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Original Article

ORIGINAL ARTICLE

First Demonstration of Double Dissociation between COMT-Met^{158} and COMT-Val^{158} Cognitive Performance When Stressed and When Calmer

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Abstract

We present here the first evidence of the much-predicted double dissociation between the effect of stress on cognitive skills [executive functions (EFs)] dependent on prefrontal cortex (PFC) by catechol-O-methyltransferase (COMT) genotype. The COMT gene polymorphism with methionine (Met) at codon 158 results in more dopamine (DA) in PFC and generally better EFs, while with valine (Val) at codon 158 the result is less PFC DA and generally poorer EFs. Many have predicted that mild stress, by raising PFC DA levels should aid EFs of COMT-Vals (bringing their PFC DA levels up, closer to optimal) and impair EFs of COMT-Mets (raising their PFC DA levels past optimal). We tested 140 men and women in a within-subject crossover design using extremely mild social evaluative stress. On trials requiring EFs (incongruent trials) of the Flanker/Reverse Flanker task, COMT-Val^{158} homozygotes performed better when mildly stressed than when calmer, while COMT-Met^{158} carriers performed worse when mildly stressed. Two other teams previously tried to obtain this, but only found stress impairing EFs of COMT-Mets, not improving EFs of COMT-Vals. Perhaps we found both because we used a much milder stressor. Evidently, the bandwidth for stress having a facilitative effect on EFs is exceedingly narrow.

Key words: acute stress, executive functions, prefrontal cortex, selective attention, rs4680

Introduction

Many workplaces and graduate programs intentionally impose a modicum of stress and anxiety, thinking it will lead to better performance, as the famous Yerkes–Dodson graph would predict (Yerkes and Dodson 1908). There is little evidence, however, that any level of stress is beneficial for higher-level cognitive performance in humans. Here, we investigated the role of mild social evaluative stress on executive functions (EFs). EFs include selective attention, self-control, working memory, and cognitive flexibility (Diamond 2013).

EFs are subserved by prefrontal cortex (PFC) and interrelated brain regions (Leh et al. 2010; Niendam et al. 2012). Dopamine (DA) is an important neurotransmitter in PFC, as it is in many brain regions. (Much of what we say here about DA also applies to norepinephrine (NE), though not all. We will address the effects on NE in the Discussion.) The best mechanism for clearing excess DA is by dopamine transporter (DAT) protein. Most DA-containing brain regions, such as the striatum, have abundant DAT, but not PFC. PFC, being unusual in having little DAT, is more dependent on secondary mechanisms for clearing DA from extracellular space (Sesack et al. 1998; Lewis et al. 2001; Durston et al. 2005). One such mechanism is via the catechol-O-methyltransferase (COMT) enzyme, which inactivates DA by catalyzing DA's O-methylation, adding a methyl group donated

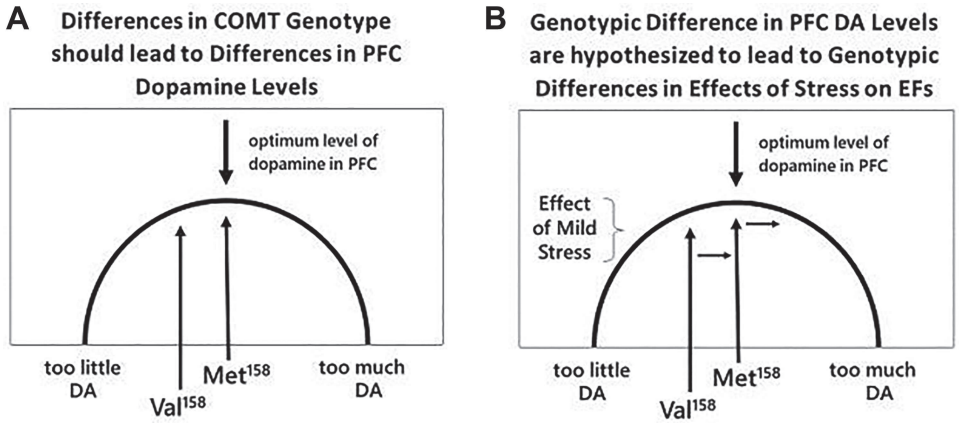

Figure 1. (A) Differences in COMT genotype should lead to differences in PFC DA levels. Adapted from Figure 4 in Diamond (2011) with permission. (B) Genotypic difference in PFC DA levels is hypothesized to lead to genotypic differences in stress reactivity. Adapted from Figure 4 in Diamond (2011) with permission.

by S-adenosylmethionine onto a hydroxyl group (Zhu 2002). The COMT enzyme accounts for >60% of DA clearance in PFC, but <15% in the striatum (Karoum et al. 1994; Männistö and Kaakkola 1999; Käenmäki et al. 2010).

The COMT gene, located at gene map locus 22q11.2, codes for the COMT enzyme. A single-nucleotide polymorphism (SNP) of that gene results in the substitution of adenosine (A) for guanosine (G) at sequence 4680, causing an amino acid substitution of methionine (Met) for valine (Val) at codon 158 (Lachman et al. 1996). Hence this common polymorphism is referred to as rs4680 or Val158Met.

The COMT enzyme is 25–33% less active in COMT-Met^{158} homozygotes than in COMT-Val^{158} homozygotes (meta-analysis: Tunbridge et al. 2019). This means that the COMT-Met^{158} variant codes for a slower COMT enzyme, leaving more DA around longer in PFC. Most studies, though not all, have found better PFC function and better cognitive performance (better EFs) in COMT-Met^{158} homozygotes than in COMT-Val^{158} homozygotes (e.g., Egan et al. 2001; Diamond et al. 2004; Bruder et al. 2005; Barnett et al. 2007; Caldú et al. 2007).

The optimal level of DA in PFC is an intermediate level (Vijayraghavan et al. 2007; Cools and D'Esposito 2011). Since the Met^{158} variant of COMT is generally associated with better EFs, one would expect that variant to yield PFC DA levels close to the intermediate level that is optimal. Since the COMT-Val^{158} genotype results in a COMT enzyme that clears DA from PFC more quickly, one would expect that genotype to yield PFC DA levels that are lower. See Figure 1*a*. Such hypotheses are consistent with findings like tolcapone (a COMT inhibitor) being found to aid the EF performance of those with a faster COMT enzyme (COMT-Vals) but to impair the EFs of those with an already slower COMT enzyme (COMT-Mets; Apud et al. 2007) and findings like amphetamine being found to enhance PFC efficiency in those we predict have less DA in PFC (COMT-Vals) but impair PFC efficiency in COMT-Mets when working memory load is high (Mattay et al. 2003).

Stress, even at levels too mild to affect other brain regions, increases DA in PFC (Deutch and Roth 1990; Cerqueira et al. 2007; Nagano-Saito et al. 2013). Many experts have thus hypothesized (1) that in persons homozygous for COMT-Met^{158}, even mild stress would increase PFC DA levels past optimal, impairing EF performance, while (2) for COMT-Val^{158} homozygotes mild stress by increasing PFC DA levels closer to the optimal point should result in better EF performance (Stein et al. 2006; Diamond 2011; Buckert et al. 2012; Qin et al. 2012; see Fig. 1*b*). (Severe stress would presumably raise PFC DA levels past optimal and negatively impact other aspects of brain function as well.) Note that the second hypothesis presents a scenario by which mild stress might be beneficial to at least the subset of the population who are homozygous for COMT-Val^{158}. We tested those 2 hypotheses here.

Two other labs previously investigated this (Buckert et al. 2012; Qin et al. 2012). Both labs found that immediately after being stressed, COMT-Vals showed better working memory and inhibitory control than COMT-Mets, but that effect was driven entirely by the worse performance of COMT-Mets under stress. The performance of COMT-Vals was essentially unaffected by stress. See Figures 2 and 3. Thus, COMT-Vals could tolerate stress better than COMT-Mets, but they were not helped by it, contrary to predictions of the investigators and others.

We reasoned that perhaps the stressors used by those 2 labs had pushed the DA levels of both groups past optimal, hence not helping either COMT genotype. We hypothesized that if the predicted double dissociation is to be found, a milder stressor would be needed. Buckert et al. (2012) used the procedure most commonly used to induce moderate, acute stress in human research subjects, the Trier Social Stress Test (Kirschbaum et al. 1993). That procedure induces social evaluative stress by first having the participant, without advance warning, give a 5-min presentation to an audience, who unbeknownst to the participant will maintain a neutral or bored expression throughout the talk. Next, the participant is to do mental math, counting backward in steps of 13 or 17. If a mistake is made, the person must start over. Qin et al.'s (2012) stress induction procedure was to show participants brief movie clips containing scenes with strongly aversive content (extreme violence). Those were interspersed between cognitive testing trials.

We wanted a milder stressor and one that would be a more natural part of cognitive testing. Therefore, in our stress session (but not in our calmer session), a male and female tester, each dressed rather formally and holding a pen and clipboard, stood just behind and to the side of the participant as he or she did each task, not saying anything but seeming to observe and evaluate. In all other respects, the 2 testing sessions were identical. We hypothesize that COMT-Met^{158} participants would show worse EFs in the stress session than in the calmer session and that

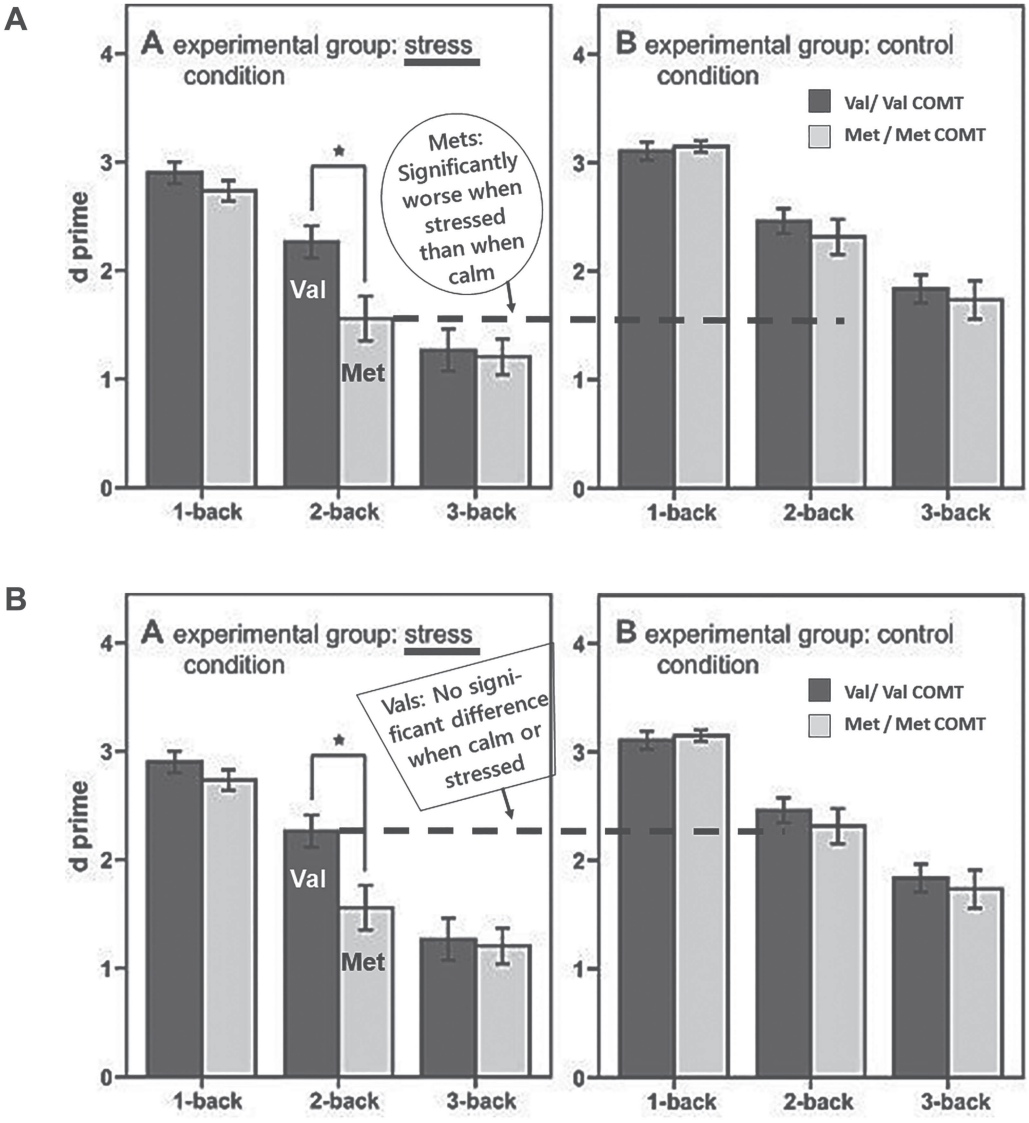

Figure 2. Buckert et al. (2012): Verbal N-back performance when calmer or stressed by COMT genotype. As predicted, under stress, young adults homozygous for COMT-Val^{158} showed better EF performance than peers homozygous for COMT-Met^{158}. Also as predicted, those homozygous for COMT-Met^{158} performed worse on the 2-back test when stressed than when calmer (see Panel A). However, contrary to predictions, COMT-Val^{158} homozygotes did not perform better when stressed than when calmer; they showed little change in performance (see Panel B). Adapted from Buckert et al. (2012) with permission. Error bars indicate standard error; *indicates a significant difference at $p < .05$.

COMT-Val^{158} would show better EFs in the stress session than in the calmer session.

Methods

Participants

We tested 156 healthy young women and men between the ages of 20 and 35 years. We excluded persons who 1) had serious health problems likely to affect cognition such as head trauma or concussions, mental health disorders or were taking any medication that might affect cognition, 2) were smokers (due to the effects of nicotine on EFs and the HPA axis; Kirschbaum and Hellhammer 1994; Ernst et al. 2001), or 3) had a history of major life traumas or were going through a particularly stressful period of their life, which might affect EFs or stress responsivity. We also excluded women who 1) were pregnant or nursing (due to the effects of those on gonadal hormone levels), 2) did not have a regular menstrual cycle (as it would have been difficult to predict their high or low estradiol phases), or 3) had taken any hormone-releasing contraceptive within the preceding 4 months. (Estradiol levels were significantly associated with differential EF performance in the stress and calmer sessions; we will be reporting on that in a separate paper.) No one who replied to our recruitment efforts failed to self-identify as a man or woman.

We recruited participants through posters at university campuses, bus stops, coffee shops, and community centers, by distributing flyers to passersby in high-density areas, advertising on an online participant list and on Craigslist, advertising on social media websites such as Facebook, and through presentations in undergraduate classrooms. We talked to potential

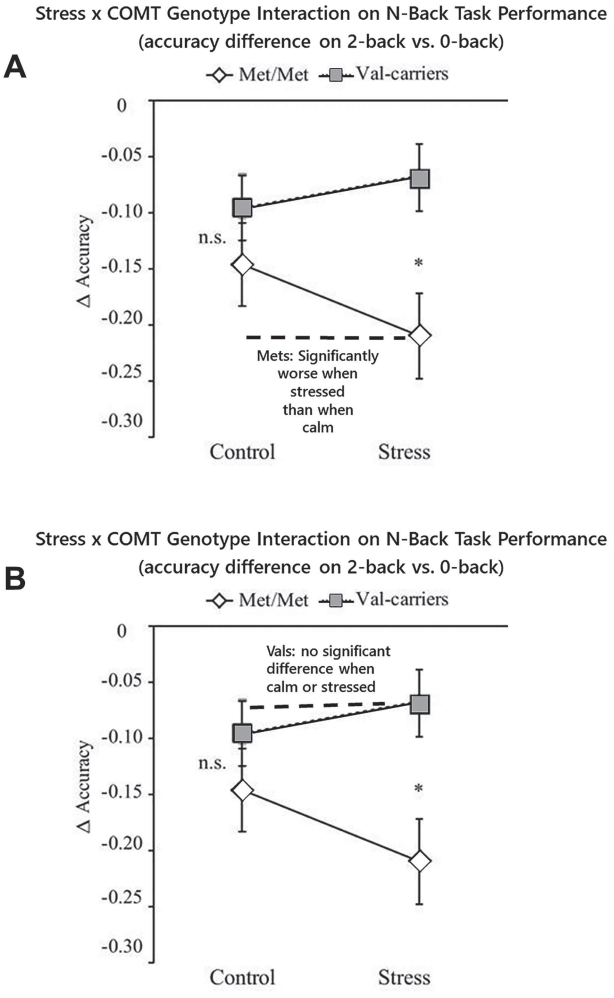

Figure 3. Qin et al. (2012): Numerical N-back performance when calmer or stressed by COMT genotype. As predicted, under stress, young adults homozygous for COMT-Val^{158} showed better EF performance than peers homozygous for COMT-Met^{158}. Also as predicted, those homozygous for COMT-Met^{158} performed worse on the N-back test when stressed than when calmer (see Panel A). However, contrary to predictions, COMT-Val^{158} homozygotes did not perform better when stressed; they showed little change in performance (see Panel B). Adapted from Qin et al. (2012) with permission. Error bars indicate standard error; *indicates a significant difference at $p < .05$.

participants over the phone to answer their questions and assess their eligibility and sent them the consent form electronically to look over before they came in. Only after all their questions had been answered before and during the informational session did we ask for their written consent. Written consent was obtained from all participants. Monetary compensation was provided ($10 for the information session, $15 for Session 1, and $25 for Session 2).

Six participants (1 male and 5 female) were excluded from data analyses either because their perceived stress level for the month leading up to one of their testing sessions was very high (2 standard deviations [SD] above the mean) or because their perceived stress for the month before one testing session was far higher than their perceived stress before their other testing session. Data analyses were performed on the remaining 140 participants. Demographic information for them is presented in Table 1. The groups were well matched on age, ethnic background, and numbers of men and women. All participants were university students or university graduates.

Procedure

Testers were blind to all participants' genotypes. Each subject participated in 1 information session and 2 testing sessions. The 2 testing sessions were roughly 1 month (1 menstrual cycle) apart (once with mild social evaluative stress and once without), order counterbalanced within each sex × genotype group. Thus, half the participants per sex × genotype group were randomly assigned to be tested first without the stressor and a month later with it; half were assigned to be tested with the reverse order (crossover design). Women were randomized to receive both their stress and calmer sessions when their estradiol levels were elevated (midluteal menstrual phase) or when their estradiol levels were lower (early follicular menstrual phase). Gonadal hormone levels at each testing session were objectively assessed via salivary radioimmunoassays.

All sessions were conducted in the Developmental Neuroscience Lab at the University of British Columbia between 12 noon and 6 PM to target relatively stable and low levels of cortisol (Weitzman et al. 1971) and because young adults tend to show better cognitive performance in the afternoon (Hasher et al. 1999). To optimize the purity of the saliva, participants were instructed to refrain from eating, drinking (except water), or brushing their teeth for at least 1 h prior to coming to the lab for any of their 3 sessions. All procedures were approved by the ethical review boards of UBC and Vancouver Coastal Health.

During the information session, a participant learned more about the study, signed the consent form, completed a demographic questionnaire, and gave a saliva sample for COMT genotyping. Female participants were asked about the length of their menstrual cycle and dates of their last and next (estimated) periods.

Each testing session lasted about 1 h. Before each testing session, participants completed the widely used Perceived Life Stress Questionnaire (Cohen et al. 1983) about stresses during the month immediately preceding testing.

To minimize the effects of daily stressors (e.g., work, commuting, or interpersonal stress) on testing performance, we gave participants 30 min to relax and calm down before each of their 2 testing sessions. Participants were free to relax in our comfortable reception room or anywhere else, inside or out, they wanted.

Thereafter, participants entered the testing room, rated their current stress level, and provided saliva samples for assays of their gonadal hormone levels and baseline level of cortisol. The first measures of blood pressure (BP) and heart rate (HR) were also taken at that time. Next, participants completed our 3 cognitive assessments, providing saliva samples for cortisol assay after each cognitive task as well as BP and HR readings after each task. At the end of the session, participants again rated their current stress level, and 15 min after the last task, they provided a final saliva sample and the final BP and HR readings.

For the stress condition, participants were informed that 2 testers would be in the room during their cognitive testing observing their performance. During testing, the tester (who was female) and a male research assistant from the lab stood behind the participant with clipboard and pen in hand, one to

Table 1 Demographic characteristics by COMT genotype

COMT genotype	Met homozygotes	heterozygotes	Met carriers (Met homozygotes + heterozygotes)	Val homozygotes
Variables				
Number of subjects	10	68	78	62
Mean age (SD)	24.9 (4.6)	24.1 (4.01)	24.2 (4.2)	24.2 (3.7)
% Female	50%	71%	68%	55%
Percentage of women tested when their estradiol levels were elevated	75%	52%	54%	47%
Percentage of women tested when their estradiol levels were lower	25%	48%	46%	53%
% European descent	64%	57%	58%	50%
% East Asian descent	0	18%	15%	24%
% Other	36%	24%	27%	26%

the right and one to the left, seeming to be silently evaluating the participant's performance while the participant performed each cognitive task. Thus, during the stress session, participants started the EF tasks at the same time that the stressor started. We were interested in the effects of increased DA in PFC. The dopaminergic response to stress is triggered immediately after the onset of stress (Hermans et al. 2014). Participants were debriefed after their stress session, even if that was their first testing session, because we did not want them coming to their second testing all stressed, expecting to have people looking over their shoulder again (or to be less likely to return for their second testing). Pains were taken to try to reassure participants who received the stress session first that in their next session no one would be in the room with them.

In the calmer condition, no one was in the testing room looking over participants' shoulders as they completed the EF tests. The tester provided instructions for each cognitive test and went through practice trials with the participant, just as in the stress condition, but then left the room while the participant took the test. After each cognitive task, the participant let the tester know he or she was finished and the tester came back in the room to explain the next cognitive task. Other than this, the 2 conditions were identical and Testing Sessions 1 and 2 were identical.

COMT Genotyping

All participants were genotyped for the COMT SNP rs4680 (Val158Met). Genotyping was carried out in Weihong Song's lab, just upstairs from our lab. Saliva samples were collected using Oragene-DNA© Self-Collection Kits (Genotek Inc.). Genomic DNA was extracted according to the protocol supplied by the manufacturer and then analyzed by PCR-restriction fragment length polymorphism (RFLP).

The Three Cognitive Tasks

In both testing sessions, participants completed 2 computerized EF tests and then a paper-and-pencil fluid intelligence test (Raven's Advanced Progressive Matrices, which assesses reasoning, arguably a higher-order EF skill). Different versions of each test were administered in Sessions 1 and 2 to minimize practice effects. In Session 1, the A version of each test was administered; in Session 2, the B version was used. The order in which the 2 EF tasks were administered was counterbalanced for each stress order and within each subject group (men, women tested when estradiol levels were lower, and women tested when estradiol levels were higher). For the first few subjects, this had not been counterbalanced to avoid another variable to control for, but counterbalancing was introduced very soon thereafter. Thus, the order of the 2 EF tasks was not perfectly counterbalanced; the Flanker/Reverse Flanker task was administered second 56% of the time. Table 2 shows the counterbalancing implemented.

The Flanker/Reverse Flanker Task. Block 1 of our Flanker/Reverse Flanker task (Munro et al. 2006; Diamond et al. 2007) presents the classic Flanker paradigm (Eriksen and Eriksen 1974). Participants are to selectively attend to the direction the center stimulus is pointing, ignoring the flanking stimuli. Participants are to press the leftmost key if the center stimulus is pointing left and the rightmost key if the center stimulus is pointing right.

Block 2 presents a Reverse Flanker condition, where participants are to focus on the flankers (the outside stimuli) and ignore the center stimulus. All flanking stimuli, in all blocks, always pointed in the same direction.

For Version A in the present study, the stimuli for Block 1 were a row of blue fish and the stimuli for Block 2 were a row of pink fish. For Version B, the stimuli for Block 1 were a 3×3 grid of carets (greater-than and less-than symbols) and the stimuli for Block 2 was a 3×3 grid of arrows (see Fig. 4).

For Block 3, the stimuli (and rules) for Blocks 1 and 2 were pseudorandomly intermixed (all participants receiving the same order of stimuli).

For all trials, stimuli appeared on the screen for 1500 ms. The inter-trial interval was 500 ms. In each of the first 2 blocks, the percentage of trials that were incongruent (where the center stimulus and flanking stimuli were pointing in opposite directions) was 35%. In the mixed block, the percentage of incongruent trials was 36% and the percentage of switch trials was 50%. Participants found Version B a bit harder than Version A, which is one of the reasons we controlled for session order since Version A was always administered in Session 1.

First participants were trained on Block 1. They were told the instructions and shown a demonstration. Then, they performed a short practice block where they received feedback on each trial. Next they were trained on Block 2 and then Block 3. Participants had to get at least 75% of the trials in any practice set correct to demonstrate they understood the rule. Had any participant erred on more than 25% of practice trials, the instructions and practice trials would have been repeated, but no participant needed that.

Table 2 Number of participants per cell, illustrating the counterbalancing that was implemented

	Order of stress and calm sessions	Met/Met	Met/Val	Val/Val	Subtotal	Total
Women tested during midluteal phase	Calm first	1 (1)	12 (6)	9 (5)	22 (12)	44
	Stress first	1 (1)	12 (6)	9 (5)	22 (12)	
Women tested during early follicular phase	Calm first	1 (1)	12 (7)	8 (4)	21 (12)	42
	Stress first	1 (1)	12 (8)	8 (4)	21 (13)	
Men	Calm first	3 (2)	10 (5)	14 (8)	27 (15)	54
	Stress first	3 (1)	10 (5)	14 (8)	27 (14)	
Total		10 (7)	68 (37)	62 (34)		140

Note: The numbers in parentheses in gray are the number of subjects who received the Flanker task second, after Hearts and Flowers. The order of task versions (A and B) is not included in the table because the B version was always administered in Session 2. For half the participants that was the stress session and for half that was the calm session.

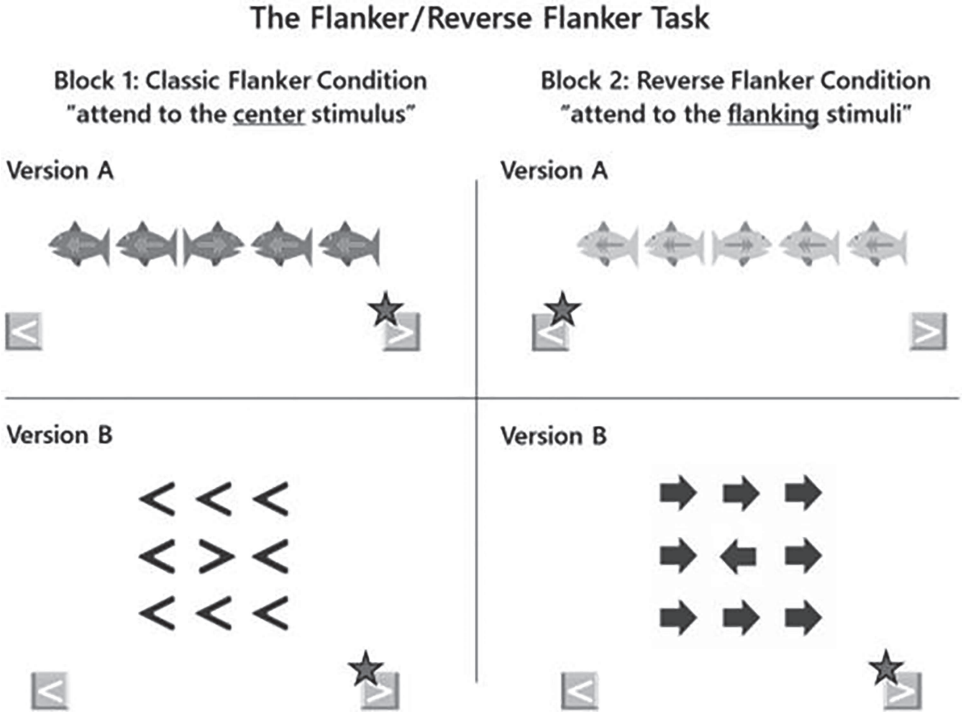

Figure 4. The Flanker/Reverse Flanker Task. Here, the fish stimuli for the Flanker condition are blue; the fish stimuli for the Reverse Flanker condition are pink. A star indicates the correct response.

The first trial in each block was excluded from response time (RT) analyses, as RT on the first trial is unreliable. Trials with RTs < 250 ms were excluded as being too fast to have been in response to the stimulus (across all participants only 4 trials were excluded for this reason). RTs that deviated from the mean for a given participant by ± 2 SD were considered outliers and were excluded from analyses (4% of trials were being excluded for this reason). RTs on trials where subjects erred were not included in the RT analyses. We were most concerned with performance on incongruent trials, the trials requiring selective attention.

The flanker task is an extremely well-established assay of EFs (specifically selective attention) and PFC functioning. It has been around since 1974, and there are over 1,300 published papers with the Flanker task in the title or abstract. Several neuroimaging studies have investigated the neural basis for Flanker task performance. Studies have found that the frontal brain regions activated for incongruent trials of the Flanker task are the superior and middle frontal gyri (i.e., dorsolateral PFC; Kawai et al. 2012), the inferior frontal gyrus (i.e., ventrolateral PFC; Morimoto et al. 2008), and the anterior cingulate cortex (ACC; Huyser et al. 2011; Siemann et al. 2016).

The Hearts and Flowers Task. For this task (Davidson et al. 2006; Wright and Diamond 2014), stimuli are presented on the left or right of a horizontal rectangle. Block 1 is the congruent block; participants are to press on the same side as the stimulus. The stimulus was either a red heart (Version A) or a black and white striped disc (Version B). Block 1 demands little or no EFs, since our natural tendency is to activate the hand on the same side as

a stimulus. Block 2 is the incongruent block, where participants are to press on the side opposite the stimulus. The stimulus was either a red flower (Version A) or a gray disc (Version B). This requires inhibiting the natural tendency to activate the hand on the same side as a stimulus, instead activating the other hand. Block 3 is the mixed block where congruent and incongruent trials are pseudorandomly intermixed.

For all trials in the Hearts and Flowers task, a crosshair was presented in the center of the rectangle for a 500-ms fixation period and then the stimulus was presented for 750 ms. The inter-trial interval was 500 ms. The percent of incongruent trials in Block 3 was 50%. Training was similar to that for the Flanker/Reverse Flanker task as were the rules for excluding trials from analyses.

The Hearts and Flowers task has been shown repeatedly to be a sensitive measure of EFs especially in children (e.g., Diamond et al. 1998; Davidson et al. 2006; Schonert-Reichl et al. 2015; Rosas et al. 2019). The frontal regions showing greater activation on incongruent than congruent trials of the Hearts and Flowers task are the middle frontal gyrus (Areas 9, 10, and 46), inferior PFC (Areas 44 and 45), the ACC (Area 24), and the SMA (supplementary motor area) and premotor cortex (Area 6; Diamond et al. 1998).

Raven's Advanced Progressive Matrices. All versions of Raven's Matrices are widely used, highly regarded tests of nonverbal logical reasoning (also known as fluid intelligence; Raven et al. 2004). Participants are to identify the missing component in a matrix of figural patterns.

Two practice trials were administered before testing. After each practice trial, the experimenter pointed out the rules that govern the progressions within the matrix to explain why a participant's answer was correct (or incorrect). No participant failed to demonstrate an understanding of the rules. As per John Raven's recommendation (personal communication), the even-numbered trials were presented in Session 2 and the odd-numbered trials were presented in Session 1. This resulted in the Session 2 version being a bit harder, since difficulty increases over trials; thus Trial 1 is easier than Trial 2, Trial 11 is easier than Trial 12, etc. This is one reason why we controlled for session order. Participants were given 25 min in each session to complete 18 trials.

Stress Assessments

BP and HR. Stress triggers activation of the sympathetic nervous system (SNS), reducing vagal control of BP and HR (Hjortskov et al. 2004). BP and HR both increase. Thus, increases in BP or HR are taken as indicative of SNS arousal and stress. HR and systolic and diastolic BP readings were taken on a digital BP monitor (Omron HEM-711ACN) immediately after the relaxation period before the onset of cognitive testing (baseline), following each cognitive task, and at the end of the session.

Cortisol. Stress causes activation of the hypothalamic–pituitary–adrenal axis, which releases cortisol. A small fraction of the cortisol released remains unbound or "free," and it is that which affects the brain (Kirschbaum and Hellhammer 2000). Cortisol levels measured in saliva agree closely with the amount of "free" cortisol in blood and hence with the amount of cortisol reaching the brain (Gozansky et al. 2005). We used SaliCaps-RE69991 test tubes (Affinity Diagnostics) for collecting saliva through spitting. We froze these samples at −20°C to precipitate mucins and then shipped them in dry ice to Clemens Kirschbaum's lab at Technische Universität Dresden. There the samples were thawed, centrifuged, and assayed for cortisol using high-sensitivity enzyme immunoassays (IBL-Hamburg, Inc.).

There is some evidence that measuring cortisol alone is less accurate than measuring the cortisol to dehydroepiandrosterone (DHEA) ratio (Gallagher and Young 2002). DHEA opposes the action of glucocorticoids and lowers cortisol levels. The Kirschbaum lab also conducted immunoassays for DHEA.

Subjective perceptions of stress. The Perceived Stress Scale (PSS-10 version) is a widely-used self-report instrument for measuring how stressed a person felt during the previous month (Cohen et al. 1983). The PSS-10 version has 10 items designed to tap how unpredictable, uncontrollable, and/or overloaded individuals feel their lives have been over the past month. Each of the 10 items is rated on a 5-point Likert scale (0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often). After inverting scores for the 4 positive items, a total score is computed by summing all scores and dividing by the number of items answered. The higher the score, the greater that person's perceived stress during the month preceding testing.

Before cognitive testing began in any session, the participant was asked to complete a one-item stress assessment: "Please circle the number corresponding to how you feel at this moment." The scale went from 0 (very relaxed) to 4 (very stressed). At the end of the session, each participant was asked to complete another one-item stress assessment: "Please circle the number corresponding to how you felt during the cognitive testing." The same 5-item scale was provided.

Gonadal Hormones

Several studies have reported that estradiol (one of the major estrogens in humans) downregulates COMT gene transcription (Jiang et al. 2003), causing COMT enzyme activity to be lower in women than men (Chen et al. 2004). As mentioned above, we will report on how the effect of stress on EFs is moderated by estradiol in a separate paper. We simply note here that the saliva sample collected when each participant arrived at our lab was stored at −20 °C and shipped in dry ice to Elizabeth Hampson's lab at the University of Western Ontario, London, ON, for assays of estradiol, progesterone, and testosterone levels. Dr Hampson is the foremost expert in assaying sex hormone levels from saliva and one of the foremost researchers on sex differences. Saliva assays were used because they offer practical advantages over serum and provide a precise estimate of the bioavailable fraction of the hormones (Becker et al. 2005; Hampson and Young 2008).

Results

Despite our best efforts to recruit as many Met homozygotes as Val homozygotes, including undersampling East Asians, since they have been found to be twice as likely to carry the Val allele (Palmatier et al. 1999), only 7% of our participants were homozygous for COMT-Met^{158}, instead of 25% as we had anticipated. Therefore, for our statistical analyses, the COMT-Met and heterozygote groups are combined. There is evidence that COMT heterozygotes resemble COMT-Mets more closely than they do COMT-Vals (Hernaus et al. 2013).

We conducted repeated-measures analyses of covariance with 2 COMT genotype groups (at least 1 Met allele [Met carriers] vs. homozygous for Val [Val homozygotes]) and 2 conditions (stress or calmer), Note, we sex (man or woman), and order

of sessions (stress first or calmer session first) as covariates. (We often refer to our condition without a social stressor as the calmer condition, rather than as the calm condition, since cognitive testing in a laboratory is probably somewhat stressful in and of itself). Initially, we also included the order of EF tasks (Flanker/Reverse Flanker tested first or Hearts and Flowers tested first), but no main effect or interaction for that was ever significant so that variable was dropped from analyses. Effect sizes are reported as partial eta squared (η_p^2). Results for interactions are only reported when they were significant.

Effectiveness of the Stress Induction

Participants did indeed experience stress in our social evaluative stress condition, as indicated by objective, physiological indicators of stress (increased BP and HR) as well as by subjective self-reports of perceived stress. Because of the many comparisons we made between groups on each stress variable across each timepoint, we required a P value of <0.001 for any result on a stress measure to be considered significant.

Participants started with comparable diastolic BP levels in the calm and stress sessions ($F[1136] = 3.03$, $P = 0.10$ [ns]). Yet, whether the stress session came first or second, participants had higher diastolic BP throughout the stress session compared with the calmer session ($F[1136] = 35.30$, $P < 0.001$, $\eta_p^2 = 0.23$; this analysis and all others control for whether stress was in Session 1 or 2). Not only was that true averaged over the 4 timepoints when BP readings were taken, but it was also true, or tended to be true, at each of those individual timepoints (after the first EF task: $F[1136] = 11.54$, $P < 0.005$, $\eta_p^2 = 0.07$; after the second EF task: $F[1136] = 25.86$, $P < 0.001$, $\eta_p^2 = 0.15$; after Raven's Matrices: $F[1136] = 15.62$, $P < 0.001$, $\eta_p^2 = 0.10$; and at the end of session: $F[1136] = 13.79$, $P < 0.005$, $\eta_p^2 = 0.08$). Further, diastolic BP relative to baseline was higher in the stress session than in the calmer session at 3 of our 4 timepoints (after the first EF task: $F[1136] = 11.05$, $P < 0.001$, $\eta_p^2 = 0.08$; after the second EF task: ($F[1136] = 22.86$, $P < 0.001$,$\eta_p^2 = 0.14$), and after Raven's Matrices: $F[1136] = 15.15$, $P < 0.001$, $\eta_p^2 = 0.10$) and tended to be higher at the remaining timepoint (end of the session: ($F[1136] = 4.03$, $P < 0.03$, $\eta_p^2 = 0.06$). See Figure 5 and Table 3.

Participants started with higher systolic BP in the stress session ($F[1136] = 18.31$, $P < 0.001$, $\eta_p^2 = 0.11$), and it remained higher than in the calm session at all timepoints until the end of session (after the first EF task: $F[1136] = 50.95$, $P < 0.001$, $\eta_p^2 = 0.27$; after the second EF task: $F[1136] = 30.29$, $P < 0.001$, $\eta_p^2 = 0.18$; after Raven's Matrices $F[1136] = 15.86$, $P < 0.001$, $\eta_p^2 = 0.10$; at the end of session: $F[1136] = 4.22$, $P < 0.04$, $\eta_p^2 = 0.06$). Controlling for initial systolic BP level, systolic BP relative to baseline levels tended to be higher in the stress session than in the calmer session ($F[1136] = 5.53$, $P < 0.02$, $\eta_p^2 = 0.03$) but that did not reach significance (see Table 3).

Participants' HRs were similar at the outset of their calm and stress sessions ($F[1136] = 0.52$, ns). However, their HRs showed a greater decrease during the calm session than during the stress session ($F[1136] = 10.64$, $P < 0.001$, $\eta_p^2 = 0.07$). This became more evident as the session progressed (see Table 3).

Baseline levels of cortisol (at the outset of the session) were similar for the calm and stress sessions ($F[1130] = 1.00$, ns). At the end of the session, cortisol levels tended to be higher in the stress session but did not reach significance ($F[1130] = 9.91$, $P < 0.003$, $\eta_p^2 = 0.06$; see Table 3). Cortisol takes longer to increase in response to stress than does DA or autonomic indicators, so we did not expect to see an increase in cortisol until toward the end of the session. We found no significant results, or even trends, for the ratio of cortisol to DHEA.

Participants rated their level of stress as minor before both the stress and the calm sessions. There was no difference in baseline level of reported stress ($F[1136] = 0.11$, ns). Participants were again asked to rate their level of stress at the end of each session. The level of self-reported stress was higher at the end of the stress session than the calm session ($F[1136] = 17.60$, $P < 0.001$, $\eta_p^2 = 0.11$). The relative level of self-reported stress (end of session vs. beginning of session) tended to be higher in the stress versus calmer session ($F[1136] = 8.98$, $P < 0.003$, $\eta_p^2 = 0.06$). See Table 3.

No stress variable showed even a trend toward a male–female difference or a difference by COMT genotype. There was no evidence that those with at least one copy of the Met allele were more stressed than Val homozygotes or vice versa (diastolic BP: $F[1135] = 0.03$, ns; systolic BP: $F[1135] = 0.34$, ns; HR: $F[1135] = 0.05$, ns; cortisol: $F[1132] = 0.03$, ns; perceived stress: $F[1135] = 0.38$, ns).

Effect of Stress on EFs

As predicted, persons with at least 1 COMT-Met^{158} allele showed better EFs when they were calmer than under mild stress. They performed significantly worse on the Flanker/Reverse-Flanker task when stressed than when calmer. On trials requiring inhibiting distraction (the incongruent trials), those with at least 1 Met allele responded faster in the calm condition than in the stress condition ($F[1,75]) = 27.64$, $P < 0.001$, $\eta_p^2 = 0.26$). See Figure 6. That difference was much more pronounced when the calm session came first ($F[1,75]) = 65.02$, $P < 0.001$, $\eta_p^2 = 0.46$).

As predicted, when performing under mild stress, COMT-Val^{158} homozygotes showed better EFs than they did when calmer. On the trials in the Flanker/Reverse-Flanker task requiring EFs (the incongruent trials), Vals responded faster in the stress session than in the calm session ($F[1, 60]) = 31.20$, $P < 0.001$, $\eta_p^2 = 0.34$). See Figure 6. That difference was more pronounced when the calm session came first ($F[1,59]) = 23.18$, $P < 0.001$, $\eta_p^2 = 0.28$). Also as predicted, Vals were faster on incongruent trials in the stress session than were participants with at least 1 Met allele ($F[1136] = 6.72$, $P < 0.03$, $\eta_p^2 = 0.04$).

This was done without the Vals sacrificing accuracy. Each genotype group showed comparable accuracy in the stress and calmer sessions (those with at least 1 Met allele: $F[1,75] = 2.05$, ns; COMT-Val homozygotes: $F[1,59] = 2.10$, ns).

Efficiency scores (which combine accuracy and speed: 1/natural-log (reaction time/%correct)) show that those with at least 1 Met allele were "less" efficient in their performance across all incongruent trials in all blocks of the Flanker/Reverse Flanker task in the stress session than in the calmer session ($F[1,75]) = 7.00$, $P < 0.01$, $\eta_p^2 = 0.10$). Those homozygous for Val were "more" efficient on incongruent trials in the stress session than in the calmer session ($F[1,59) = 4.98$, $P = 0.02$, $\eta_p^2 = 0.06$).

We had assumed that Met carriers would perform better than Val homozygotes in the calmer session because many studies have found better EF performance by COMT-Mets than COMT-Vals in normal laboratory testing (our calmer condition). We did not find that, however. There was no difference in performance by COMT genotype in the calm condition ($F[1,75] = 0.178$, ns). Interestingly, the 2 other studies that previously investigated the hypotheses investigated here (Buckert et al. 2012; Qin et al. 2012) also found no difference in performance in the calm condition by COMT genotype on their EF tasks (a verbal and numerical

Table 3 Values of stress indicators at various time points during each testing session

Stress measurement	Time point	Stress condition	Compared to baseline level	Calm condition	Compared to baseline level	Comparing stress versus calm session	Controlling for baseline level, comparing stress versus calm
Diastolic BP							
mmHg, mean & (SD)	Start of session	69 (9)		67 (8)		ns	
	After first EF task	70 (9)	*	68 (9)	ns	****	****
	After second EF task	70 (8)	*	67 (10)	ns	****	****
	After Raven's	71 (10)	**	67 (8)	ns	****	****
	End of session	71 (9)	*	69 (7)	ns	***	*
	Mean for session	70 (7)	*	68 (7)	ns	****	***
Systolic BP							
mmHg, mean & (SD)	Start of session	107 (13)		104 (13)		****	
	After first EF task	108 (13)	ns	102 (13)	*	****	**
	After second EF task	107 (13)	ns	101 (13)	**	****	*
	After Raven's	107 (17)	ns	103 (12)	ns	****	*
	End of session	106 (13)	ns	103 (14)	ns	**	*
	Mean for session	108 (13)	ns	103 (11)	ns	****	*
HR							
heartbeat/min,	Start of session	67 (11)		66 (11)		ns	
mean & (SD)	After first EF task	65 (10)	****	65 (11)	**	ns	ns
	After second EF task	67 (11)	ns	64 (10)	****	*	**
	After Raven's	64 (12)	****	61 (11)	****	*	***
	End of session	65 (11)	****	62 (10)	****	**	***
	Mean for session	66 (10)	****	64 (9)	****	**	***
Cortisol							
nmol/l, mean & (SD)	Start of session	8.128 (6.89)		8.275 (6.49)		ns	
	After first EF task	8.257 (15.41)	ns	7.106 (6.28)	ns	ns	ns
	After second EF task	7.573 (6.12)	ns	6.865 (5.09)	ns	ns	ns
	After Raven's	8.242 (3.48)	ns	7.255 (4.33)	ns	ns	ns
	End of session	8.356 (6.62)	***	7.035 (4.56)	ns	***	ns
	Mean for session	8.111 (9.04)	ns	7.376 (5.18)	ns	ns	ns
Perceived Stress							
scale of 1–5, mean &	Start of session	2.2 (0.92)		2.2 (0.88)		ns	
(SD)	End of session	3.4 (1.04)	****	2.7 (0.93)	****	****	****

ns, not significant. Start of session = Baseline. Hence, "controlling for baseline level" means controlling for the level at the start of the session. Given the large number of comparisons above, we divided the usual P value of 0.05 by 50, yielding a required P value here of 0.001.
*P value < 0.05.
**P value < 0.01.
***P value < 0.005.
****P value < 0.001.

N-back task, respectively). Perhaps that has to do with some stress already being present in the calmer session, since taking a cognitive test in a laboratory might be a bit stressful in and of itself. Other laboratory studies, however, have found better performance by Met/Mets than by Val/Vals, so we are not sure why some studies find no difference and others find better EF performance by Met/Met individuals.

There were no male versus female differences in EF performance or in how stress affected EF performance. (Stress affected the EF performance of women with elevated estradiol levels differently than it affected men or women when their estradiol levels were lower; those results will be reported in a separate paper.) There were also no differences by whether the Flanker/Reverse Flanker task was administered first or the Hearts and Flowers task was administered first. When the calmer session came first, the difference in performance between the calm and stress sessions was greater for both genotype groups than when the stress session came first (Met carriers: $F[1,75] = 4.02$, $P = 0.05$, $\eta_p^2 = 0.03$; Val homozygotes: $F[1,59] = 5.72$, $P = 0.02$, $\eta_p^2 = 0.08$). This difference in the calm versus stress RT difference by whether the calm session came first or second was more pronounced for Val homozygotes (47 ms difference) than for Met carriers (3 ms difference): $F[1136] = 23.64$, $P < 0.05$, $\eta_p^2 = 0.13$. When the stress session came first, despite debriefing, participants were still not as relaxed for the calm session as they were when the calm session came first. Indicative of that, diastolic BP was higher at the beginning of the calm session when that session came second than when it came first ($F[1136] = 3.824$, $P < 0.05$, $\eta_p^2 = 0.02$) and higher throughout the calm session when it came second rather than first ($F[1136] = 5.30$, $P < 0.02$, $\eta_p^2 = 0.03$).

Ceiling effects on the Hearts and Flowers task obscured any difference in performance by stressed versus calmer, genotype, or their interaction. This task has been shown to be a very sensitive EF measure in young children (e.g., Davidson et al. 2006; Schonert-Reichl et al. 2015; Rosas et al. 2019); however, while one study reported effects in adults (Diamond et al. 1998), other studies have found ceiling effects in teens and adults

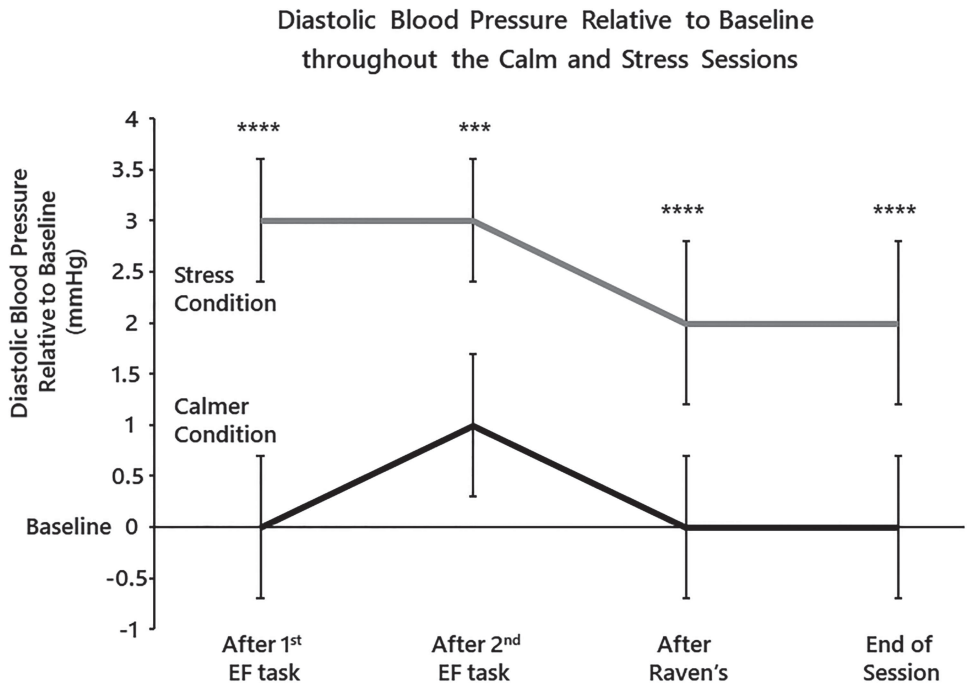

Figure 5. Diastolic BP levels relative to baseline at the outset of the session with mild social evaluative stress and the calmer session. Error bars indicate standard error.

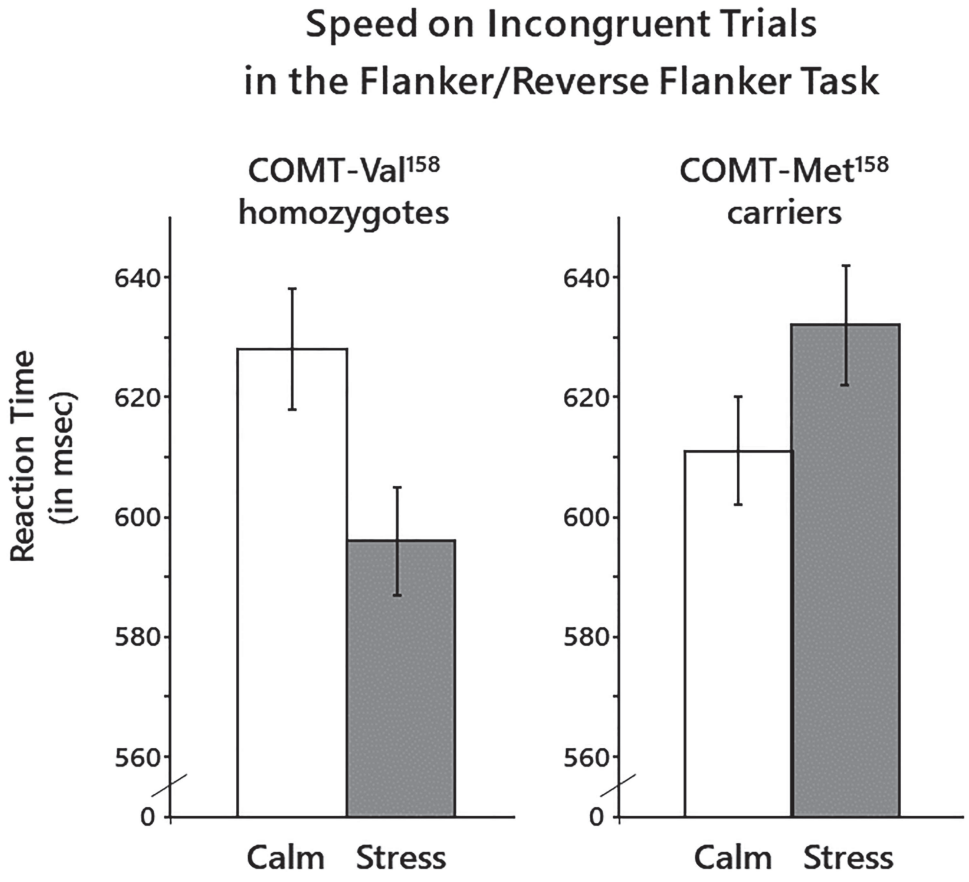

Figure 6. Effect of mild stress on speed on incongruent trials in the Flanker/Reverse Flanker task by COMT genotype. Error bars indicate standard error.

Table 4 Characteristics of the present study and the studies by Buckert et al. (2012) and Qin et al. (2012)

Study	Country where study took place	Stressor	Timing of the stressor	EF task	Sex of participants	Age of participants in years
Buckert et al. study	Germany	Trier Social Stress Test	Before cognitive testing	Verbal N-back task	Male and female	24.5 ± 4.2
Qin et al. study	the Netherlands	Short movie clips containing scenes with strongly aversive content (extreme violence)	Interspersed between trials of the cognitive test	Numerical N-back task	Male	23.7 ± 5.5
Present study	Canada	A male and female research assistant looking over a person's shoulders while s/he took EF tests	Concurrent with the cognitive test	Flanker/Reverse Flanker task	Male and female	24.1 ± 3.9

(e.g., Kitil 2020), consistent with what we observed here. We also found no difference in performance on Raven's Advanced Matrices by condition, genotype, or their interaction. The B version of Raven's was harder than the A version and that obscured any difference by condition or genotype.

Discussion

This psychoneuroendocrinological study investigated how the effect of mild stress on the EF ability of selective attention (ignoring distractors) is modulated by the COMT Val158Met polymorphism, which influences DA availability in PFC. We found that a very mild psychosocial stressor (2 research assistants standing behind, one to the left and one to the right, observing and seemingly evaluating the participant's performance while the person was taking cognitive tests) impaired the performance of young adult COMT-Met^{158} carriers and improved the performance of young adult COMT-Val^{158} homozygotes. This is the first demonstration of that double dissociation. This was found specifically on those trials of the Flanker/Reverse Flanker task that require the most cognitive control (incongruent trials, which require focused attention on the target and inhibition of attention to distractors). Since mild stress increases DA in PFC, we had predicted the results obtained because increased DA in PFC should push PFC DA levels past optimal for COMT-Mets but bring PFC DA up closer to optimal for COMT-Vals.

Two other attempts to demonstrate this double dissociation found that mild stress impaired the EF performance of COMT-Mets but did not improve the EF performance of COMT-Vals. Instead, the EF performance of COMT-Vals remained resilient in the face of mild stress (i.e., it did not suffer), but it was not helped. We hypothesize that the reason we found the double dissociation and the other 2 studies did not is because our stressor was milder. Buckert et al. (2012) used the Trier Social Stress Test (Kirschbaum et al. 1993). Qin et al. (2012) did not use social evaluative stress; instead they stressed participants by showing short movie clips containing scenes with strongly aversive content (extreme violence). Thus, across all 3 studies, we find a consistent story that while it is clear that even stress that is quite mild impairs the EFs of COMT-Mets, the benefit of mild stress to COMT-Vals is sufficiently tenuous that 2 studies did not find it and we found it on one EF-dependent measure with an extremely mild stressor.

There are, of course, other possible interpretations. Perhaps we found a significant facilitation by stress in the performance of COMT-Vals when others did not because the other 2 studies had too few subjects (see Table 4). Perhaps we found it because our stressor was task-relevant, whereas the stressors in the other 2 studies were not. We are not aware of any studies that have compared EF performance with a task-relevant stressor and a task-irrelevant one, or of any explanation for why task-related stress (but not task-irrelevant stress) should be beneficial to some individuals (COMT-Vals). Our stressor might not only have been stressful but also distracting, since it occurred while participants were taking our tests. It is hard to see how increased distraction could have helped Val homozygotes to perform better, however, and that is the one result we found that other studies had not. (Buckert et al. (2012) and Qin et al. (2012) both found impaired performance by Met homozygotes or Met carriers in the stress condition, as did we. The new result is the stress facilitation effect for COMT-Vals.)

We used a different EF task from the other 2 studies. Our task (Flanker/Reverse Flanker) puts more of a premium on inhibitory control of attention (inhibiting attention to distractors), whereas N-back tasks such as those used by Buckert et al. and Qin et al. put more of a premium on working memory, though our task also required working memory and N-back tasks require inhibitory control when lures appear. We would not expect that this difference in tasks or task requirements to account for the difference in findings, however. Acute stress has been shown to impair working memory (Schoofs et al. 2008; Shields et al. 2016) and to impair selective attention, making individuals more distractible (Sänger et al. 2014; Shields et al. 2016). Also, there is much evidence that both N-back (Herrmann et al. 2007; Simioni et al. 2017) and Flanker (Krämer et al. 2007; Mueller et al. 2011) tasks are sensitive to the level of DA in PFC, which is affected by COMT genotype.

Both Buckert et al. (2012) and Qin et al. (2012) used accuracy as their dependent measure; we used speed, which is usually more sensitive in adults than accuracy. Another study, using the Trier Social Stress Test as the stressor and the N-back task as the EF measure, found as we did that stress significantly affected RT but not percentage of correct responses (Schoofs et al. 2008). It is quite common for an effect to show up sometimes in accuracy and sometimes in speed, but not both. There was no evidence of a speed–accuracy trade-off in our data;

accuracy did not vary across the stress and calmer sessions for either genotype. In addition, we found the same double dissociation when we combined speed and accuracy into an efficiency score.

It is possible that the Trier Social Stress Test not only stresses individuals but also depletes EF resources in requiring that one quickly mentally construct a talk, remember what you came up with long enough to present the talk, and then do a difficult mental math exercise. Baumeister (2014) and Muraven and Baumeister (2000) have shown that self-control or cognitive control may be a limited resource and that prior exertion of cognitive control (as required by the Trier test) might deplete it so that it is less available for what comes next (i.e., the cognitive testing). The depletion of EF resources might negatively affect people regardless of COMT genotype. That could potentially be why Buckert et al. (2012) found no benefit for COMT-Vals after the Trier stressor, though Baumeister's work on self-control depletion has come under criticism (Lurquin and Miyake 2017).

We did not find some differences that other studies have reported. Male–female differences in the physiological response to stress have been reported with men showing a bigger cortisol response to stress and women occasionally showing a greater autonomic effect (Kudielka and Kirschbaum 2005; Cornelisse et al. 2011; Reschke-Hernández et al. 2017), though other studies have not found that sex difference (Seeman et al. 1995; Kudielka et al. 2004). A stronger stressor than used here might be needed to see that sex difference. Some studies have found a stronger subjective experience of stress in women than in men (e.g., Zimmer et al. 2003), though other studies have not (Frankenhaeuser et al. 1976; Schommer et al. 2003). We found no sex difference on any stress indicator. COMT-Met^{158} homozygotes or carriers have been reported in several studies to show more pronounced stress responses than COMT-Vals (Armbruster et al. 2012; Hernaus et al. 2013; Serrano et al. 2019), but here we found no difference in any stress indicator by COMT genotype. COMT-Mets have often been found to show better EF performance at baseline than COMT-Vals (Egan et al. 2001; Diamond et al. 2004; Bruder et al. 2005; Barnett et al. 2007), but we did not find that here, though neither did Buckert et al. (2012), Qin et al. (2012) nor others (de Frias et al. 2010; Wardle et al. 2013).

COMT-Mets usually perform better on EF tasks at baseline. Individuals with better working memory capacity typically perform better on EF tasks in baseline, control conditions (Engle 2002). It is highly likely that COMT-Mets generally have better working capacity. Thus, that COMT-Mets are impaired by stress is consistent with results from cognitive and social psychology showing that the detrimental effects of social presence or social evaluation on performance of EF tasks is greater for individuals with better working memory capacity. For example, social presence more negatively affects response inhibition on the Simon task (Belletier et al. 2015) and selective attention on a visual search task (Wühr and Huestegge 2010) for those with better working memory capacity. Indeed, even simply being watched by an evaluative other positioned opposite the participant (and who therefore could not see the participant's performance) has been found to cause those with higher working memory capacity to choke on a classic measure of EFs (Belletier and Camos 2018). Similarly, Beilock and Carr (2005) found that individuals with better working memory capacity are more likely to fail under pressure. Note that this means that it is exactly those individuals with presumably the highest potential for success (those with the highest working memory capacity) whose performance on demanding cognitive tasks is most adversely affected by stress.

All 3 studies—ours, Buckert et al. (2012), and Qin et al. (2012)—also differed in the timing of the stressor in relation to when participants performed EF tasks. In Buckert et al.'s study, the stress occurred immediately prior to testing. In Qin et al.'s study, the stressor (disturbing movie clips) was interspersed between test trials. In our study, the stressor occurred during the test trials. For the 50% of participants who were tested on the Flanker/Reverse Flanker task second, the stressor had already begun during the Hearts and Flowers task. We found no difference in any results by the order in which the tasks were administered.

Since the dopaminergic response to stress is triggered immediately after the onset of stress (Hermans et al. 2014) and the mode of action we were interested in was the effect of increasing levels of DA in PFC, we did not want a lag between the stressor and cognitive testing. Cortisol takes longer to increase in response to stress than does DA or autonomic indicators. The increase in cortisol depends on hypothalamic release of corticotropin-releasing hormone to activate the pituitary gland to release adrenocorticotropic hormone to finally stimulate the adrenal gland to secrete cortisol. In contrast, DA release in and to PFC is directly activated by the amygdala in response to a psychological stressor. Indeed, lesions to the amygdala prevent the DA increase in PFC in response to psychological stress (Feenstra et al. 1992; Goldstein et al. 1996).

It is incorrect to equate the effects of cortisol with those of stress. A meta-analysis by Shields et al. (2016) found that stress effects on cortisol do not moderate stress effects on either working memory or cognitive inhibition (e.g., selective attention). For example, the opposite temporal effects of cortisol administration and of stress on working memory strongly suggest that the effects of cortisol and stress on working memory are dissociable. Shields et al. found that the effects of stress on EFs differed markedly from the effects of cortisol on EFs. In addition, a number of studies have found that cortisol responsivity neither parallels nor reflects the subjective experience of stress (reviews: Campbell and Ehlert 2012; Kudielka and Kirschbaum 2005). For example, Campbell and Ehlert found that of 30 studies reporting correlations between cortisol responses and perceived emotional stress, only 8 studies (27%) found a significant association between the two. Shields et al. (2019) found cortisol responses to be unrelated to *any* of the effects of mild stress in their study. Shafiei et al. (2012) found that the effects of stress on decision-making were not mimicked by the effects of physiological doses of corticosterone in their study, concluding that the effects of stress on decision-making do not seem to be mediated entirely, if at all, by enhanced glucocorticoid activity.

DA is not the only catecholamine in PFC. Much of what we have said about DA in PFC also applies to NE in PFC, although not all. NE also shows an inverted U-shaped curve, with PFC function and EFs being optimal at an intermediate level of NE and impaired when there is too little or too much NE in PFC (Arnsten 2009). NE levels in PFC also increase rapidly when one is stressed, as with DA responding to amygdala stimulation (Feenstra et al. 1992; Goldstein et al. 1996). DA is a precursor of NE, so any effect on DA should have knock-on effects on NE. COMT should theoretically catabolize NE as well as DA. However, we were unable to find any scientific studies demonstrating that. Indeed surprisingly, tolcapone, which inhibits COMT enzymatic activity, increasing DA levels, has not been found to increase NE levels (Laatikainen et al. 2013).

The idea that a modicum of stress should be beneficial for performance on challenging cognitive tasks, based primarily on animal studies using non-EF tasks, has led some employers to intentionally stress their employees and some educators to intentionally stress their students. Yet evidence that stress improves the performance of both men and women on demanding cognitive tasks is quite hard to find. Although mild stress can sometimes aid the cognitive performance of males, it has almost never been found to aid females, which we take up in our paper in preparation on the effects of estradiol and progesterone in moderating how stress affects cognition.

It appears that to the extent that stress aids performance on cognitively demanding tasks, it is that extremely mild stress (as used here) can aid a minority of the population (those homozygous for COMT-Val^{158}). More severe mild stress has been found to impair COMT-Mets and help no one (COMT-Vals showed no benefit from stress; Buckert et al. 2012; Qin et al. 2012). Perhaps employers, supervisors, and teachers should rethink whether stress is really a good thing. Our results suggest that, while it is possible for stress to have a positive effect on higher cognitive function, only extremely mild stress seems to do that and even then it does it only for some.

We think it incorrect to equate arousal with stress. There is a difference between the excitement and exhilaration of being challenged or having one's interest greatly piqued, and the anxiety of feeling stressed. It is possible that most people will do better at cognitively demanding tasks if they care less about winning, "acing it," or impressing others, but do it instead for the sheer pleasure of doing it. Certainly there is evidence that pressure to perform well can be as detrimental to performance as intentionally imposing other stress (Putwain et al. 2010).

Our results may be specific to social evaluative stress. Feeling stressed because you are worried about what others might think of you or might think of your performance (social evaluative stress) does not appear to be beneficial to performance on demanding cognitive tasks for most people (except for COMT-Val^{158} homozygotes and then only if the social evaluative stress is quite mild). Fear of experiencing shame or embarrassment—or worrying about doing well in the eyes of others—does not appear to be conducive to EFs being at their best for most people most of the time. There appears to be an exceedingly narrow bandwidth for psychosocial stress having a facilitative effect on EFs both in terms of intensity of the stress and in terms of genotype. There are many different kinds of stress, though, and effects and time courses might well differ by type of stress.

Notes

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