nor the MLPS were detected.

Gender Difference in Session 2 Working Memory Scores

Gender emerged as a significant predictor of Session 2 score (but not working memory change score) in both MLPS models, such that males showed a higher Session 2 score than females. A follow-up analysis revealed that these gender differences were present in Session 1 as well suggesting that these gender differences may be independent of stress. These results are somewhat consistent with a study demonstrating that that males remembered more items in three complex span tasks (including operation span and symmetry span). Notably in this study, males also made more processing errors, suggesting a different task strategy by males, and effect sizes for gender differences were small (Redick et al., 2012). Though we did not analyze gender differences in processing errors, it is possible that gender differences were driven by strategy differences (i.e., preference for item storage vs. accurate processing). Further, these working memory tasks involve visuo-spatial processing and math; performance in both these domains show gender differences. Males show higher mathematics ability (though this may be related factors such as stereotype threat; Hyde, Fennema, Ryan, Frost, & Hopp, 1990).

Similarly, males show relatively stronger visual-spatial ability (Bouchard Jr & McGee, 1977). Last, there were no differences between male and female performance in change score analyses suggesting that stress-related increases or decreases in working memory performance did not vary as a function of gender.

Stress and MLPS Interactions on Working Memory

Tests of the interaction between the dopaminergic MLPS and acute stress predicting composite working memory were not significant in the primary analyses. These results are inconsistent with prior work suggesting a moderating role of stress on the relationship between dopaminergic genetic variation and working memory (Buckert et al., 2012) and with research demonstrating the augmenting role of acute stress on dopamine (Abercrombie et al., 1989; Imperato et al., 1991). Here, potential methodological and substantive explanations for our null findings are explored.

Possible methodological explanations for null findings.

Two methodological explanations may contribute to lack of significant results in the primary planned analyses. First, two of the six genetic variants were out of Hardy-Weinberg Equilibrium which may indicate genotyping errors. One of these variants, *DRD2* 141C, was found to have the largest descriptive effect size of the five variants studied in relation to reward-related brain activity (Nikolova et al., 2011). Thus, inaccuracies in this potentially critical variant may have masked effects in the present study. Analyses run without the genetic variants out of Hardy-Weinberg Equilibrium revealed an equivalent null pattern. However, the removal of key genetic variants from this revised MLPS may have left too few variants to observe a significant, additive effect.

Despite genotyping concerns, the *COMT* Val158Met variant—reported to interact with stress in Buckert et al. (2012) even without other variants—was in Hardy-Weinberg Equilibrium in the present study, hinting that null effects were not exclusively driven by an insufficient number of variants. Second, a larger sample may have provided greater power to detect significant effects. However, theoretical assumptions of additivity suggest the MLPS technique should enhance power relative to studies employing single variants. Sample size was comparable to or larger than related investigations (e.g., Buckert et al., 2012).

Possible substantive explanations for null findings.

Differences between complex span tasks and other working memory measures.

Key differences in experimental design may have precluded detection of interaction effects between stress and dopamine MLPS. Prior studies have used various working memory tasks, and the tasks themselves may have had differential effects on stress reactivity. For example, in the present study, complex span task instructions were modified as to decrease the implication of negative evaluate threat, which emerged as a significant meta-analytic predictor of cortisol reactivity across an array of lab-based stress induction paradigms (Dickerson & Kemeny, 2004). Despite this, it is possible that pressure to maintain accuracy during processing trials served as a mild stress-induction in itself in both the control and stress groups. This notion is consistent with prior research demonstrating that cognitive tasks may elicit dopamine release dependent on their difficulty (Aalto, Brück, Laine, Någren, & Rinne, 2005). Consistent with this notion, Buckert et al. (2012) used an n-back task with varying levels of difficulty (1-, 2-, and 3-

back) and found an interaction of *COMT* Val158Met and stress on working memory in only the 2-back condition (moderate difficulty relative to the 1- and 3-back conditions), although a Type I error for the 2-back condition or Type II errors for the other conditions cannot be ruled out. Potentially, working memory tasks that are too easy or too challenging may not show any enhancing or diminishing effects of a stress manipulation given that performance may be more influenced by task difficulty. Thus, it is possible that task-elicited dopamine release masked the effect of the stress manipulation and was potentially more influential than dopaminergic genetic variation.

In addition to potential differences in task difficulty, our cognitive tasks differ from Buckert et al. (2012) conceptually. Buckert et al. (2012) examined working memory using an n-back task which prior research has found to be only weakly correlated with complex span tasks, and potentially more related to familiarity-based responding than controlling distraction from general proactive interference (Kane, Conway, Miura, & Colflesh, 2007; Redick & Lindsey, 2013). Thus, it is possible that dopamine and stress may interact to predict an aspect of executive control (i.e., control over habitual or familiar responding) but may have a weaker or no effect on working memory capacity.

Possibly greater regional specificity of individual variants than anticipated.

Our lack of finding of a MLPS x Stress interaction may also be the result of misconceiving the role of dopaminergic genetic variation. Though prior research suggests that genetic variation often works additively to influence traits (Fisher, 1919; Plomin et al., 2009) and that key findings suggest an additive role of striatal and prefrontal dopamine (Cools et al., 2008, 2007), others have suggested that striatal and prefrontal

dopamine work antagonistically; higher prefrontal dopamine inhibits striatal dopamine (Meyer-Lindenberg et al., 2002; Saunders, Kolachana, Bachevalier, & Weinberger, 1998). Further, even if both striatal and prefrontal dopamine work synergistically, their effects may not be purely additive. Thus, a subset of individual variants coding for prefrontal vs striatal dopamine may have shown predicted effects on working memory; the present study, however, minimized multiple testing by examining the MLPS rather than individual variants or subsets of variants. Furthermore, consistent with a role of prefrontal dopamine, a prior study showed an interaction between *COMT* Val158Met and acute stress predicting working memory (Buckert et al., 2012). It is possible that this genetic variant, which has greater influence on prefrontal dopamine relative to striatal dopamine (Morón et al., 2002; Sesack et al., 1998), detected an effect given its greater specificity to prefrontal dopamine. Additionally, as suggested earlier, the additive MLPS may have also ignored interactions between variants or masked effects of one variant by coding its effects similarly to other variants, although the theoretical assumptions inherent in polygenic additive models suggest that gene-gene epistatic (or emergenic) interactions are unlikely. In sum, the MLPS may be multidimensional in a regionally-dependent fashion, contrary to expectations. Exploratory analyses (discussed below) are consistent with this hypothesis.

Task-Specific Exploratory Analyses

Null results for the primary planned analyses were also possibly due to differences between working memory tasks. Though we did not have a priori hypotheses regarding different effects of stress and MLPS in each complex span task separately,

correlation analyses between the tasks across sessions revealed an unexpected pattern: In Session 1, the tasks were significantly correlated (r=.241), consistent with previously reported correlations between the short-form (r=.33; Oswald et al., 2015) and long-form (rs=.38-.48; Brewer & Unsworth, 2012; Unsworth, Brewer, & Spillers, 2009; Unsworth & Spillers, 2010) of these tasks. However, in Session 2, the tasks were not significantly correlated (r=.094).

The key difference between Session 1 and Session 2 was the acute stress induction and control protocol in Session 2. Though prior research has not examined a differential role of stress on symmetry span and operation span tasks, the effect of stress may have varied for two reasons. First, participants completed the operation span task *before* the symmetry span task. It may be that task novelty attenuated by the time the symmetry span task was administered, leading to reduced levels of stress induced by the tasks themselves; it is also possible that the effects of the TSST on working memory are particularly fleeting, leading to different impacts on the first and second working memory tasks, despite their brevity. Second, operation span tasks require participants to make judgements on numerous mathematical operations. Cognitive tasks involving arithmetic may be more sensitive to the effects of stress especially for those higher in math anxiety. Indeed, prior research has documented poorer performance on computation-based working memory tasks for those with higher math-related anxiety (Ashcraft & Kirk, 2001).

MLPS and acute stress interact to predict operation span change score.

We explored whether the primary planned analyses produced the expected results in each complex span task separately. No significant interaction effects of Stress and either the six- or four-variant MLPS on symmetry span change score or Session 2 score for symmetry span were found. However, a significant interaction of Stress and the six-variant MLPS on operation span change score emerged which survived FDR correction for multiple testing. In the Control condition, participants with lower MLPSs showed a small but non-significant improvement in score whereas participants with higher MLPSs showed a small but non-significant decrease in score. In the Stress condition, all participants showed improved operation span scores in Session 2: Participants with lower MLPSs showed a small but non-significant improvement whereas participants with higher MLPSs showed a significant improvement. This finding is contrary to our hypotheses (stress would enhance performance for those with low MLPSs and diminish performance for those with high MLPSs) and contrary to a key prior study examining a *COMT* variant (Buckert et al., 2012).

Sensitivity analyses and possible interpretations.

Exploratory sensitivity analyses were run to better understand factors that may have driven significant results. Analyses revealed that the effects of individual variants x Stress may have differed. Notably, *COMT* Val158Met x Stress was in the opposite direction relative to the other variants, though this interaction effect was not significant. The pattern for *COMT*, though non-significant, appears somewhat consistent with Buckert et al.'s findings: in the Control condition, participants with higher *COMT* scores

(i.e., more Met alleles) showed an increase in operation span score at Session 2 relative to Session 1 whereas participants with lower COMT scores showed a decrease in operation span score. Notably, *COMT* Val158Met is the only variant that shows a high degree of specificity to prefrontal dopamine modulation (Morón et al., 2002; Sesack et al., 1998) whereas several other variants are thought to primarily influence striatal dopamine (Camps et al., 1989). Thus, these results may be consistent with prior studies demonstrating a regulatory role of the PFC on striatal dopamine in which greater prefrontal dopamine activity is associated with reduced striatal activity (Jaskiw, Karoum, & Weinberger, 1990; Pycock, Kerwin, & Carter, 1980). Though both prefrontal and striatal dopamine contribute to working memory functioning (Seamans & Yang, 2004), these effects may not be purely additive as initially hypothesized.

The opposite relationship between prefrontal and striatal dopamine polymorphisms also suggests that individual variants may behave differently under stress. Though both the prefrontal cortex and striatum experience an efflux of dopamine in response to stress (Abercrombie et al., 1989; Imperato et al., 1991), it may be that individuals with higher PFC dopamine are negatively affected by stress whereas individuals with higher striatal dopamine show greater stress-related working memory gains due to greater motivation and engagement. Indeed, prior research has shown that greater ventral striatal reactivity is associated with greater positive affect (linked to motivation) in response to recent life stress relative to lower ventral striatal reactivity (Nikolova, Bogdan, Brigidi, & Hariri, 2012) and is associated with less anhedonia (i.e., loss of interest and motivation) in response to early life stress (Corral-Frías et al., 2015).

Thus, greater striatal dopamine (i.e., putatively higher MLPSs) may have been adaptive under acute stress allowing participants to preserve positive affect and motivation and show greater improvement in operation span performance.

An alternate explanation of unexpected results is that the Control condition of the TSST may have induced a sufficient amount of stress to see the expected effect of the *Stress* condition in the *Control* condition. Though participants in the Control condition did not experience a significant increase in cortisol, evidence suggests that dopamine efflux rather than cortisol mediates the relationship between stress and working memory (Lataster et al., 2011; Nagano-Saito et al., 2013). Thus, participants in the Control group may have experienced a relatively minor stressor decreasing performance for those with higher MLPSs but facilitating performance in those with lower MLPSs. Indeed, the only prior study examining an interaction of a dopaminergic genetic variant and stress lacked a TSST Control condition and thus, stress was unlikely to be induced for participants that did not undergo the TSST (Buckert et al., 2012). However, this explanation does not account for unexpected results in the Stress condition. Potentially, as noted earlier, an alternate mechanism such as heightened reward sensitivity bolstering working memory improvement under stress, may be at play in the Stress condition though this is purely speculation.

Population stratification analyses conducted in the largest racial sub-group (Black participants) revealed a consistent pattern. Given the diminished sample size in the population stratification analysis, we did not interpret *p*-values and instead, focused on the effect size and direction. The effect size and direction of the MLPS x Stress term

(*b*=.585) was consistent with the effect size of the MLPS x Stress term in the original analysis (*b*=.384). Further, re-running analyses in the full sample while covarying minority status did not alter results. Thus, despite unexpected group differences in minority status, our conclusions are ultimately the same.

Non-significant MLPS x stress effect on operation span session 2 score.

Notably, no significant interactions were demonstrated examining operation span Session 2 scores. Though stress improved operation span performance (especially for those with higher MLPSs), stress, nor its interaction with the MLPS, predicted Session 2 operation span score. Further, in Session 2, among participants in the Stress condition, there was no significant correlation between MLPS and Session 2 score (r=.201, *p*=.166). Thus, it may be that the effects of stress are particularly salient in *improving* operation span score among those with higher MLPSs, though their score itself was not significantly higher than those with lower MLPSs.

Limitations and Future Directions

Despite numerous strengths including the use of a novel MLPS, a robust stress manipulation, and well-validated working memory tasks, this study possesses several limitations. First, violations in Hardy-Weinberg Equilibrium may have been suggestive of errors in genotyping and necessitated using fewer variants than planned; it is unclear if lack of significant findings were driven solely by lack of a real effect versus potential inaccuracies in two variants included in the primary analyses of six variants. Alternatively, significant exploratory results may have similarly been driven by potential genotyping errors. Though we re-ran analyses excluding two variants out of equilibrium,

focusing on fewer variants may have precluded detection of the anticipated effect. Second, ambiguity in coding some of the genetic variants (e.g., *DRD4* VNTR; Nikolova et al., 2011; Stice et al., 2012) and the aggregation of both prefrontal and striatal variants present potential sources of inconsistency for the additive MLPS. Given discrepancies in the effects of individual variants in interaction with stress, further molecular biological research clarifying the roles and effects of each genetic variant and the roles of striatal and prefrontal dopamine in interaction with stress on working memory will strengthen dopaminergic MLPS research. Last, our study does not account for other factors that may affect working memory performance and stress reactivity (e.g., trait anxiety and task difficulty) that could be incorporated into future studies.

Conclusions

The present study aimed to address a gap in the literature regarding whether the mixed relationship between stress and working memory, and dopamine and working memory, could be explained by the interaction of stress and dopaminergic genetic variation. We did not find the expected interaction between stress and dopamine MLPS. However, exploratory analyses in one measure of working memory revealed an interaction between dopaminergic genetic variation and stress in the opposite direction of hypotheses. These results highlight the potential importance of studying striatal vs. prefrontal dopamine's effect on working memory, suggest the importance of utilizing and examining differences between multiple working memory tasks, and demonstrate benefit of using both idiographic and nomothetic approaches in working memory research.

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APPENDIX A

TABLES AND FIGURES

Table 1. Genetic Variants and Coding

Genetic Variant	**Genotypes**	**Coding**
DRD4 VNTR	7-repeat carrier	1
	All others	0
COMT Val158Met	Met/Met	1
	Val/Met	.5
	Val/Val	0
DAT1 VNTR	9-repeat carrier	1
	10-repeat	0
DRD2 - 141C Ins/Del	Del carrier	1
	Ins/Ins	0
ANNK Taq1A	C/C	1
	C/T	0.5
	T/T	0
DRD2 C957T	T/T	1
	T/C	0.5
	C/C	0

Table 2. Prior MLPS Studies and Variants Used

	Polymorphisms									
Citation Dependent Variable	*DAT1* 40-bp VNTR	*DRD2* 141C Ins/Del	*DRD2* C957T	*ANNK1* Taq1A	*DRD4* 48-bp VNTR	*DRD4* C521T	*COMT* Val^{158}Met	rs123 64283	rs4532	rs6280
Nikolova et al. (2011) ventral striatal reactivity to reward task	✓	✓		✓	✓		✓			
Stice et al. (2012) brain reactivity to reward	✓	✓ *		✓**	✓**		✓			
Davis et al. (2013) food addiction	✓	✓	✓	✓			✓	✓		
Davis and Loxton (2013) addiction-prone personality traits	✓	✓	✓	✓			✓	✓		
Sapuram et al. (under revision) sensation-seeking and RSA through sensation-seeking	✓	✓	✓	✓	✓	✓	✓			
Pearson-Fuhrop et al. (2014) depression in healthy adults	✓			✓			✓		✓	✓
Eisenstein et al. (2017) negative Schizophrenia symptoms	✓			✓	✓**		✓**			

Note: *denotes coding that varies slightly but is in the same direction relative to the coding scheme of the present study.
**denotes coding that is in the opposite direction of the coding scheme of the present study.

Table 3. Linear Regression Results of Primary Analyses

Change score analyses	***b***	**SE(*b*)**	***t***	***p*-value**
Six variant model				
Gender	-0.006	0.138	-0.046	0.963
Six-variant MLPS	-0.108	0.085	-1.269	0.204
Stress	0.036	0.134	0.272	0.786
MLPS x Stress	0.210	0.116	1.803	0.071
Four variant model				
Gender	0.006	0.139	0.043	0.966
Four-variant MLPS	-0.042	0.129	-0.328	0.743
Stress	0.036	0.138	0.258	0.796
MLPS x Stress	0.142	0.161	0.886	0.376
Session 2 analyses	***b***	**SE(*b*)**	***t***	***p*-value**
Six variant model				
Gender	0.504	0.151	3.335	0.001
Six-variant MLPS	-0.107	0.095	-1.124	0.261
Stress	0.038	0.146	0.261	0.794
MLPS x Stress	0.130	0.131	0.997	0.319
Four variant model				
Gender	0.512	0.150	3.402	0.001
Four-variant MLPS	0.000	0.137	-0.003	0.988
Stress	0.019	0.150	0.130	0.897
MLPS x Stress	0.120	0.173	0.693	0.489

Note: In change score analyses, N=84 and in Session 2 analyses, N=88.

Table 4. Correlations of Working Memory Tasks

	1	2	3	4
1. Operation Span Session 1	--			
2. Operation Span Session 2	.665***	--		
3. Symmetry Span Session 1	.209*	.104	--	
4. Symmetry Span Session 2	.174	.075	.545***	--

Note. *p<.05, **p<.01, ***p<.001, two tailed. N=89

Table 5. Linear Regression Results of Operation Span Analyses

Change score analyses	***b***	**SE(*b*)**	***t***	***p*-value**	**FDR *p*-value**
Six variant model					
Gender	-0.152	0.178	-0.854	0.393	
Six-variant MLPS	-0.157	0.111	-1.412	0.158	
Stress	-0.228	0.170	-1.340	0.180	
MLPS x Stress	0.384	0.152	2.520	0.012	0.048
Four variant model					
Gender	-0.132	0.181	-0.726	0.468	
Four-variant MLPS	-0.123	0.166	-0.741	0.459	
Stress	-0.226	0.177	-1.278	0.201	
MLPS x Stress	0.286	0.209	1.369	0.171	0.228
Session 2 analyses	***b***	**SE(*b*)**	***t***	***p*-value**	
Six variant model					
Gender	0.356	0.221	1.608	0.108	
Six-variant MLPS	-0.120	0.140	-0.856	0.392	
Stress	-0.134	0.213	-0.629	0.529	
MLPS x Stress	0.279	0.192	1.451	0.147	0.228
Four variant model					
Gender	0.363	0.220	1.648	0.099	
Four-variant MLPS	0.007	0.202	-0.033	0.974	
Stress	-0.160	0.216	-0.743	0.457	
MLPS x Stress	0.210	0.256	0.822	0.411	0.411

Note: In change score analyses, N=88 and in Session 2 analyses, N=89.

Table 6. Linear Regression Results of "*N*-1" Sensitivity Analyses Predicting Operation Span Change

Interaction Terms	***N***	***b***	**SE(*b*)**	***t***	***p*-value**
MLPS without *DRD4* VNTR x Stress	88	0.368	0.181	2.033	0.042
MLPS without *COMT* Val158Met x Stress	88	0.435	0.151	2.881	0.004
MLPS without *DAT1* VNTR x Stress	88	0.458	0.165	2.776	0.005
MLPS without *DRD2* - 141C Ins/Del x Stress	88	0.392	0.189	2.074	0.038
MLPS without *ANNK* Taq1A x Stress	88	0.333	0.170	1.959	0.050
MLPS without *DRD2* C957T x Stress	88	0.368	0.176	2.091	0.036

Note: Only the interaction terms are reported above for clarity. No simple main effects of MLPS or Stress were found.

Table 7. Linear Regression Results of Individual Variant Sensitivity Analyses Predicting Operation Span Change

Interaction Terms	***N***	***b***	**SE(*b*)**	***t***	***p*-value**
DRD4 VNTR x Stress	88	0.602	0.357	1.686	0.092
COMT Val158Met x Stress	87	-0.762	0.527	-1.446	0.149
DAT1 VNTR x Stress	88	0.024	0.372	0.065	0.949
DRD2-141C Ins/Del x Stress	88	0.585	0.360	1.625	0.104
ANNK Taq1A x Stress	88	1.286	0.511	2.517	0.012
DRD2 C957T x Stress	88	0.893	0.476	1.876	0.061

Note: Only the interaction terms are reported above for clarity. No simple main effects of MLPS or Stress were found.

Table 8. Linear Regression Results of Symmetry Span Analyses

Change score analyses	***b***	**SE(*b*)**	***t***	***p*-value**
Six variant model				
Gender	0.238	0.204	1.165	0.244
Six-variant MLPS	-0.046	0.127	-0.364	0.716
Stress	0.247	0.197	1.254	0.210
MLPS x Stress	0.033	0.175	0.191	0.848
Four variant model				
Gender	0.128	0.106	1.211	0.226
Four-variant MLPS	0.094	0.176	0.536	0.592
Stress	0.119	0.108	1.102	0.270
MLPS x Stress	-0.049	0.174	-0.279	0.781
Session 2 analyses	***b***	**SE(*b*)**	***t***	***p*-value**
Six variant model				
Gender	0.620	0.200	3.094	0.002
Six-variant MLPS	-0.025	0.123	-0.201	0.841
Stress	0.286	0.193	1.482	0.138
MLPS x Stress	-0.086	0.171	-0.502	0.616
Four variant model				
Gender	0.617	0.200	3.082	0.002
Four-variant MLPS	0.061	0.180	0.337	0.736
Stress	0.264	0.199	1.329	0.184
MLPS x Stress	-0.035	0.229	-0.152	0.879

Note: In change score analyses, N=87 and in Session 2 analyses, N=89.

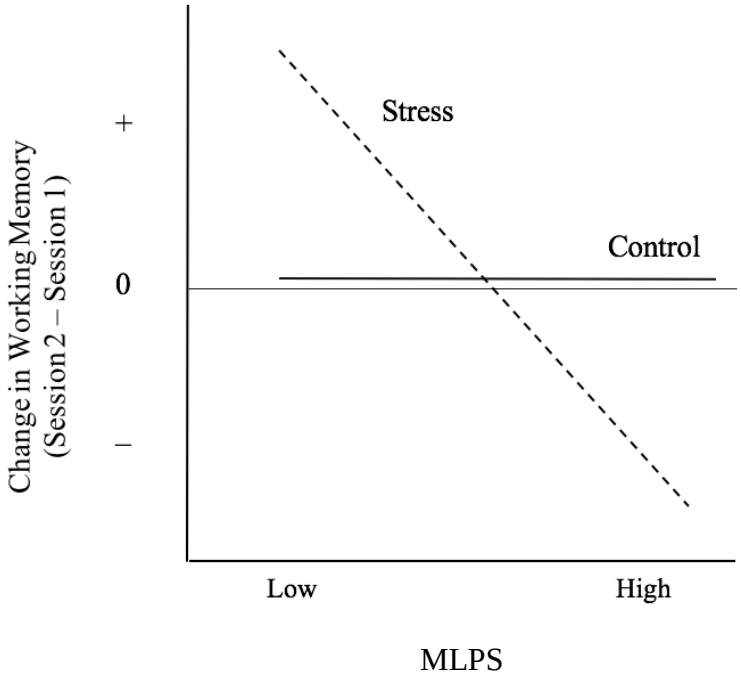

Figure 1. Hypothesized Relationship Between the Dopaminergic MLPS and Working Memory Change as a Function of Stress. X-axis at 0 represents no change in working memory. Participants in the control condition were not expected to experience a change in working memory across the 2 sessions. In the stress condition, working memory was expected to improve in Session 2 relative to Session 1 for participants with a lower dopaminergic MLPS whereas working memory was expected to decline in Session 2 relative to Session 1 for participants with a higher dopaminergic MLPS.

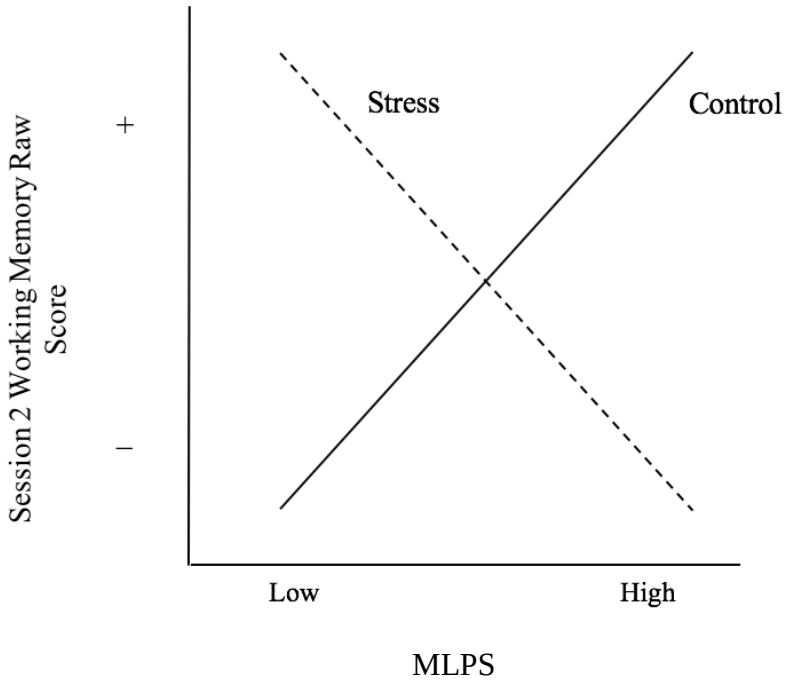

Figure 2. Hypothesized Relationship Between the Dopaminergic MLPS and Session 2 Working Memory as a Function of Stress. In the control condition, participants with a higher MLPS were expected to show better working memory than participants with a lower MLPS. In the stress condition, participants with a lower MLPS were expected to show better working memory than participants with a higher MLPS.

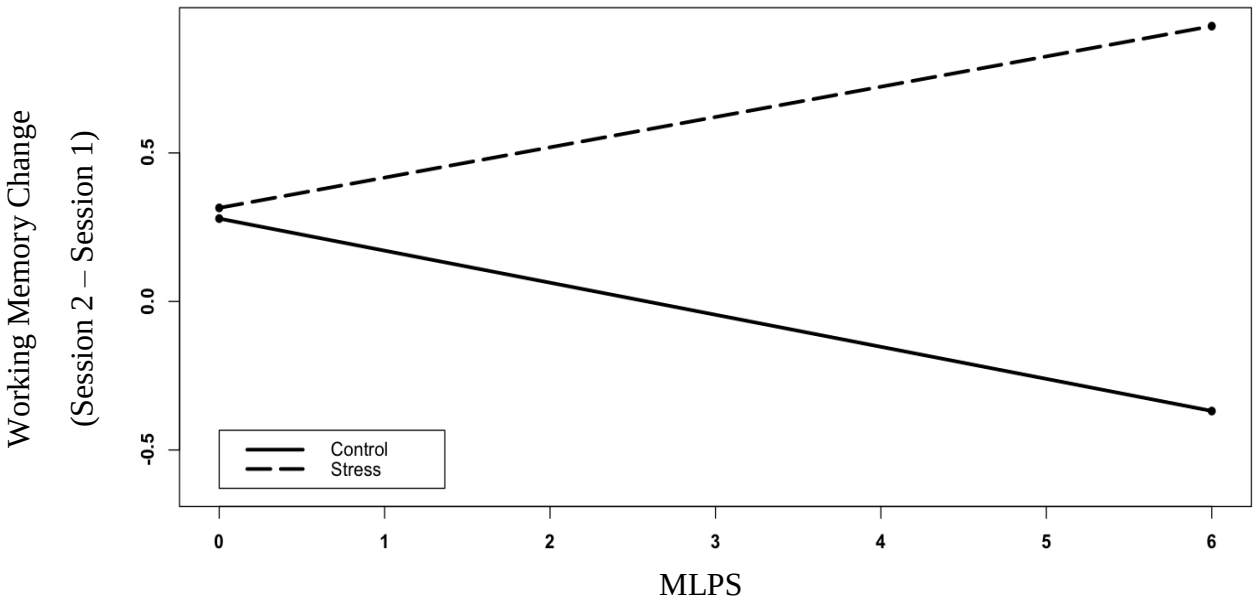

Figure 3. The MLPS x Stress Interaction Approached Significance in Predicting Working Memory Change Score. In the control condition, participants with lower MLPSs showed a small, non-significant increase in Session 2 relative to Session 1 score whereas participants with higher MLPSs showed a small, non-significant decrease in score. In the stress condition, participants with lower MLPSs showed a small, non-significant increase in score whereas participants with higher MLPSs showed a larger, non-significant increase in score. Working memory change score units are expressed as standard deviations based on Session 1 norms. X-axis at 0 represents no change in working memory.

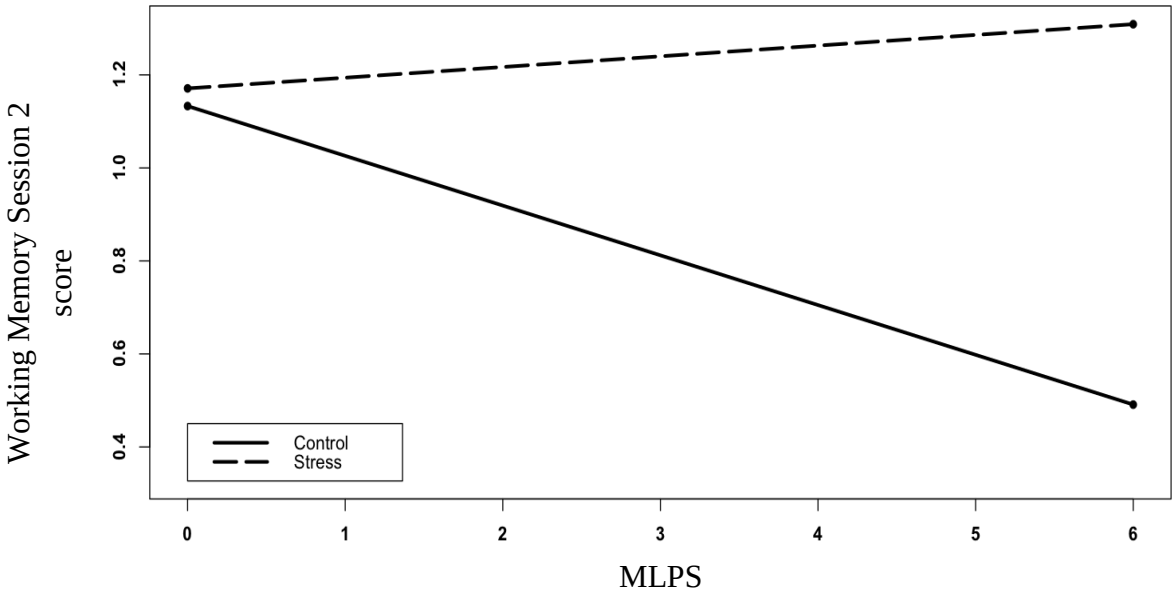

Figure 4. The MLPS x Stress Interaction was Not a Significant Predictor of Session 2 Score. Session 2 score units are expressed as standard deviations based on Session 1 norms.

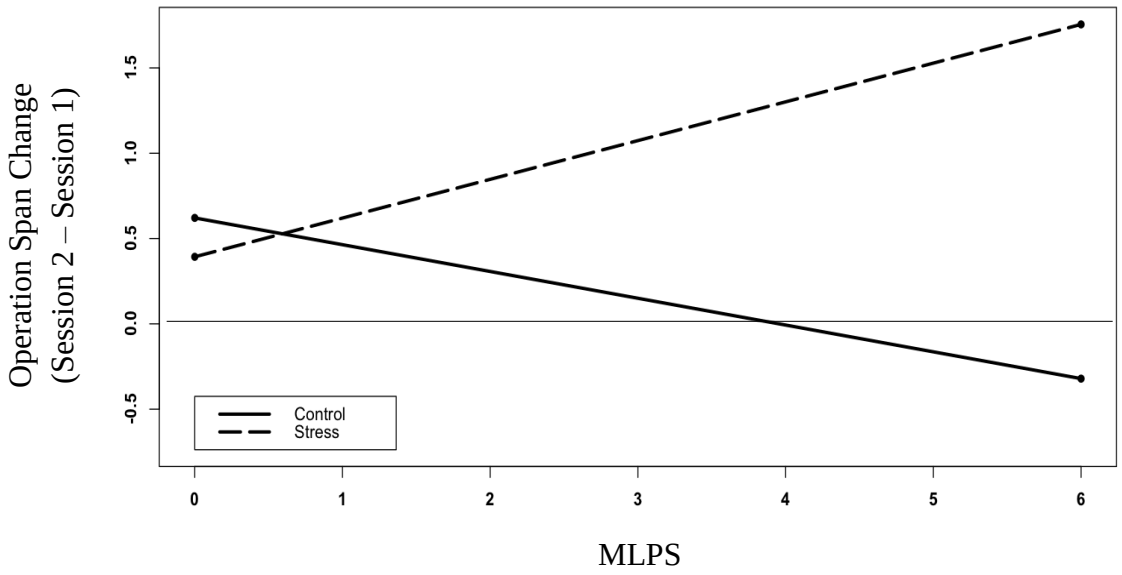

Figure 5. Simple Slopes Analysis Revealed that the Six-variant MLPS Affected Operation Span Change Score as a Function of Stress. In the control condition, lower MLPSs showed a slight, non-significant increase in operation span score whereas higher MLPSs showed a slight, non-significant decrease in operation span score in Session 2 relative to Session 1. In the Stress condition, participants showed improved operation span score: Participants with lower MLPSs showed a slight, non-significant increase whereas participants with higher MLPSs showed a significant increase in operation span score in Session 2 relative to Session 1. Operation span change score units are expressed as standard deviations based on Session 1 norms. X-axis at 0 represents no change in operation span.

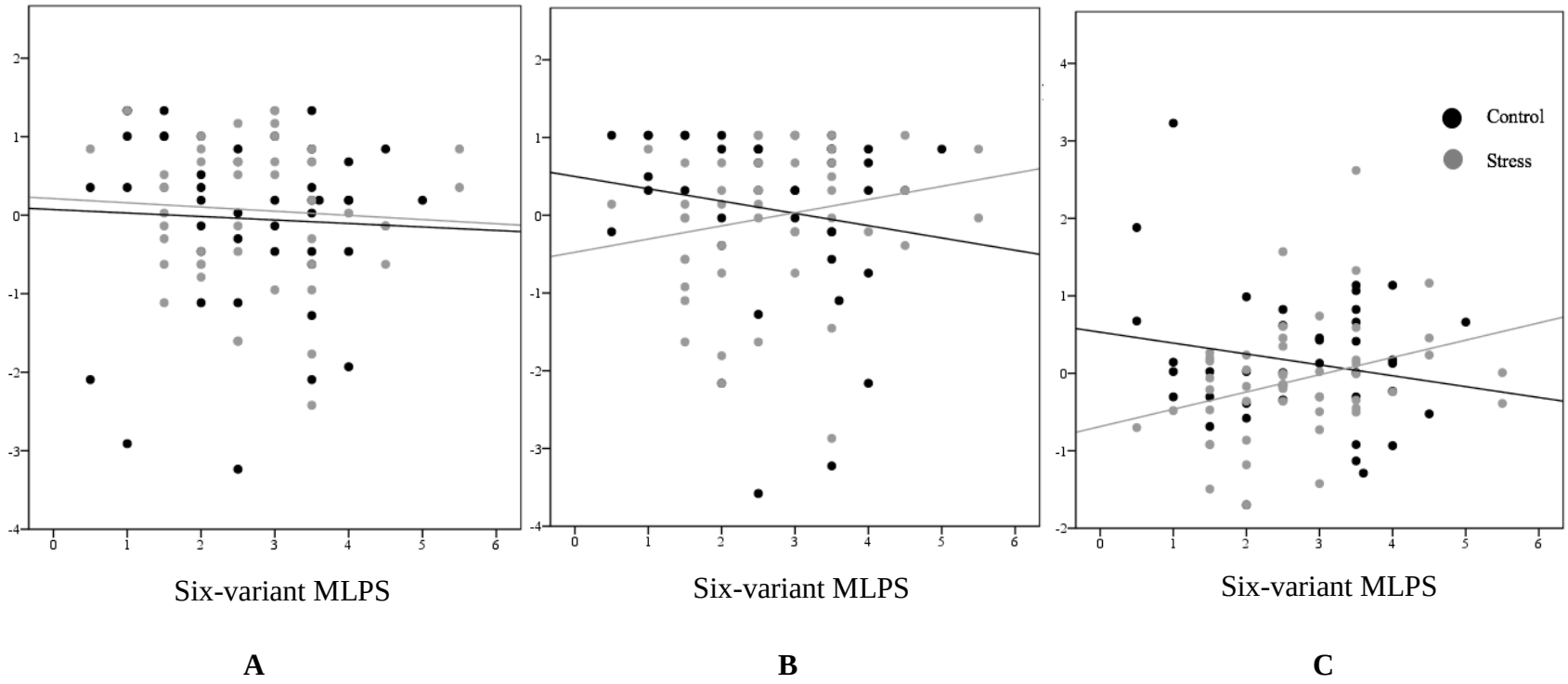

Figure 6. Bivariate Correlation Plots of Operation Span Score and Six-variant MLPS by Stress Condition. **A** Operation span Session 1 z-score, **B** Operation span Session 2 score standardized with respect to Session 1 norms, **C** Operation span change score (Session 2 – Session 1)

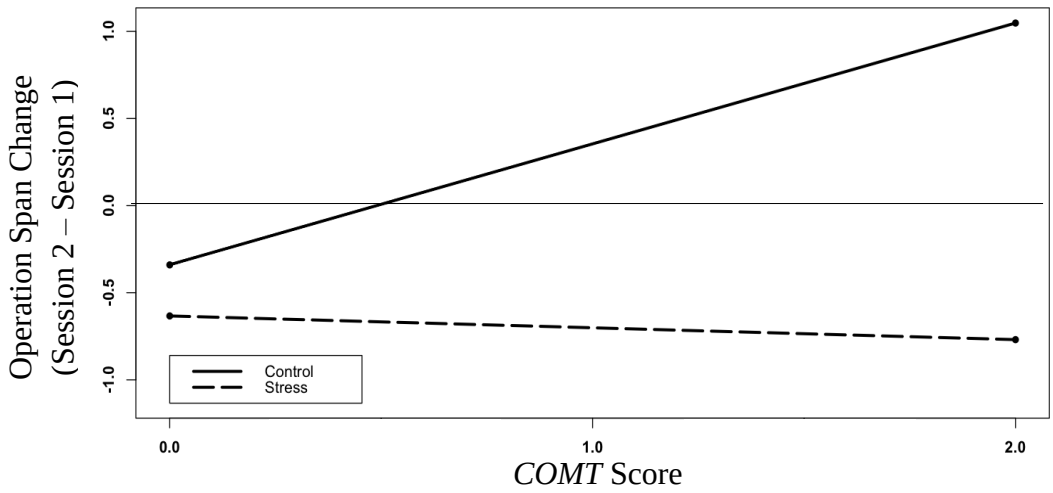

Figure 7. The *COMT* x Stress Interaction Predicting Operation Span Change Score did Not Reach Significance. However, the direction of the data appeared contrary to the MLPS x Stress interaction. In the control condition, participants with lower MLPSs showed a small, non-significant decrease in score at Session 2 relative to Session 1 whereas participants with higher MLPSs showed a small, non-significant increase in score. In the stress condition, participants showed a small, non-significant decrease in score seemingly regardless of MLPS. Operation span change score units are expressed as standard deviations based on Session 1 norms. X-axis at 0 represents no change in operation span.

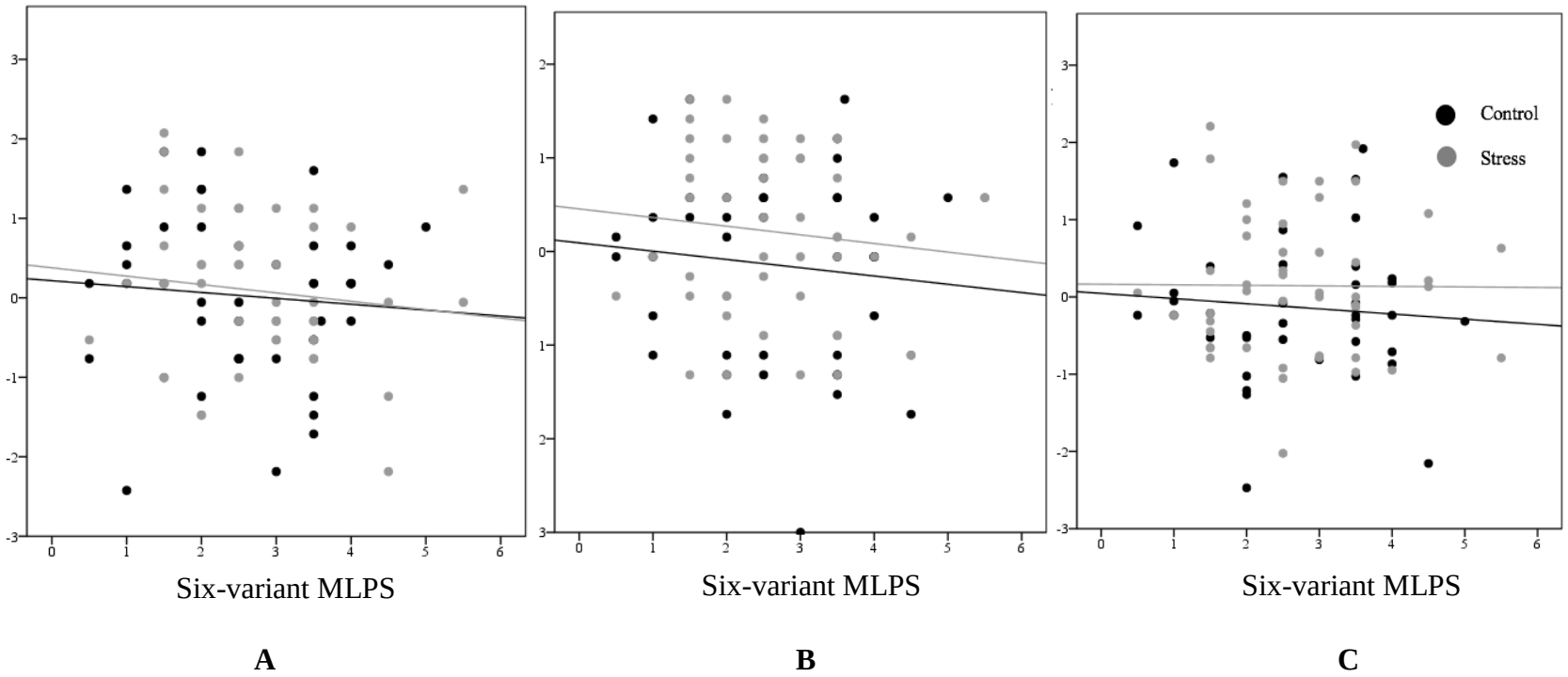

Figure 8. Bivariate Correlation Plots of Symmetry Span Score and Six-variant MLPS by Stress Condition. **A** Symmetry span Session 1 z-score, **B** Symmetry span Session 2 score standardized with respect to Session 1 norms, **C** Symmetry span change score (Session 2 – Session 1)

APPENDIX B

CHALLENGE CONDITION EXAMPLE BEHAVIORAL SCRIPT

Speech portion:
Both confederates begin with a mildly pleasant facial expression and neutral to interested body language, e.g., sit up and slightly lean forward in your chair

Administer all directions with a firm, stern tone of voice.

Possible timing in speech	**Confederate 1 (dissatisfied)**	**Confederate 2 (bored)**
0:00	Scribble notes on your paper	Slump shoulders & posture
0:30	Furrow brow with slightly confused look	Quiet sigh of fatigue
1:00	Continue scribbling	Stare into space
1:30	Look more confused	Play with hair
2:00	Shuffle papers	Slight eye roll
2:30	Look at other confederate and shrug shoulders as if to ask "what do you think?"	Look at other confederate and slightly shake head "no"
3:00	Subtle grimace; rub the bridge of your nose	Cross arms, squirm
3:30	Make a conspicuous X mark on your papers	Look at your watch briefly
4:00	Glance at your phone then put it away	Widen eyes and breathe in and out deeply
4:30	Exchange dissatisfied glance with other confederate	Exchange dissatisfied glance with other confederate
5:00	Tap fingers on table	Fidget with finger nails

Arithmetic portion: Conspicuously make tally marks on your paperwork for errors/restarts. Maintain dissatisfied or bored body language and stern tone of voice.