Published in final edited form as:

Int J Psychophysiol. 2013 November ; 90(2): . doi:10.1016/j.ijpsycho.2013.06.023.

The Catechol-O-Methyltransferase Val¹⁵⁸Met Polymorphism Modulates Organization of Regional Cerebral Blood Flow Response to Working Memory in Adults

Alicia F. Heim^a, Melissa J. Coyne^b, M. Ilyas Kamboh^c, Christopher Ryan^d, and J. Richard Jennings^e

Alicia F. Heim: heimaf@upmc.edu; Melissa J. Coyne: melissaj.coyne@gmail.com; M. Ilyas Kamboh: kamboh@pitt.edu; Christopher Ryan: RyanCM@upmc.edu; J. Richard Jennings: Jenningsjr@upmc.edu

^aTDH E-1329 Psychophysiology Lab, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, Phone: 1-412-246-5420, Fax: 1-412-246-6210

^bTDH E-1329 Psychophysiology Lab, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America

^cDepartment of Human Genetics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, United States of America

^d713 Oxford Building, Forbes Ave., University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America

^eTDH E-1329 Psychophysiology Lab, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, Phone: 1-412-246-6220, Fax: 1-412-246-6210

Abstract

This study examined the effect of Catechol-O-Methyltransferase (COMT) Val¹⁵⁸Met genotypes on the co-activation of brain areas involved in cognition during a working memory (WM) task. The pattern of concomitant region of interest (ROI) activation during WM performance varied by genotype: Val/Val showing the least and Met/Met the most covariance. There were no differences of performance on the WM task between the COMT genotypes. However, relatively better performance was associated with less concomitance of dorsolateral prefrontal cortex (DLPFC) and cingulate cortex for Val/Val, but more concomitance of DLPFC with AH for Met/Met. Within genotypes WM performance was significantly correlated with rCBF to the amygdala/hippocampus (AH) for Val/Val ($r = 0.44$, $p = 0.009$), to the parietal lobe for Val/Met ($r = 0.29$, $p = 0.03$), and to the thalamus for Met/Met ($r = 0.32$, $p = 0.04$). Different genotypes showed different regional specificity and concomitant activation patterns suggesting that varying dopamine availability induces different brain processing pathways to achieve similar WM performance.

Keywords

Catechol-o-methyltransferase (COMT); Dopamine; Working Memory; PET

Working memory, a term first used by Miller, Galanter and Pribram (1960), is a construct that is central to both cognitive psychology and neuroscience. The concept of working memory proposes that there is a system which holds information “on-line” temporarily before it is translated to long-term memory, forgotten, or results in some kind of action. This information is then available to support other ongoing processing, e.g. keeping track of intermediate terms when doing mental arithmetic. The three-component model of working memory proposed by Baddeley and Hitch (1974) employs the executive controller, which focuses one’s attention, and two “slave” systems, the phonological loop and the visuospatial sketch pad, which hold “on-line” speech-based and visual information respectively. Working memory is an important construct that is thought to underlie higher cognitive function such as learning, language comprehension, planning and reasoning (Baddeley 1986). Working memory is closely related to executive functioning and its role in allocating attentional resources for the performance of cognitive tasks (Baddeley, 1996).

Goldman-Rakic (1996) was one of the first to describe the circuitry of the prefrontal cortex and its relationship to working memory. Working memory is typically associated with increased activation in the prefrontal cortex as well as the parietal lobe, though other brain areas are involved and different types of working memory tasks (N-back, delayed response, spatial, verbal etc.) have been shown to elicit differing patterns of activation in brain areas (Cabeza & Nyberg, 2000). The current study examined regional cerebral blood flow (rCBF) using positron emission tomography during a spatial n-back working memory task as a function of putative genetically-related variation in dopamine function.

Dopamine (DA) appears to be one of a number of neural transmitters that modulate brain processing during working memory (Brozoski, Brown, Rosvold, & Goldman, 1979; Cools, Gibbs, Miyakawa, Jagust, & D’Esposito, 2008; Dash, Moore, Kobori, & Runyan, 2007; Malhotra et al., 2002). Animal studies, which can assess dopamine rather directly, implicate a number of brain regions in the dopamine circuit that are relevant to memory and to the current investigation: the amygdala, the hippocampus (Peleg-Raibstein et al., 2005; Schacter & Wagner, 1999), the thalamus (Sánchez-González, García-Cabezas, Rico, & Cavada, 2005), and the prefrontal cortex (Schacter & Wagner, 1999). DA transmission from these subcortical brain regions to the PFC has been implicated in normal memory processes as well as in the modulation of attention (Peleg-Raibstein et al., 2005; Sánchez-González et al., 2005; Seamans, Floresco, & Phillips, 1998). Advances in technology permit inference of similar dopamine activity in human studies; e.g., hippocampal D2 dopamine receptors have been implicated in human working memory (Goto and Grace, 2008). Based on prior work, we selected the following regions of interest (ROI’s) from a group of previously determined ROI’s: the DLPFC, the thalamus, and the amygdala/hippocampus. Additionally, based on prior human findings, looking at working memory, the cingulate cortex (Bertolino et al., 2006b; Cladu et al., 2007; Egan et al., 2001) and the posterior parietal area (Cabeza & Nyberg, 2000; Gazzaley et al., 2004; Jennings, van der Veen, & Meltzer, 2006) were also included as ROI’s. Anterior cingulate activation may, however, reflect task difficulty rather than be specifically related to working memory (Cabeza & Nyberg 2000). In sum, these ROI choices were based on available ROI’s as well as prior literature suggesting that working memory is based on a coordinated interaction between a network of brain areas with a portion of the network showing modulation by dopamine (Gazzaley et al., 2004). (See: Bertolino et al., 2006b; Cabeza & Nyberg, 2000; Cladu et al., 2007; Hampson, Driesen, Skudlarski, Gore, & Constable, 2006; Owen, McMillan, Laird, & Bullmore, 2005). The ROI’s were then examined to investigate whether genetically related variation in dopamine availability might modulate coordinated functional activation in different networks supporting working memory—presumably networks differing in their dependence on functional dopaminergic circuitry.

Dopamine function has been shown to vary with the genetic COMT polymorphism-Val¹⁵⁸Met (Malhotra et al., 2002; Dickinson & Ellevåg, 2009). This polymorphism regulates the amount of COMT enzyme produced. The COMT enzyme degrades dopamine that is released in the brain; therefore variations in the amount of COMT enzyme directly influence the availability of dopamine in the brain. The functional polymorphism Val¹⁵⁸Met in the COMT gene codes for a substitution of methionine (Met) for valine (Val) at codon 158 (Malhotra et al., 2002). The Val allele produces a protein that has three to four times greater enzymatic activity than the protein produced by the Met allele (Männistö & Kaakkola, 1999). This means that those who are homozygous for the Val allele have increased COMT enzyme activity and therefore less dopamine availability; those who are homozygous for the Met allele have decreased COMT enzyme activity and higher levels of dopamine; and those who are heterozygous (Val/Met carriers) have COMT enzyme activity that lies somewhere between their homozygous counterparts (Egan et al., 2001; Raz, Dahle, Rodrigue, Kennedy, & Land, 2009).

Dopamine is dose-specific in relation to working memory in that stimulation of dopamine receptors in the PFC produces an inverted-U response whereby too much or too little dopamine inhibits cognitive performance (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). Additionally, it is hypothesized that the COMT Val¹⁵⁸Met polymorphism affects both tonic and phasic dopamine transmission which has been shown to influence cognitive flexibility and stability and thus working memory (Bilder, Volavka, Lachman, & Grace, 2004). Therefore, COMT enzyme activity likely is not simply or linearly related to performance on frontally-mediated cognitive tasks (Cools & D'Esposito, 2011; Egan et al., 2001; Malhotra et al., 2002; Raz et al., 2009; Stokes, Rhodes, Grasby, & Mehta, 2011).

The effect of the COMT Val¹⁵⁸Met polymorphism on working memory has been measured in various ways. A number of studies looking at schizophrenic patients as well as healthy controls have shown that subjects with the Val/Val genotype are less 'efficient' (greater activation in the PFC for the same level of performance) when performing working memory tasks than other genotypes (Bertolino et al., 2006a; Egan et al., 2001; Mattay et al., 2003; Mier, Kirsch, & Meyer-Lindenberg, 2010). Though this finding has been relatively consistent across patient populations as well as in healthy controls, the effect of the COMT polymorphism varies when investigating performance. Barnett, Scoriels and Munafò (2008) and Stefanis et al. (2004) found no association between COMT genotype and working memory performance during a n-back task, while Diaz-Asper et al. (2008) and Goldberg et al. (2003) found that subjects with the Val/Val genotype performed significantly less accurately during the 1-back task than the other two genotypes. A fixed effects analysis of seven studies that looked at n-back performance, however, indicated some association of better performance for subjects who are Val allele carriers, though this association did not remain significant when a random effects analysis was conducted (Barnett et al., 2008). Further complicating the literature, Wilko et al. (2010) found gender-specific effects; the Val/Val genotype was associated with significantly better performance than the other two genotypes, but only in males. These conflicting results have led to suggestions that factors such as anxiety may also play a role in the performance differences (Eysenck & Calvo, 1992). A further factor is task difficulty in that simple tasks may benefit from greater dopamine concentration than more complex task, i.e. an interaction between task requirements and processing changes induced by the inverted U relationship between dopamine and performance (Yerkes & Dodson, 1908).

The present study seeks to contribute to the existing literature by examining how genotype relates to the pattern of cerebral blood flow activation across areas known to relate to DA and working memory in hopes of uncovering a possible explanation for the variability in performance seen across COMT genotypes in the literature. Dopamine availability may

modulate brain areas-- reorganizing the working memory processing such that different genotypes may be associated with different processing streams that have different sensitivities to task characteristics. Such differential sensitivity to task characteristics might underlie the variability in performance/genotype relationships that have previously been observed. We examined the effect of different Val¹⁵⁸Met genotypes on the co-activation of brain areas involved in cognition during a 2-back working memory task in a sample of normal, reasonably healthy individuals. Prior publications on the same data set have reported the consistency of working memory brain activations with prior work on the 2-back task as well as reported an overall relationship between performance data and degree of rCBF activation in the posterior parietal cortex (Jennings et al. 2005, Jennings et al. 2006). The current report focuses on the genetic modulation of the relationship of brain blood flow and working memory.

Methods

Participants

Existing data from two studies were used to examine the relationship of the COMT polymorphism to Positron Emission Tomography (PET) derived cerebral blood flow. A database was formed from common measures taken from two imaging studies that focused on the influence of blood pressure levels on cognitive and cerebral function (Jennings et al., 2005, Jennings et al., 2006). Subjects were between 35–70 years old and selected for either normotensive levels of blood pressure or early stage hypertension. High levels of blood pressure, serious chronic disease, and prescription medication use influencing neural or cardiovascular function (including anti-hypertensive medications) served as exclusion criteria (see details in Jennings et al., 2005; Jennings et al., 2006). All participants provided informed consent that was approved by the Institutional Review Board of the University of Pittsburgh. The current report focuses on 129 individuals for whom data were available for brain imaging, COMT genotype, and cognitive performance.

In both studies testing consisted of background psychometric, neuropsychological, demographic measures, and a PET brain imaging session. Working memory performance was evaluated from a spatial 2-back task performed in the scanner. A nonparametric signal detection measure, A' , was used to assess accuracy of performance on this task (Grier, 1972). This measure incorporates both the hit rate (number of target items correctly identified) and the false-alarm rate (number of non-targets falsely identified as targets), (Grier, 1972).

The brain imaging session for both studies included a spatial 2-back task in which the participant was required to press a button if the spatial location of a letter on a computer screen was identical to the letter location from two screens ago ("target"). An alternate button was pressed if the current letter's spatial location did not match ("non-target"). This requires the maintenance in memory of the two prior locations as well as the current one. Each letter was presented for 400 milliseconds followed by a 1,600 millisecond pause before the next letter was presented. rCBF of two 5-minute trials of this task were compared to the rCBF of two comparable trials of a control task with minimal memory load—pressing the left most button if the letter was on the left of the screen, the right button if on the right of the screen.

Genetics

COMT genotyping was performed as described previously (Bergman-Jungeström & Wingren, 2001). Participants were classified into one of three COMT genotype categories:

homozygous for the Met allele- (Met/Met), homozygous for the Val allele- (Val/Val) or heterozygous- (Val/Met).

PET technique

PET scans were obtained in three-dimensional imaging mode using a Siemens/CTI ECAT HR+ PED scanner (63 transaxial planes, 2.4mm slice thickness; Munich, Germany). Participants were positioned in the scanner so that the glabellar-inion line was parallel to the axis of the scanner. Additionally, participants were fitted with a short 21-gauge radial arterial catheter and an IV line for the injection of ^{15}O water. A 10-minute transmission scan using rotating $^{68}\text{Ge}/^{68}\text{Ga}$ rods was performed for attenuation calculations. Estimates of rCBF were measured during each task by recording the cerebral-radioactivity distribution of a 11- or 7-mCi bolus of freely diffusible ^{15}O water, which was injected 30s after the initiation of each task. Beginning with each bolus injection, a 180s scan, divided into 20 sequential frames, was obtained during each task. Each scan was followed by a 7-min rest period for a total of 10-min between injections. The PET data were corrected for radioactive decay, photon attenuation and scatter. Reconstructed image resolution was 7.1mm (transverse) and 6.7mm (axial). All PET images were corrected for small head movements using Automated Image Registration (Woods, Mazziotta, & Cherry, 1993).

The PET rCBF was assessed based on pre-assigned regions of interest (ROI). ROIs were defined prior to data collection based on prior findings of association with working memory, sensitivity to hypertension, and cerebrovascular ‘watershed’ areas. ROI’s used in the current analysis were only those selected for relationship to working memory and hence possible sensitivity to dopamine. We report the mean rCBF blood flow during the 2-back task for the selected regions: amygdala-hippocampus (level of temporal horn of lateral ventricles), dorsolateral prefrontal cortex (medial aspect of Brodmann area [BA] 9 superior to lateral ventricles), anterior cingulate (level of lateral ventricles (BA24, 32), posterior parietal (BA39 and BA40 superior to lateral ventricles), and thalamus (at the level of the splenium and genu of the corpus callosum), as well as the change in blood flow for the 2-back task relative to the control task. All analyses used change in rCBF between the 2-back and control condition with the exception of the reported rCBF means shown in Table 2. Total CBF was estimated from multiple circular sampling areas encompassing grey matter areas at three different levels. Overall activation in response to the 2 back task for these ROI’s is reported in Jennings, van der Veen, and Meltzer (2006).

ROI’s were outlined by hand on the four slices that captured the selected brain areas by experienced technicians. Figure 1 illustrates placement of the ROI’s. Positron counts within these regions were modeled with a two compartment model that yielded estimates of rCBF taking into account time delays and outflow (Price et al., 2002; Iida et al., 1988). Positron counts were derived from the ROI’s for each individual participant and the rCBF for each ROI then composed the data points for subsequent statistical analysis.

Analysis

COMT genotype, (Val/Val, Val/Met, Met/Met), served as a grouping variable in the analyses of variance focusing on cognitive performance and rCBF measures. Age, blood pressure, and education covariates were added in the analyses implemented as a general linear model using both univariate and multivariate dependent measures. Age, education, and blood pressures to a lesser degree have well accepted influences on cognitive performance which we wished to examine in conjunction with the cortical changes. Pearson product moment correlations were computed to assess the relationship of rCBF to performance as well as the relationship among the rCBF measures during task activation. Correlations between areas are conceptually similar to functional connectivity common in

MRI research. Our correlations show areas that show similar blood flow changes during the task challenge across the genetic groups and within the genetic groups. The analyses cannot reveal any anatomical connectivity, but rather a functional similarity, i.e. the same situation as with MRI functional connectivity. Our correlations are based on quantitative flow indices in a priori defined regions of interest—as such, experiment wise capitalization on chance is much less likely using our PET indices. Analyses, including analyses of differences between correlations, were performed in Statistica 10 (Statsoft, Oklahoma City, OK).

Multiple comparison issues were addressed by limiting the analysis of the COMT polymorphism to the pre-determined ROI's from the brain imaging. Correlation analyses were checked to ensure that more correlations (or differences between correlations) were significant than would be expected by chance using the .05 significance level. This was uniformly the case.

Results

Demographic Data

One-way analyses of variance (or chi-square test) over genotype (Val/Val, Val/Met, Met/Met) showed the comparability of basic features of the three groups (Table 1). Differences were minimal. Despite initial data collection selection based on blood pressure status, the sample remained reflective of the general population. The proportion of subjects with hypertension in our sample is not significantly different than that of the general population, test for difference between proportions, $p = .35$ based on age-appropriate comparison of proportion of hypertensives in our sample and in the national sample, Table 70 (National Center for Health Statistics, 2011). An assessment of the distribution of the Val¹⁵⁸Met polymorphism across participants confirmed that the polymorphism was in Hardy-Weinberg equilibrium ($\chi^2(2, 129) = 2.84, p > .05$).

Blood Flow

Table 2 presents mean rCBF during the 2-back task as well as the change in rCBF during the 2-back task relative to the control task as a function of genotype as well as across genotypes. Differences due to genotype were not significant (F 's (12, 220) = 1.1–1.2, p 's $> .3$) in the analyses of variance performed. The multivariate analyses of variance, however, did yield a significant effect of age ($F(7,82) = 2.1, p < .05$). Due to this the interaction of age and genotype was assessed individually for the blood flow change in each ROI. In no case, however, did either the main effect of genotype (F 's (2,117) = .1 to 1.9, ns) or the age by genotype interaction (F 's (4,117) = .3 to .9, ns) prove to be statistically significant.

Age Sensitivity

Due to the observations in this data set and others of the influence of age, we repeated subsequent analyses with a subsample constrained to fall into a smaller age range than our overall sample. Changes in the results within the subsample would suggest that characteristics of either the younger or more elderly individuals in our sample were altering the pattern of results. For the subsample we narrowed our age range to include only those individuals within 1 standard deviation from the mean age (mean = 58.1 $\pm$ $SD = 7$). No qualitative or statistically significant differences were observed between the results obtained below and the results obtained for the restricted age subsample.

Working Memory Performance

The different COMT genotypes did not significantly differ in accuracy of performance on the 2-back task used in the scanner. The non-parametric measure of accuracy, A was .86 (.03) for Val/Val, .84 (.02) for Val/Met, and .82 (.02) for Met/Met.

Analyses of the correlation between working memory performance in the scanner and regional cerebral blood flow (rCBF) activation (change between 2-back and control tasks) for different COMT genotypes showed relationships within genotype for different cerebral areas. Table 3 shows that participants who are Val homozygotes showed a significant correlation between performance and amygdala/hippocampus activation. Heterozygotes showed a significant correlation between performance and the parietal area blood flow change. Met homozygotes showed a correlation for the thalamic area. Descriptively, the pattern of correlations was more similar between Val/Met and Met/Met genotypes relative to the Val/Val correlations. Differences between correlations for the three genotypes were not, however, statistically significant.

Correlations in Blood Flow between Brain Areas of Interest

Correlations between changes in rCBF activation in the ROI's were examined to determine if activation during working memory elicited region specific activations for some genotypes but correlated activation between regions for others. Correlations between areas were generally high (all significant, $p < .05$), but significant differences among the genotypes are evident. Relative to the other genotypes, the Val homozygotes was characterized by less correlation between areas during working memory performance. The Met homozygotes showed correlated flows related to limbic areas: blood flow change in the dorsolateral prefrontal cortex (DLPFC) was related to blood flow in the limbic anterior cingulate ($r = .82$) and amygdala/hippocampus ($r = .83$) ROI's. Anterior cingulate blood flow change also correlated with thalamic flow change ($r = .74$) for the Met homozygotes. In contrast, the Val/Met genotype showed strong correlations between DLPFC and parietal areas ($r = .83$) as well as DLPFC and thalamic areas ($r = .84$).

Additionally, within correlated regions, significant differences among the genotypes are evident. Correlations between the AH/DLPFC for Met homozygotes is significantly greater than that of Val/Met ($p < .05$) or Val/Val ($p < .01$). For cingulate/DLPFC and cingulate/thalamus the correlation is significantly greater for Met/Met than Val/Met ($p < .01$). For parietal/DLPFC the correlation is significantly greater for Val/Met than Met/Met ($p < .05$). For the thalamus/DLPFC the correlation is significantly greater for Val/Met than Val/Val ($p < .05$) (Table 4, Figure 2). The relationship between the cingulate cortex and DLPFC is illustrated in Figure 3 for the separate COMT polymorphism genotypes.

Performance and Coordination of Activation

The differences between genotypes in the degree to which brain areas were co-activated raised the question of whether co-activation was associated with better or poorer memory performance. This question was addressed by relating the absolute difference between the rCBF responses of different ROI's to performance on the 2-back memory task, separately for each genotype. The absolute difference was taken to permit region specific activation for an individual to be assessed, i.e. regions could differ by being relatively less or more active in comparison to showing similar activation. In order to reduce the influence of extreme values, correlations were computed on the natural logarithm of the absolute difference between the change scores for the two areas. Positive correlations indicate that better memory performance was related to a greater difference in the responsivity (more region specific activation) of the two areas. Negative correlations indicate that better memory performance was related to less difference in degree of response (less region specific activation) between brain areas (i.e., greater coordination of level of response). Significant differences between genotypes were shown; for example, greater regional specificity of response level between the DLPFC and cingulate was significantly related to better performance for the Val/Val genotype ($r = .40$) but not for the Val/Met genotype ($r = -.29$). Greater regional specificity of response level between the DLPFC and amygdala/

hippocampus was associated with better performance for Met/Met homozygotes ($r = .44$) but not for Val/Val homozygotes ($r = -.28$). Additionally, within genotypes, for Val/Val, better memory performance was associated with greater regional specificity of response level between the DLPFC and the cingulate ($r = .40$) and with less specificity (greater communality) of response level between the DLPFC and the AH ($r = -.28$). For Met/Met the opposite is true: less specificity of response level between the DLPFC and the cingulate ($r = -.13$) is related to better 2-back task performance, whereas greater specificity of response level between the DLPFC and AH ($r = .44$) is related to better 2-back task performance. Table 5 presents these results with the associated statistical differences indicated. Note that correlations over the entire sample ignoring genotype were not statistically significant. Across genotypes correlations were $r = .10$ for cingulate to DLPFC, $r = .19$ for amygdala/hippocampus to DLPFC, $r = .13$ for parietal for DLPFC and $r = .02$ for AH to thalamus.

Discussion

We examined the Val¹⁵⁸Met COMT polymorphism modulation of working memory and the brain activation underlying this process. Each genotype was characterized by a different pattern of concomitant brain area activation and a different relationship to working memory performance. The current study, however, failed to replicate previous findings of differences in activation across COMT genotypes during working memory tasks. ROI's were examined that had been previously related to working memory; these included the amygdala/hippocampus, the DLPFC, the cingulate cortex, the posterior parietal, and the thalamus (Jennings et al., 2006; Hampson et al., 2006; Owen et al., 2005).

Integrating the results from our analyses suggests a differential engagement of portions of the brain's dopamine circuitry that depends on the Val¹⁵⁸Met COMT polymorphism. This is evident in that although performance and activation did not differ significantly across genotype, the activation required to achieve the observed similar level of performance did differ within genotype.

Dopamine availability was related to the degree of concomitant activation of brain areas during performance. Concomitant activation was highest for the Met homozygote in which COMT activity is relatively less than in the Val/Met and Val/Val groups. The Val/Val genotype showed generally the least concomitant activation, such co-activation was low in dopamine-related areas, although hippocampal activation was independently related to working memory performance. In contrast, the greater dopamine availability within the Met/Met group seemed to bias toward shared processing within dopamine-related areas, perhaps, via basal ganglion loop activity as indicated by the thalamic to performance correlation.

A number of studies have shown COMT's modulation of functional connectivity (conceptually similar to the correlational approach with PET ROI's used in this analysis) between brain regions during task performance (Drabant et al., 2006; Sambataro et al., 2009). In a relevant article focusing on two age extremes that used functional magnetic resonance imaging and a 1-back task, Sambataro et al. (2009) showed similar results for coordination between various brain areas and the PFC, though differed in results looking only at DLPFC activation. They showed COMT genotype to modulate activation in BA 9 during a 1-back working memory task with Val homozygotes showing greatest activation followed by Val/Met then Met/Met (Sambataro et al., 2009). Though there is some overlap between this area and our DLPFC ROI, we did not find the same pattern of COMT genotype modulation of activation (see Table 2).

However, like Sambataro et al. (2009) we showed the least coordination of activation between the DLPFC and the parietal for Met/Met carriers. Additionally, we also found

coordination of activation between the cingulate cortex and the DLPFC is highest in the Met/Met genotype. However, unlike Sambataro and colleagues we did not find the same pattern of Met load effect (i.e. greater activation for Val/Val > Val/Met > Met/Met for DLPFC-parietal coordination, and greater activation for Met/Met > Val/Met > Val/Val for cingulate-DLPFC coordination). While our two studies show substantial methodological differences, e.g., PET relative to MRI, age span examined, specific task employed, whole brain voxel relative to pre-specified ROIs, the general trend of the overlapping findings support the COMT genotype modulation of brain activity underlying working memory.

The relationship between dopamine availability and working memory performance, however, continues to challenge interpretation. One attempt to integrate the seemingly disparate results in the literature may be helpful in understanding our results; De Frias et al. (2010), proposed a tonic/phasic DA hypothesis. This suggests a tonically greater availability of dopamine in the Met/Met carriers with phasic activation characterizing the Val allele. Met allele carriers have increased tonic dopamine stimulation of cortical D₁ receptors which stabilizes and maintains relevant information. Val allele carriers have a selective decrease in tonic dopamine subcortically, which results in activation of phasic dopamine transmission known to be associated with the updating and manipulating of information (cognitive flexibility) (de Frias et al., 2010; Rosa, Dickinson, Apud, Weinberger & Elvevåg, 2010).

For Val/Val homozygotes the increased activation in the amygdala/hippocampus thus may modulate 2-back task accuracy via hippocampal D₂ receptors and the hippocampal-PFC pathway (de Frias et al., 2010; Goto & Grace, 2008). That is, a specific phasic activation largely independent of other dopamine-related areas determines task accuracy—an interpretation consistent with phasic demands of the 2-back task that requires continual updating of three memory items.

In the presence of high amounts of dopamine (as is the case for those with the Met/Met genotype), processing via a network of areas seems to occur-- with the efficiency of this modulated by the shared thalamic activation. Met allele carriers have consistently shown heightened reactivity and connectivity in corticolimbic circuits (Drabant et al., 2006). We have replicated the MRI assessed connectivity findings with our theoretically similar correlational analyses of our PET data and found a trend for similarly heightened reactivity among Met carriers (trends in Table 2, Wilks = .85, $F = 1.76$, $df = 10, 204$, $p = .07$). However, we failed to show the specifically heightened hippocampal activation reported by de Frias et al. (2010) for the Met allele during a 2-back task. We did observe that the degree of amygdala/hippocampal activation did modulate accuracy as did the specificity of this change vis a vis the DLPFC.

The intermediate Val/Met genotype shows functional link between the dopamine-related prefrontal cortex and the posterior parietal cortex. Interestingly in the absence of genetic data, working memory is often associated with DLPFC and posterior parietal activation-- with performance most closely related to parietal change, e.g., Jennings et al., 2006. The DLPFC is highly involved in the dopamine circuit (Li, Cullen, Anwyl, & Rowan, 2003; Schacter & Wagner, 1999). This is evident in both the performance correlation in the Val/Met group as well as its general concomitance with other areas (Table 4). Our results are, of course, mute on whether dopamine availability initiated the differences in brain processing patterns or whether these patterns initiated the differences in dopamine.

There are a number of limitations in this study. We assessed a single COMT polymorphism; it is likely however that multiple polymorphisms contribute to working memory maintenance and performance. We were also only able to observe one working memory task during the PET scan, the spatial 2-back task and the processing requirement of different

tasks likely modulate relationships with dopamine availability. The broad age range (35–70 years old) in this study may have complicated the findings as DA levels are known to vary with age. However, there was not a significant age difference between genotypes and a sensitivity analysis examining only 51 to 65 year olds showed no differences from the overall results. The samples were drawn to compare normotensive and mildly hypertensive individuals; individual with later stage hypertension were excluded. Generalization is thus limited to those in the normotensive to mild hypertensive range. Finally, the current research was restricted to pre-selected ROI's limiting our coverage of the brain and excluding some relevant areas with known associations to COMT, DA, and working memory e.g., striatal regions). This reduces our expected experiment-wise error but raises the possibility of significant brain changes that were missed in our analyses. The number of significant correlations and differences between correlations in our primary analyses exceeded that expected by chance. Despite this, replication remains the strongest test of the robustness of results such as those we have presented.

Conclusion

Our results suggest that genetic variation in dopamine regulation relates to the organization of brain processing for working memory. Differential activation and co-activation of brain areas are associated with working memory performance for the different COMT Val¹⁵⁸Met genotypes, though there were no differences in activation across genotypes. Although 2-back performance was similar, different genotypes showed different regional specificity and concomitant activation patterns suggesting that varying dopamine availability induces different brain processing pathways to achieve comparable WM performance. Our findings reveal complex interactions which we may have only imperfectly captured. In general, the effect of the COMT polymorphism on working memory may appear inconsistent due to complex interactions with age, type of task, and the action of other genes (Raz et al., 2009). Future research will be able to provide a more accurate picture of the interactions between these important brain areas and the influence of dopamine via COMT on working memory performance.

Acknowledgments

We acknowledge the grant support of NHLBI HL57529, NHLBI HL101959 and NIA AG03653. This report is based on a larger project with additional primary contributions by Dr. Matthew Muldoon, Julie Price, and Dr. Carolyn C. Meltzer. Study sponsors did not have a direct role in this study.

Abbreviations

COMT	Catechol-O-Methyltransferase
DLPFC	dorsolateral prefrontal cortex
AH	amygdala/hippocampus
WM	working memory
DA	dopamine
ROI	region of interest

References

- Baddeley, AD.; Hitch, G. Working memory. In: Bower, GA., editor. *The Psychology of Learning and Motivation*. Academic Press; 1974. p. 48-79.
- Baddeley, AD. *Working Memory*. Oxford Univ. Press; New York, USA: 1986.

- Baddeley AD. Exploring the central executive. *Q J Exp Psychol.* 1996; 49A:5–28.
- Barnett JH, Scoriels L, Munafò MR. Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. *Biol Psychiatry.* 2008; 64:137–144.10.1016/j.biopsych.2008.01.005 [PubMed: 18339359]
- Bergman-Jungeström M, Wingren S. Catechol-O-methyltransferase (COMT) gene polymorphism and breast cancer risk in young women. *Br J Cancer.* 2001; 85:859–62. 10.1054/bjoc.2001.2009. [PubMed: 11556837]
- Bertolino A, Caforio G, Petruzzella V, Latorre V, Rubino V, Dimalta S, Scarabino T. Prefrontal dysfunction in schizophrenia controlling for COMT Val185Met genotype and working memory performance. *Psychiat Res-Neuroim.* 2006a; 147:221–226.10.1016/j.psychres.2006.04.001
- Bertolino A, Blasi G, Latorre V, Rubino V, Rampino A, Sinibaldi L, Dallapiccola B. Additive effects of genetic variation in dopamine regulating genes on working memory cortical activity in human brain. *J Neurosci.* 2006b; 26:3918–3922.10.1523/jneurosci.4975-05.2006 [PubMed: 16611807]
- Bilder RM, Volavka J, Lachman HM, Grace AA. Catechol-o-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology.* 2004; 29:1943–1961.10.1038/sj.npp.1300542 [PubMed: 15305167]
- Brozoski TJ, Brown R, Rosvold HE, Goldman PS. Cognitive deficit caused by regional depletion of dopamine in the prefrontal cortex of rhesus monkeys. *Sci.* 1979; 205:929–931.10.1126/science.112679
- Cabeza R, Nyberg L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci.* 2000; 12:1–47. [PubMed: 10769304]
- Caldú X, Vendrell P, Bartrés-Faz D, Clemente I, Bargalló N, Jurado MA, Junqué C. Impact of the COMT Val(108/158) Met and DAT genotypes on prefrontal function in healthy subjects. *Neuroimage.* 2007; 37:1437–1444.10.1016/j.neuroimage.2007.06.021 [PubMed: 17689985]
- Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biol Psychol.* 2011; 69:e113, e125.10.1016/j.biopsych.2011.03.028
- Cools R, Gibbs SE, Miyakawa A, Jagust W, D'Esposito M. Working memory capacity predicts dopamine synthesis capacity in the human striatum. *J Neurosci.* 2008; 28:1208–1212.10.1523/jneurosci.4475-07.2008 [PubMed: 18234898]
- Dash PK, Moore AN, Kobori N, Runyan JD. Molecular activity underlying working memory. *Learn Mem.* 2007; 14:554–563.10.1101/lm.558707 [PubMed: 17690339]
- de Frias CM, Marklund P, Eriksson E, Larsson A, Oman L, Annerbrink K, Nyberg L. Influence of COMT gene polymorphism on fMRI-assessed sustained and transient activity during a working memory task. *J Cogn Neurosci.* 2010; 22:1614–1622. [PubMed: 19642882]
- Diaz-Asper CM, Goldberg TE, Kolachana BS, Straub RE, Egan MF, Weinberger DR. Genetic variation in catechol-o-methyltransferase: Effects on working memory in schizophrenic patients, their siblings and healthy controls. *Biol Psychiatry.* 2008; 63:72–79.10.1016/j.biopsych.2007.03.031 [PubMed: 17707347]
- Dickinson D, Eilivåg B. Genes, cognition and brain through a COMT lens. *Neurosci.* 2009; 164:72–87.10.1016/j.neuroscience.2009.05.014
- Drabant EM, Hariri AR, Meyer-Lindenberg A, Munoz KE, Mattay VS, Kolachana BS, Weinberger DR. Catechol-O-methyltransferase Val¹⁵⁸Met genotype and neural mechanisms related to affective arousal and regulation. *Arch Gen Psychiatry.* 2006; 63:1396–1406. [PubMed: 17146014]
- Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Weinberger DR. Effect of COMT Val 108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Nat Acad Sci U S A.* 2001; 98:6917–6922.10.1073/pnas.111134598
- Eysenck M, Calvo M. Anxiety and performance: The processing efficiency theory. *Cogn Emot.* 1992; 6:409–434.10.1080/02699939208409696
- Gazzaley A, Rissman J, D'Esposito M. Functional connectivity during working memory maintenance. *Cogn Affect Behav Neurosci.* 2004; 4:580–99. [PubMed: 15849899]
- Grier JB. Nonparametric indexes for sensitivity and bias: Computing formulas. *Psychol Bull.* 1972; 75:424–429. [PubMed: 5580548]
- Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Weinberger DR. Executive subprocesses in working memory: Relationship to catechol-O-methyltransferase

- Val158Met genotype and Schizophrenia. *Arch Gen Psychiatry*. 2003; 60:889–896. [PubMed: 12963670]
- Goldman-Rakic PS. Regional and cellular fractionation of working memory. *Proc Natl Acad Sci*. 1996; 93:13473–13480. [PubMed: 8942959]
- Goto Y, Grace AA. Dopamine modulation of hippocampal-prefrontal cortical interaction drives memory-guided behavior. *Cereb Cortex*. 2008; 18:1407–1414.10.1093/cercor/bhm172 [PubMed: 17934187]
- Hampson M, Driesen N, Skudlarski P, Gore J, Constable R. Brain connectivity related to working memory performance. *J Neurosci*. 2006; 26:13338–13343. 10.1523/JNEUROSCI.3408-06.2006. [PubMed: 17182784]
- Iida H, Higano S, Tomura N, et al. Evaluation of regional differences of tracer appearance in cerebral tissues using [15O]water and dynamic positron emission tomography. *J Cereb Blood Flow Metab*. 1988; 8:285–288. [PubMed: 3257762]
- Jennings JR, van der Veen FM, Meltzer CC. Verbal and spatial working memory in older individuals: A positron emission tomography study. *Brain Res*. 2006; 1092:177–189.10.1016/j.brainres.2006.03.077 [PubMed: 16709401]
- Jennings JR, Muldoon MF, Ryan C, Price JC, Greer P, Sutton-Tyrell K, Meltzer CC. Reduced cerebral blood flow response and compensation among patients with untreated hypertension. *Neurol*. 2005; 64:1358–1365.10.1212/01.WNL.0000158283.28251.3C
- Li S, Cullen WK, Anwyl R, Rowan MJ. Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. *Nat Neurosci*. 2003; 6:526–531.10.1038/nn1049 [PubMed: 12704392]
- Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *Am J Psychiatry*. 2002; 159:652–654.10.1176/appi.ajp.159.4.652 [PubMed: 11925305]
- Männistö PT, Kaakkola S. Catechol-O-methyltransferase (COMT): Biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. *Pharmacol Rev*. 1999; 51:593–628. [PubMed: 10581325]
- Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Weinberger DR. Catechol-O-methyltransferase Val-158-Met genotype and individual variation in the brain response to amphetamine. *Proc Nat Acad Sci U S A*. 2003; 100:6186–6191.10.1073/pnas.0931309100
- Mier D, Kirsch P, Meyer-Lindenberg A. Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. *Molecular Psychiatry*. 2010; 15:918–927. [PubMed: 19417742]
- Miller, GA.; Galanter, E.; Pribram, KH. *Plans and the structure of behavior*. New York: Holt, Rinehart, & Winston; 1960.
- National Center for Health Statistics. *Health, United States. With special feature on Socioeconomic status and health*. Hyattsville; Maryland: 2011. 2012
- Nelson, HE. *National Adult Reading Test (NART): Test Manual*. Windsor: NFER- Nelson; 1982.
- Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp*. 2005; 25:46–59.10.1002/hbm.20131 [PubMed: 15846822]
- Peleg-Raibstein D, Pezze MA, Ferger B, Zhang WN, Murphy CA, Feldon J, Bast T. Activation of dopaminergic neurotransmission in the medial prefrontal cortex by N-methyl-D-aspartate stimulation of the ventral hippocampus in rats. *Neurosci*. 2005; 132:219–232.10.1016/j.neuroscience.2004.12.016
- Price JC, Drevets WC, Ruszkiewicz J, et al. Sequential [15O]water PET studies in baboons: pre- and post-amphetamine. *J Nucl Med*. 2002; 43:1090–1100. [PubMed: 12163636]
- Raz N, Dahle CL, Rodrigue KM, Kennedy KM, Land S. Effects of age, genes, and pulse pressure on executive functions in healthy adults. *Neurobiol Aging*. 2009; 32:1124–1137.10.1016/j.neurobiolaging.2009.05.015 [PubMed: 19559505]
- Rosa EC, Dickinson D, Apud J, Weinberger DR, Elvevåg B. COMT Val158Met polymorphism, cognitive stability and cognitive flexibility: an experimental examination. *Behav Brain Funct*. 2010; 6.10.1186/1744-9081-6-53 [PubMed: 20205779]

- Sambataro F, Reed JD, Murty VP, Das S, Tan HY, Callicott JH, Mattay VS. Catechol-o-methyltransferase val158methionine polymorphism modulates brain networks underlying working memory across adulthood. *Biol Psychiatry*. 2009; 66:540–548.10.1016/j.biopsych.2009.04.014 [PubMed: 19539269]
- Sánchez-González MA, García-Cabezas MA, Rico B, Cavada C. The primate thalamus is a key target for brain dopamine. *J Neurosci*. 2005; 25:6076–6083.10.1523/JNEUROSCI.0968-05.2005 [PubMed: 15987937]
- Schacter DL, Wagner AD. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus*. 1999; 9:7–24. [PubMed: 10088896]
- Seamans JK, Floresco SB, Phillips. D1 receptor modulation of hippocampal- prefrontal cortical circuits integrating spatial memory with executive functions in the rat. *J Neurosci*. 1998; 18:1613–1621. [PubMed: 9454866]
- StatSoft, Inc. STATISTICA (data analysis software system), version 10. 2011. www.statsoft.com
- Stefanis NC, Van Os J, Avramopoulos D, Smyrnis N, Evdokimidis I, Hantoumi I, Stefanis CN. Variation in catechol-o-methyltransferase val158met genotype associated with schizotypy but not cognition: A population study in 543 young men. *Biol Psychiatry*. 2004; 56:510–515.10.1016/j.biopsych.2004.06.038 [PubMed: 15450787]
- Stokes PRA, Rhodes RA, Grasby PM, Mehta MA. The effects of the COMT val108/158met polymorphism on BOLD activation during working memory, planning and response inhibition: a role for the posterior cingulate cortex. *Neuropsychopharmacology*. 2011; 36:763–771.10.1038/npp.2010.210 [PubMed: 21150912]
- Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AFT. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nat Neurosci*. 2007; 10:376–384.10.1038/nn1846 [PubMed: 17277774]
- Wilko M, Hauser J, Tomaszewska M, Dmitrzak-W glarz M, Skibinska M, Szczepankiewicz A, Borkowska A. Influence of dopaminergic and serotonergic genes on working memory in healthy subjects. *Acta Neurobiol Exp (Wars)*. 2010; 70:86–94. [PubMed: 20407490]
- Woods RP, Mazziotta JC, Cherry SR. MRI-PET registration with automated algorithm. *J Comput Assist Tomogr*. 1993; 17:536–546. [PubMed: 8331222]
- Yerkes RM, Dodson JD. The relation of strength of stimuli to rapidity of habit-formation. *Journal of Comparative Neurology and Psychology*. 1908; 18:459482.

Highlights

- COMT Val158Met polymorphism and co-activation of brain areas during working memory
- 129 participants, aged 35 to 70 years
- rCBF to performance correlations differ regionally for different genotypes
- Degree of shared activation and importance for performance is genotype specific
- Dopamine availability may alter brain networks to achieve comparable performance

Figure 1.

Illustration of ROIs. PFC is dorsolateral prefrontal cortex, PAR is posterior parietal cortex, AC is anterior cingulate, AMG/HIP is amygdala hippocampus, THA is thalamus, circular areas were summed to evaluate global CBF. Unlabelled regions outlined were not assessed for purposes of this investigation.

Figure 2.

Correlations in blood flow between brain areas of interest. Brain areas connected by any line are significantly correlated for all genotypes ($p < .05$). Correlations between the AH/DLPFC for Met homozygotes is significantly greater than that of Val/Met ($p < .05$) or Val/Val ($p < .01$). For Cingulate/DLPFC and Cingulate/Thalamus the correlation is significantly greater for Met/Met than Val/Met ($p < .01$). For Parietal/DLPFC the correlation is significantly greater for Val/Met than Met/Met ($p < .05$). For the thalamus/DLPFC the correlation is significantly greater for Val/Met than Val/Val ($p < .05$).

Figure 3.

Correlation between rCBF change (2-back task less control task) for the anterior cingulate and the dorsolateral prefrontal cortex. Lines of best fit and data markers are presented separately for the Val/Val, Val/Met, and Met/Met polymorphisms of COMT.

Table 1

Demographic Data^a

Variables	COMT Polymorphisms				P Value
	Val/Val	Val/Met	Met/Met	Overall	
Sample Size	34	55	40	129	...
Gender (male/female)	23/11	34/21	30/10	87/42	ns ^c
Age (years)	58.9 (7.1)	57.0 (7.6)	59.0 (6.1)	58.1 (7.0)	ns
Body Mass Index	29.3 (4.7)	29.3 (5.1)	28.4 (4.0)	29.0 (4.6)	ns
IQ (NART) ^b	113.3 (8.8)	110.5 (8.3)	108.7 (10.3)	110.7 (9.1)	ns
Systolic blood pressure (mmHg)	133.8 (15.7)	138.6 (14.7)	131.0 (17.4)	135.0 (16.0)	ns
Education, years	15.9 (3.1)	15.3 (2.2)	14.7 (2.5)	15.3 (2.6)	ns

^aData are expressed as mean (SD) unless otherwise indicated.

^bIQ is intelligence quotient as estimated from the National Adult Reading Test (NART) (Nelson, 1982).

^cChi square

Table 2

Mean rCBF and change in rCBF in Regions of Interest during the 2-back Task Relative to Control Task as Classified by COMT Genotype^a

	Val/Val	Val/Met	Met/Met	All
Cingulate Cortex (mean rCBF)	41.66(9.91)	43.33(8.07)	40.81(8.85)	41.87(8.55)
Amygdala Hippocampus (mean rCBF)	35.01(6.03)	35.15(6.52)	33.16(5.91)	34.29(6.35)
Dorsolateral Prefrontal (mean rCBF)	39.36(9.24)	42.05(8.92)	39.89(8.14)	40.39(8.64)
Posterior Parietal (mean rCBF)	42.49(10.58)	45.76(10.48)	42.88(7.35)	43.79(9.31)
Thalamus (mean rCBF)	54.98(13.87)	56.08(14.36)	54.01(12.66)	55.36(12.99)
Global Blood Flow (mean)	41.03(6.76)	42.54(6.87)	40.56(5.87)	41.44(6.51)
Cingulate Cortex (change)	1.80(3.70)	.579(5.59)	2.92(3.46)	1.75(4.57)
Amygdala Hippocampus (change)	-.19(2.95)	-1.4(3.94)	-.45(3.22)	-.70(3.38)
Dorsolateral Prefrontal Cortex (change)	.49(2.44)	-.25(4.54)	1.50(3.91)	.64(4.06)
Posterior Parietal (change)	1.63(4.39)	2.08(5.51)	2.50(3.98)	2.18(4.63)
Thalamus (change)	1.35(5.13)	-.01(9.02)	2.88(5.50)	1.66(7.28)
Global Blood Flow (change)	.25(2.79)	.11(3.75)	1.21(3.09)	.65(3.26)

^aData are expressed as mean (SD) unless otherwise indicated. Values are ml/min/100 ml of tissue.

Correlation Between WM Accuracy (A) and Regional Cerebral Blood Flow Activation for Different Val158Met Genotypes

Table 3

	Amygdala	Hippocampus	Cingulate Cortex	Parietal Lobe	DLPFC ^a	Thalamus
Val/Val	0.44 ^c		0.15	0.18	0.02	0.26
Val/Met	0.05		0.25	0.29 ^b	0.18	0.15
Met/Met	0.12		0.21	0.24	0.29	0.32 ^b

^aDL PFC is dorsolateral prefrontal cortex

^bindicates $p < .05$.

^cindicates $p < .01$.

Table 4

Correlation of rCBF change between brain areas during performance of the 2-back task*

	Amygdala Hippocampus		Cingulate Cortex		Parietal Lobe		Dorsal Lateral Prefrontal Cortex(DLPFC)	
	Val/Val	Met/Met	Val/Val	Met/Met	Val/Val	Met/Met	Val/Val	Met/Met
DLPFC	.52 ^a	.62 ^a	.65	.82 ^B	.65	.83 ^C	—	—
Thalamus	.68	.46	.64	.74 ^D	.76	.73	.63 ^e	.84 ^E
								.71

* All correlations are statistically significant, $p = .05$.

Uppercase superscripted values in the table are significantly different from correlations within the compared ROI's if a correlation shares the same lower case letter superscript ($p < .05$) or the same italicized letter superscript $p = .01$. See figure 2 for diagrammatic presentation.

Table 5

Correlation of degree of region specific rCBF response during the 2 back memory task to performance on the task (A) overall and for the three COMT polymorphisms

	Val/Val	Val/Met	Met/Met
Cingulate to DLPFC	.40 ^{AB}	-.29 ^a	-.13 ^c
Amygdala-Hippocampus to DLPFC *	-.28 ^{bc}	.15	.44 ^C
Parietal to DLPFC	.08	.16	.18
Amygdala-Hippocampus to Thalamus	.01	.05	.11

* DLPFC is dorsolateral prefrontal cortex.

Correlations sharing the same superscripted letter are significantly different from each other ($p < .05$) and differences are judged from the correlation with the capitalized letter superscript.