Catechol-O-methyltransferase (COMT) genotype affects cognitive control during total sleep deprivation

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Abstract
Adaptive decision making is profoundly impaired by total sleep deprivation (TSD). This suggests that TSD impacts fronto-striatal pathways involved in cognitive control, where dopamine is a key neuromodulator. In the prefrontal cortex (PFC), dopamine is catabolized by the enzyme catechol-O-methyltransferase (COMT). A functional polymorphism (Val158Met) influences COMT’s enzymatic activity, resulting in markedly different levels of prefrontal dopamine. We investigated the effect of this polymorphism on adaptive decision making during TSD. Sixty-six healthy young adults participated in one of two in-laboratory studies. After a baseline day, subjects were randomized to either a TSD group (n=32) with 38 h or 62 h of extended wakefulness or a well-rested control group (n=34) with 10 h nighttime sleep opportunities. Subjects performed a go/no-go reversal learning (GNGr) task at well-rested baseline and again during TSD or equivalent control. During the task, subjects were required to learn stimulus—response relationships from accuracy feedback. The stimulus—response relationships were reversed halfway through the task, which required subjects to learn the new stimulus—response relationships from accuracy feedback. Performance on the GNGr task was quantified by discriminability ($d'$) between go and no-go stimuli before and after the stimulus—response reversal. GNGr performance did not differ between COMT genotypes when subjects were well-rested. However, TSD exposed a significant vulnerability to adaptive decision making impairment in subjects with the Val allele. Our results indicate that sleep deprivation degrades cognitive control through a fronto-striatal, dopaminergic mechanism.

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1. Introduction

Sleep deprivation affects neurobehavioral performance across a variety of cognitive domains in differential ways (Killgore, 2010; Lim & Dinges, 2010). There are large, trait-like inter-individual differences in cognitive responses to sleep deprivation (Van Dongen, Baynard, Maislin, & Dinges, 2004), underlain by systematic inter-individual differences in sleep/wake homeostasis (Rétey et al., 2006; Van Dongen, Bender & Dinges, 2012) and partially determined by a number of genetic variants (Bodennmann et al., 2012; Goel, Banks, Ling, Mignot, & Dinges, 2011; Satterfield, Wisor, Field, Schmidt, & Van Dongen, 2015; Viola et al., 2007). While the reasons why different cognitive functions are affected by sleep deprivation differentially have been discussed theoretically (Van Dongen, Belenky, & Krueger, 2011), they largely remain to be studied experimentally (Jackson et al., 2013).

Vigilant attention is among the cognitive functions most widely studied in this context. It is substantially degraded by total sleep deprivation (TSD), causing significant instability in performance (Doran, Van Dongen, & Dinges, 2001; Lim & Dinges, 2008). However, impairment in vigilant attention is dissociable from impairment in other aspects of cognition (Jackson et al., 2013; Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010). We recently demonstrated that adaptive decision making, in addition to – and distinct from – vigilant attention, is profoundly degraded by TSD (Whitney, Hinson, Jackson, & Van Dongen, 2015). This effect cannot be explained as a mere function of lapses in vigilant attention – we showed that masking as much as 40% of the feedback on the GNGr (simulating an overabundance of attentional lapses) did not produce the level of impairment on the GNGr that we saw during TSD (Whitney et al., 2015, supplement). The neurobiological mechanisms underlying the specific effect of sleep deprivation on adaptive decision making are as yet unknown.

Adaptive decision making requires cognitive control to balance cognitive stability – the ability to maintain task-relevant information in the focus of attention – with cognitive flexibility – the ability to update task-relevant information based on changes in contingencies, while at the same time suppressing irrelevant information in order to appropriately adapt behavior (Braver, 2012; Cools & Robbins, 2004). On a reversal learning task that requires adaptive decision making, we previously found that cognitive flexibility is considerably impacted by TSD, while stability is relatively maintained compared to well-rested baseline (Whitney et al., 2015). This finding points to the involvement of fronto-striatal pathways subserving cognitive control (Botvinick & Braver, 2015; Cole & Schneider, 2007; Cools, 2016; Klanker, Feenstra, Denys, Lo, & Tsing, 2013). Notably, damage to the orbital frontal cortex (OFC) results in impaired cognitive flexibility similar to our finding during TSD (Fellows, 2007; Frank & Claus, 2006).

Dopamine is a key neuromodulator in the fronto-striatal circuits involved in cognitive control (Floresco, Zhang, & Enomoto, 2009; Frank & Claus, 2006; Izquierdo et al., 2016; Klanker et al., 2013; Waltz, 2017). The prefrontal cortex (PFC) in particular is sensitive to fluctuations in dopamine, with marked downstream effects on cognitive performance. The association between PFC-mediated cognition and dopaminergic tone shows an inverted-U relationship (Cools & DeEsposito, 2011; Cools & Robbins, 2004; Fallon, Williams-Gray, Barker, Owen, & Hampshire, 2013). That is, both sub- and supra-optimal dopamine levels in the PFC and/or the striatum result in cognitive performance deficits. While this is readily noticeable in psychiatric and neurological disorders such as schizophrenia and Parkinson’s disease (Cools, Barker, Sahakian, & Robbins, 2001; Cools & Robbins, 2004; Tunbridge, Harrison, & Weinberger, 2006), it can also be observed in non-clinical populations as a consequence of genetic polymorphisms of the dopaminergic system (Klanker et al., 2013; Savitz, Solms, & Ramesar, 2006).

Within the PFC, dopamine levels are modulated by the enzyme catechol-O-methyltransferase (COMT). COMT is localized in the extrasynaptic spaces, where it metabolizes dopamine and renders it inactive (Chen et al., 2004; Savitz et al., 2006). The gene coding for COMT contains a single nucleotide polymorphism (SNP), which involves a valine (Val) to methionine (Met) substitution at codon 158 (Val158Met) (Lachman et al., 1996). The Met and Val alleles differentially affect COMT’s enzymatic activity and thus influence PFC dopamine levels. The Met allele reduces the enzymatic activity of COMT three-to four-fold relative to the Val allele, leading to increased dopamine availability (Chen et al., 2004; Lachman et al., 1996; Weinshilboum, Otterness, & Szumalanski, 1999). Associations between COMT Val158Met genotypes and differences in PFC functioning and cognitive performance under well-rested conditions have been well established (Cools & DeEsposito, 2011; Dickinson & Elvevåg, 2009; Klanker et al., 2013; Mione et al., 2015).

Altered dopaminergic signaling in fronto-striatal circuits that mediate cognitive control may be part of the mechanisms underlying the substantial impairment in adaptive decision making previously documented during TSD (Whitney et al., 2015). Here we investigate whether the COMT Val158Met polymorphism mediates the impact of TSD on adaptive decision making.

2. Methods

We assessed adaptive decision making during TSD using a reversal learning paradigm (Whitney et al., 2015). N = 66 subjects each participated in one of two in-laboratory studies. In each study, subjects were assigned to either a TSD group (n = 32) or a well-rested control group (n = 34). Subjects performed a go/no-go reversal learning (GNGr) task, measuring adaptive decision making, once at baseline and once during TSD or well-rested control. Subjects were grouped by COMT genotype to investigate genotype–phenotype relationships associated with impairment in adaptive decision making during TSD.

2.1. Subjects

N = 66 healthy young adults (26.2 ± 4.5 years; 27 females) participated in one of two in-laboratory studies conducted in the Sleep and Performance Research Center at Washington State University Spokane. Subjects underwent rigorous
screening procedures, which included physical examination, history, blood and urine chemistry, breathalyzer test, baseline polysomnography, and a battery of questionnaires (see supplemental material for further screening details).

The studies were approved by the Institutional Review Board (IRB) of Washington State University. Subjects provided written informed consent and were financially compensated for their time.

2.2. Study design

Study 1: Forty-one healthy young adults (26.5 ± 4.7 years; 17 females) participated in a 4-day (3-night) laboratory study. All subjects had one baseline day with a 10 h sleep opportunity (22:00–08:00). They were then randomized to either a TSD condition (n = 20) with 38 h of extended wakefulness followed by a 10 h recovery sleep opportunity (22:00–08:00) on the third night, or a well-rested control condition (n = 21) with a 10 h sleep opportunity (22:00–08:00) on both the second and third nights. The laboratory conditions are described in the supplemental material.

Subjects performed the GNGr task twice during the study, once at baseline (6 h awake) and again 24 h later during TSD (30 h awake) or well-rested control (6 h awake). Both task administrations occurred at 14:00. Two equivalent versions of the GNGr task, which differed only in the specific stimuli presented, were administered in randomized, counterbalanced order. The GNGr task was the first of three performance tasks in a larger test battery.

Additionally, subjects performed a 10 min psychomotor vigilance test (PVT; Lim & Dinges, 2008) as a measure of vigilant attention. The PVT was administered every 2–4 h during scheduled wakefulness. Here we used the PVT test bouts that were administered immediately prior to the GNGr, at 13:00 during baseline (5 h awake) and again 24 h later during SD (29 h awake) or well-rested control (5 h awake). See the supplemental material for a description of the PVT.

Study 1 has been described elsewhere (Chavali, Riedy, & Van Dongen, 2017), but the GNGr data and genotype–phenotype relationships presented here have not been published before.

Study 2: Twenty-five healthy young adults (25.8 ± 4.1 years; 10 females) participated in a 7-day (6-night) laboratory study. All subjects had two baseline days, each with a 10 h sleep opportunity (22:00–08:00). They were then randomized to either a TSD condition (n = 12) with 62 h of extended wakefulness or a well-rested control condition (n = 13) with two 10 h sleep opportunities (22:00–08:00). The study ended with two 10 h recovery sleep opportunities (22:00–08:00). The laboratory conditions are described in the supplemental material.

Subjects performed an abbreviated version of the GNGr task during the first day in the laboratory for practice. Following, subjects performed the GNGr task three times during the study, once at baseline (7 h awake), again 48 h later during TSD (55 h awake) or well-rested control (7 h awake), and again another 48 h later after recovery sleep. Each task administration occurred at 15:20. Three equivalent versions of the GNGr task, which differed only in the specific stimuli presented, where administered in randomized, counterbalanced order. Data from the third task administration (after recovery sleep) are not included here.

Subjects also performed a 10 min PVT every 2 h during scheduled wakefulness. Here we used the PVT test bouts that were administered immediately prior to the GNGr, at 15:00 during baseline (7 h awake) and again 48 h later during SD (55 h awake) or well-rested control (7 h awake). See supplemental material for a description of the PVT.

Study 2, including the GNGr data and subject sample, has been reported on previously (Whitney et al., 2015), but the genotype–phenotype relationships presented here have not been published before.

2.3. Reversal learning task

We employed a reversal learning task to measure adaptive decision making (Whitney et al., 2015). The specific task we used was a go/no-go reversal learning (GNGr) task, which was based on a standard go/no-go paradigm requiring subjects to respond to a specific set of stimuli (go stimuli) while withholding a response to a different set of stimuli (no-go stimuli). The probability of go and no-go stimuli was the same. Importantly, subjects were required to use accuracy feedback, provided in the form of hypothetical monetary gains and losses, to learn stimulus–response mappings. Additionally, approximately halfway through the task there was a reversal of contingencies, and subjects were to use accuracy feedback to learn the new stimulus–response mappings and adjust their response behavior.

Subjects performed the GNGr task on a desktop computer in their individual bedrooms. Prior to each task administration, subjects were presented with an instruction screen explaining how to perform the task. They were told that the goal of the task was to earn as much hypothetical money as possible. At the beginning of the task, four two-digit numbers were assigned to the go stimulus set and four two-digit numbers were assigned to the no-go stimulus set. Subjects were unaware of which numbers belonged to which stimulus set, and were required to learn the correct stimulus–response relationships from accuracy feedback. The reversal of the stimulus–response relationships approximately halfway through the task was not announced; subjects were required to discover the new stimulus–response relationships through accuracy feedback. See Fig. 1.

In both studies, subjects were given 4 practice trials at the beginning of each test bout, which were excluded from analysis. In study 1, subjects performed two versions of the GNGr, with either 56 or 64 pre-reversal trials. In study 2, subjects performed an additional version of the task, which had 60 pre-reversal trials. After the reversal, there were 40 post-reversal trials, regardless of the task version. For analysis purposes, data were grouped into 4 pre-reversal trial blocks (with 14, 15 or 16 trials in each block) and 4 post-reversal trial blocks (with 10 trials per block).

A signal detection framework (Stanislaw & Todorov, 1999) was used to calculate the discriminability index (d′) as a measure of subjects’ ability to discriminate between go and no-go stimuli. Hits and false alarms were assessed and used to calculate the d′ value for each pre-reversal and each post-reversal trial block. Each subject’s d′ values were used as the
primary outcome measure of GNGr performance. Hit and false alarm rates were considered as secondary outcome measures.

2.4. Genotyping

From each subject, a venous whole blood sample was collected in a Vacutainer tube coated with ethylenediaminetetraacetic dipotassium dihydrate (K2EDTA) during a pre-study screening session. The blood samples were aliquoted and immediately stored at −80 °C until time of analysis. Details of the assay for the Val158Met SNP are provided in the supplemental material.

2.5. Statistical analysis

The genotype distribution in our subject sample was examined for deviation from Hardy–Weinberg equilibrium using a χ² goodness-of-fit test. Logistic regression was used to test COMT genotypes in the sample for differences in gender and race/ethnicity distributions; one-way analysis of variance (ANOVA) was used to test for age differences.

The discriminability index, d’, was used as the primary outcome measure of GNGr task performance. Hit rate (percent of correct responses to go stimuli) and false alarm rate (percent of incorrect responses to no-go stimuli) were analyzed as secondary outcome measures. Data were aggregated (not averaged) across the four pre-reversal trial blocks (pre-reversal phase) and across the four post-reversal trial blocks (post-reversal phase), separately for each subject in each of the two studies. The first administration of the task, during baseline, was labeled session 1. As the experimental circumstances in the two study conditions (TSD and control) were identical at baseline, the session 1 data were pooled across the two conditions. The second administration of the task, during TSD or well-rested control, was labeled session 2. In our statistical analysis framework, the session 2 data were differentiated by condition. The same statistical framework was used for lapses (response times ≥ 500 ms) on the PVT (see supplemental material).

To analyze the primary and secondary outcome measures, therefore, mixed-effects ANOVA was used with fixed effects of session, by condition interaction, phase, session by phase interaction, and session by condition by phase interaction. In addition, fixed effects were included for COMT genotype (Met/Met, Val/Val), alone and in interaction with the other fixed effects (see Table S1). Because the duration of wakefulness during TSD was different between the two studies, study number was included as a covariate. GNGr task version was also included as a covariate. A random effect over subjects was placed on the intercept. The primary statistical outcome of interest was the interaction between condition and COMT genotype.

The mixed-effects ANOVA was repeated controlling for age, gender, race/ethnicity, and menstrual cycle, respectively, to confirm robustness of the results.

3. Results

The demographics and COMT Val158Met genotypes of our subject sample are shown in Table 1. The genotype distributions are presented in Table 2. The variant allele (Met) was in the subject population at a frequency of .48. The ancestral allele (Val) was in our subject population at a frequency of .52. The allele frequencies were found to be in Hardy–Weinberg equilibrium (χ²<.01, p = .99) and similar to those reported in the literature (Jawinski et al., 2016; Valomon et al., 2014). The genotype distributions did not vary significantly by age (F<2.63, p = .72), or race/ethnicity (χ²<2.19, p = .38).

Fig. 2 shows the discriminability index (d’) data for pre- and post-reversal performance on the GNGr task during session 1 (baseline) and session 2 (TSD or well-rested control), by COMT genotype. During session 1 (Fig. 2, left), GNGr performance was similar for all subjects, regardless of genotype. During session 2, however, marked genotype differences emerged in the TSD condition, as compared to the control condition (Fig. 2, right).

In the control group, all COMT genotypes showed improved performance during session 2 as compared to session 1, reflecting the practice effect previously observed for the GNGr task (Whitney et al., 2015). In the TSD group, subjects homozygous for the Met allele also showed improved performance, but subjects heterozygous or homozygous for the Val allele showed poor performance, both pre- and post-reversal, during session 2 as compared to session 1 (Fig. 2). We previously found that TSD causes considerable performance deficits on the GNGr task (Whitney et al., 2015). The present results reveal that the Met allele of COMT Val158Met provides resilience to this effect, while carriers of the Val allele are
particularly vulnerable. Especially in subjects homozygous for the Val allele, post-reversal performance was profoundly impacted, to the point of performing no better than chance. Our statistical results are shown in the supplemental material (Table S1). Focusing here on the primary statistical outcome of interest, there was a significant interaction between session 2 condition and COMT genotype ($F_{2,973} = 4.41, p = .012$), indicating that the COMT genotype effect was specific to TSD. Also, when the session 2 data were expressed relative to the session 1 (baseline) data, the same pattern of results was seen (see Fig. S1). The finding also held true when controlling for age, gender, race/ethnicity, and menstrual cycle. There were no statistically significant effects in the absence of TSD during session 1 (see Fig. S2). Analysis of hit rates and false alarm rates further confirmed our finding (see Fig. S3).

The proportion of variance explained by COMT genotype in GNGr pre-reversal performance impairment during TSD was 3.89%. Furthermore, the proportion of variance explained by COMT genotype in post-reversal performance impairment during TSD was as much as 8.35%. This is substantial compared to variance explained by gene polymorphisms during TSD as previously reported for vigilant attention (Satterfield et al., 2015).

### Table 1 – Subject demographics and COMT Val158Met genotypes.

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th></th>
<th>Study 2</th>
<th></th>
<th>Combined</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TSD</td>
<td>Control</td>
<td>Total</td>
<td>TSD</td>
<td>Control</td>
<td>Total</td>
</tr>
<tr>
<td><strong>n</strong></td>
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<td>41</td>
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<tr>
<td>Val/Val</td>
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<td>5</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

*a Subjects reporting more than one race were classified as mixed.

### Table 2 – COMT Val158Met genotype counts and frequencies in the overall sample.

<table>
<thead>
<tr>
<th>COMT Genotype</th>
<th>Met/Met</th>
<th>Val/Met</th>
<th>Val/Val</th>
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<tr>
<td><strong>Genotype count</strong></td>
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<tr>
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<tr>
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<td>.46</td>
<td>.22</td>
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</table>

*a Calculated based on Hardy–Weinberg equilibrium.<br>b Valomon et al. (2014), 115 healthy subjects.

![Fig. 2](image_url) Means (±standard errors) for the discriminability index ($d'$) on the GNGr task, pre- and post-reversal, as a function of COMT genotype. Left: session 1 (baseline), pooled over conditions ($N = 66$) as the experimental circumstances were identical. Right: session 2, differentiated between the well-rested control condition ($n = 34$) and the TSD condition ($n = 32$).
For vigilat attention performance on the PVT, in contrast with the results for adaptive decision making performance on the GNGr, subjects heterozygous for the COMT Val158Met polymorphism showed the greatest level of impairment during TSD (see Fig. S4).

4. Discussion

In this laboratory research, sleep deprivation revealed a considerable vulnerability in adaptive decision making for subjects with the Val allele of COMT Val158Met, either as heterozygotes or homozygotes (Fig. 2, right). There were no significant differences between genotypes at baseline during session 1 (Fig. 2, left, and Fig. S2) or in the well-rested control group during session 2 (Fig. 2, right). The impairment in the carriers of the Val allele was thus specific to TSD. Moreover, the same genotype effect was not seen for vigilant attention as measured with the PVT (Fig. S4). Thus, the impairment observed in the carriers of the Val allele elucidates the differential effect of sleep deprivation on adaptive decision making.

The amount of variance explained by COMT genotype for GNGr post-reversal performance impairment during TSD (i.e., 8.35%) is among the highest reported for any gene associated with sleep-deprived performance documented to date (see Satterfield et al., 2015). As such, our finding sheds new light on earlier work that suggested that COMT genotype has little impact on cognitive performance (Ihne et al., 2016) – a conclusion that was drawn based on observations made under baseline conditions. Our results suggest that with moderate sample sizes, a powerful intervention such as TSD (or, for example, transcranial direct current stimulation; Nieratschker, Kiefer, Giel, Krüger, & Plewnia, 2015), a relatively high prevalence of each of the genotypes (see Table 1), and a performance task that captures specifically relevant aspects of cognition (such as the GNGs), are key elements for a strong phenotype–genotype relationship as needed to expose a genotypic performance vulnerability.

Neuroimaging research has shown that the Val158Met polymorphism of the COMT gene influences cognitive control processes (Jaspar et al., 2013). COMT activity affects dopamine levels within the PFC (Chen et al., 2004; Savitz et al., 2006), which is a key part of the fronto-striatal circuitry subserving cognitive control (Botvinick & Braver, 2015; Cole & Schneider, 2007; Cools, 2016; Klanker et al., 2013). Dopamine is important in cortical and striatal circuits for modulating glutamatergic and GABAergic signaling by balancing inhibitory and excitatory actions (Winterer & Weinberger, 2004). Dopamine transmission within the PFC occurs through a dual-state function (Durstewitz & Seamans, 2008), where the low-activity Met allele of COMT Val158Met, which is associated with high dopamine availability, favors a D1 receptor-dominated state that promotes stability of information; whereas the high-activity Val allele, which is associated with low dopamine availability, favors a D2 receptor-dominated state that promotes fast updating of information and improves cognitive flexibility (Bilder, Volavka, Lachman, & Grace, 2004; Cools, 2016; Durstewitz & Seamans, 2008; Winterer & Weinberger, 2004).

The trade-off between cognitive stability and cognitive flexibility involves a delicate balance between PFC and striatal dopamine signaling (Cools, 2016; Cools & D’Esposito, 2011; Fallon et al., 2013). Our results suggest that TSD disrupts this balance, especially in carriers of the Val allele. Expressed in terms of the inverted-U relationship between PFC-mediated cognition and dopaminergic tone (Cools & D’Esposito, 2011; Cools & Robbins, 2004; Fallon et al., 2013), it appears that under conditions of TSD, the dopaminergic tone associated with the Val allele is no longer beneficial to cognitive flexibility, and the Met allele now promotes optimal dopaminergic tone for adaptive decision making.

5. Conclusion

Building on the earlier observation that TSD profoundly impairs the ability of subjects to effectively acquire information and adapt to changes in that information based on feedback (Whitney et al., 2015), we found that subjects vary substantially in their vulnerability to this effect based on COMT Val158Met genotype. This finding is consistent with the idea that altered dopaminergic signaling in fronto-striatal circuits mediating cognitive control may be part of the mechanisms underlying substantial impairment in adaptive decision making during TSD.

The ability to adapt to changes in situational demands are critical in operational settings, especially in safety-sensitive industries where sleep loss is pervasive. Because the ancestral Val allele is common in the general population (46.9% worldwide; Cross, Ivacic, Stefanski, & McCarty, 2010), the real-world implications of the vulnerability it confers to adaptive decision making impairment due to sleep loss are potentially substantial.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cortex.2017.11.012.


Fiorenzi, M. T., et al. (2015). Both the COMT Val158Met single-nucleotide polymorphism and sex-dependent differences


