Prefrontal-Hippocampal Coupling During Memory Processing Is Modulated by COMT Val158Met Genotype

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Background: *Studies in humans and in animals have demonstrated that a network of brain regions is involved in performance of declarative and recognition memory tasks. This network includes the hippocampal formation (HF) as well as the ventrolateral prefrontal cortex (VLPFC). Studies in animals have suggested that the relationship between these brain regions is strongly modulated by dopamine.*

Methods: *Using fMRI in healthy humans matched for a series of demographic and genetic variables, we studied the effect of the COMT val158met polymorphism on function of HF and VLPFC as well as on their functional coupling during recognition memory.*

Results: *The COMT Val allele was associated with: relatively poorer performance at retrieval; reduced recruitment of neuronal resources in HF and increased recruitment in VLPFC during both encoding and retrieval; and unfavorable functional coupling between these two regions at retrieval. Moreover, functional coupling during retrieval was predictive of behavioral accuracy.*

Conclusions: *These results shed new light on individual differences in responsivity and connectivity between HF and VLPFC related to genetic modulation of dopamine, a mechanism accounting at least in part for individual differences in recognition memory performance.*

Key Words: COMT val158met, connectivity, declarative memory, dopamine, hippocampus, prefrontal cortex

A remarkable feature of the brain is its capacity to encode and retrieve a seemingly endless number of stimuli in the form of declarative memory. Studies in humans have demonstrated that a network of brain regions is associated with performance of declarative tasks. Neuronal activity in the hippocampal formation (HF) is modulated both during encoding and retrieval (for review, see (Schacter and Wagner 1999). Likewise, the inferior frontal gyrus in the ventrolateral prefrontal cortex (VLPFC) is involved in encoding of verbal and nonverbal information (Kelley et al 1998; Poldrack et al 1999; Wagner et al 1998b) as well as in retrieval of this information (Buckner et al 1995; Gabrieli et al 1998; Passingham et al 2000), most likely by supporting memory formation only indirectly (Fernandez and Tendolkar 2001).

Less attention has been devoted to the interaction between the HF and VLPFC during encoding and retrieval. Anatomic and electrophysiologic studies have demonstrated that the prefrontal cortex and the hippocampal formation are reciprocally connected both via monosynaptic and polysynaptic pathways (Rosene and Van Hoesen 1977; Thierry et al 2000). The behavioral significance of these pathways is implicated by lesion studies in humans and in animals suggesting that interactions between prefrontal cortex and medial temporal regions might be especially important in performing memory tasks involving effortful retrieval (Gaffan and Harrison 1988; Levine et al 1998). Furthermore, functional imaging studies in humans have demonstrated coactivation of VLPFC along with medial temporal lobe structures during performance of memory tasks (for review, see Schacter and Wagner 1999).

There is compelling evidence that dopamine, which regulates neuronal firing in prefrontal cortex and in hippocampus (Li et al 2003; Schacter and Wagner 1999), is also an important modulator of hippocampal and prefrontal cortical interactions. Electrical stimulation of the ventral hippocampus activates dopamine transmission in prefrontal cortex (Peleg-Raibstein et al 2005). Ventral tegmental area dopaminergic projections exert a complex gating action over prefrontal neuronal activity by inhibiting firing in the hippocampal–prefrontal pathway (Floresco et al 2003). Behavioral evidence in animals indicates that the ability to use previously acquired spatial information to guide response on a radial arm maze requires D1 receptor activation in prefrontal cortex and D1 receptor modulation of hippocampal inputs to the prefrontal cortex (Seamans et al 1998).

Regulation of dopamine signaling and neurotransmission in the cortex is critically affected by catechol-O-methyl-transferase (COMT; Matsumoto et al 2003), which inactivates via methylation dopamine and other catecholamines. COMT is densely expressed in the hippocampus and in prefrontal cortex (Matsumoto et al 2003), areas in which it may be particularly important in determining dopamine levels (Gogos et al 1998; Karoum et al 1993). A common mutation in the COMT gene causing a valine-to-methionine substitution, Val158Met, leads to significant reduction in the activity of the enzyme in brain (Chen et al 2004). Recent studies in humans (Bertolino et al 2004; Egan et al 2001; Mattay et al 2003) have demonstrated a relationship between this functional polymorphism with WM performance and related dorsolateral prefrontal cortex (DLPFC) physiology measured with functional MRI (fMRI). Carriers of the high-activity Val allele show inefficient cortical processing of working memory as reflected by lower performance along with greater prefrontal

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cortical blood oxygen level–dependent (BOLD) response compared with low-activity Met allele carriers. Further studies in healthy humans with fMRI have also demonstrated that the COMT Val158Met genotype modulates neuronal activity in anterior cingulate during effortful attention (Blasi et al 2005), as well as in the hippocampus during emotionally unpleasant stimuli (Smolka et al 2005). Importantly, in the latter case the Met allele was associated with increased hippocampal activation. Consistent with these latter findings, another behavioral study in healthy adults has also demonstrated that Met carriers perform better than Val carriers on tests of declarative memory (de Frias et al 2004). These various findings converge on the conclusion that the action of dopamine in the cortex (and consequently of COMT) varies according to the anatomic region receiving the projection, the nature of incoming stimuli, and the nature of the synaptic contacts (pre- vs. post-synaptic).

Based on such fMRI studies in humans, we hypothesized that during both encoding and retrieval of a recognition memory task, COMT Met/Met healthy individuals would have greater HF engagement, more efficient activation of the VLPFC (lesser engagement) as assessed with fMRI. Moreover, on the basis of electrophysiologic studies suggesting that hippocampal-evoked firing of prefrontal neurons is strongly modulated by dopamine, we also predicted that COMT Met/Met individuals would have more beneficial functional coupling between these two regions during processing of recognition memory.

Methods and Materials

Subjects

From a larger cohort of 40 subjects, we studied 27 healthy Caucasian subjects (12 men, mean age ± SD 28.7 ± 5.6) selected after a series of matching criteria across val/met genotype groups. Demographic variables that were matched across groups included handedness (Edinburgh Inventory .75 ± .33), parental socioeconomic status (Hollingshead Scale 44.7 ± 19.3), and full-scale IQ (Wechsler Adult Intelligence Scale—Revised; 118.1 ± 9.5). Exclusion criteria included any psychiatric diagnosis (assessed with Structure Clinical Interview for DSM-IV), history of significant drug or alcohol abuse (no active drug use in the past year), head trauma with loss of consciousness, and any significant medical condition. To control for known potentially confounding variables and because recognition memory performance and hippocampal activity during recognition memory have been associated with a functional polymorphism in the targeting region of the brain-derived neurotrophic factor (BDNF) gene (Val66Met; Egan et al 2003; Hariri et al 2003) as well as with the e4 allele of the apolipoprotein (APO) E gene (Bookheimer et al 2000), we controlled for both of these genetic variables by precisely matching the subjects.

This study was approved by the local internal review board at the University of Bari. After complete description of the study, written informed consent was obtained from all subjects. All data relative to the subjects have not been previously reported.

Genotype Determination

COMT Val158 Met genotype was determined on the basis of the Taqman allelic discrimination procedure as described elsewhere (Chen et al 2004). We also genotyped subjects for the BDNF Val66Met and APO E genotypes using the Taqman 5′ exonuclease allelic discrimination assay (Egan et al 2003).

Recognition Memory Paradigm

The fMRI paradigm consisted of the encoding and subsequent retrieval of novel, complex scenes, a task that has consistently been shown to produce activation of the hippocampal formation and of the ventrolateral prefrontal cortex in human neuroimaging experiments (Gabrieli et al 1997; Hariri et al 2003; Zeineh et al 2003). Stimuli were presented in a blocked paradigm, which has been shown to provide robust power and sensitivity for BOLD signal change in the hippocampal region (Birn et al 2002). Four encoding blocks were followed by four retrieval blocks in an interleaved design with a passive rest condition, resulting in a total of 18 blocks. Each block was 20 sec long, producing a total scan time of 6 min. During encoding blocks, subjects viewed six images, presented serially for 3 sec each, and determined whether each image represented an "indoor" or "outdoor" scene (Hariri et al 2003). An equal number of "indoor" and "outdoor" scenes were presented in each encoding block. All scenes were of neutral emotional valence and were derived from the International Affective Picture System (Lang et al 1997). During subsequent retrieval blocks, subjects again viewed six images, presented serially for 3 sec each and determined whether each scene was "new" or "old." In each retrieval block, half the scenes were "old" (i.e., presented during the encoding blocks) and half were "new" (i.e., not presented during the encoding blocks). The order of "indoor" and "outdoor" scenes as well as "new" and "old" scenes were randomly distributed throughout the encoding and retrieval blocks, respectively. During the interleaved rest blocks, subjects were instructed to fixate on a centrally presented crosshair. Before the beginning of each block, subjects viewed a brief (2-sec) instruction: "Indoor or Outdoor?" "New or Old?" or "Rest." During scanning, all subjects responded by button presses with their right hand, allowing for determination of behavioral accuracy and reaction time.

fMRI Acquisition Parameters

Each subject was scanned using a GE Signa 3T scanner (General Electric, Milwaukee, Wisconsin). The BOLD functional images were acquired with a gradient-echo echo planar imaging (EPI) sequence and covered 24 axial slices (4 mm thick, 1 mm gap) that began at the cerebral vertex and encompassed the entire cerebrum and the majority of the cerebellum (repetition time/echo time 2000/28 msec; field of view 24 cm; matrix 64 × 64; Hariri et al 2003). All scanning parameters were selected to optimize the quality of the BOLD signal while maintaining a sufficient number of slices to acquire whole-brain data.

Image Analysis

Analysis of the fMRI data was completed using statistical parametric mapping (SPM99; http://www.fil.ion.ucl.ac.uk/spm). Images for each subject were realigned to the first volume in the time series to correct for head motion, spatially normalized into a standard stereotactic space (Montreal Neurological Institute template) using a 12-parameter affine model, and smoothed to minimize noise and residual differences in gyral anatomy with a Gaussian filter, set at 10 mm full-width at half-maximum. Voxel-wise signal intensities were ratio normalized to the whole-brain global mean. For each experimental condition, a boxcar model convolved with the hemodynamic response function (HRF, SPM99) at each voxel was modeled. Predetermined condition effects at each voxel were calculated using a *t* statistic, producing a statistical image for the contrasts of encoding versus rest and retrieval versus rest for each subject. These individual contrast images were then used in second-level random effects models,

which account for both scan-to-scan and subject-to-subject variability, to determine task-specific regional responses at the group level for the entire sample (main effects of task, $p < .005$, uncorrected, $k = 3$). To detect the association between COMT genotype and fMRI activation in the HF and in VLPFC, the contrast images of all subjects (both for encoding and retrieval) were included in a regression analysis with SPM. Genotype was coded as a covariate by the number of *Met* alleles (*Val/Val* = 0, *Val/Met* = 1, and *Met/Met* = 2). Because of our strong a priori hypothesis regarding the differential response of the HF as well as of the VLPFC and our use of a rigorous random effects statistical model, a statistical threshold of $p < .005$, $k = 3$, with a further family-wise error (FWE) small volume correction for multiple comparisons (using a 10-mm radius sphere centered around the coordinates in HF and in VLPFC published in previous studies, $p = .05$; Buckner et al 1995; Fernandez and Tendolkar 2001; Gabrieli et al 1998; Kelley et al 1998; Passingham et al 2000; Poldrack et al 1999; Schacter and Wagner 1999; Wagner et al 1998a, 1998b, 1998c), was used to identify significant responses for all comparisons in these anatomic regions. Whole-brain image analyses for all predetermined condition effects were also calculated using second-level random effects models. Because we had no a priori hypotheses regarding the activity of brain regions outside of the HF and of the VLPFC, we used a statistical threshold of $p = .05$, corrected for multiple comparisons across all voxels, for these whole-brain comparisons.

Functional Connectivity Analysis

To further address the relationship between COMT genotype and HF as well as VLPFC, we performed a functional connectivity analysis as in previous reports (Meyer-Lindenberg et al 2005; Pezawas et al 2005). As an operational definition, two brain areas are said to be functionally connected if their BOLD signals covary over time (Friston et al 1999). The hippocampal formation (including the hippocampus proper, the enthorinal cortex, and the parahippocampal gyrus), the inferior frontal gyrus, and the parietal cortex in the inferior and superior parietal lobuli (as a control region) were defined in normalized space using a publicly available brain atlas (Wake Forest University PickAtlas, www.fmri.wfubmc.edu/downloads). Average activity within the HF was extracted for each scan. The time course of bilateral HF activity was then extracted for all participants, mean-centered and used as a covariate in a subsequent single-subject analysis of covariance to identify voxels whose activity showed significant covariation, positive or negative, with HF BOLD signal (Meyer-Lindenberg et al 2005). Although this approach does not identify anatomic or causal connections between brain regions, we have previously shown that this method, applied to fMRI data sets, is able to identify biologically relevant patterns of connectivity that agree well with known neuroanatomy (Pezawas et al 2005). To avoid confounding the connectivity measures by coactivation, calculations were performed after estimated effects of the block-design task were removed. Using Statistical Parametric Mapping version 99 software, effects at each voxel were estimated according to the general linear model, and regionally specific effects were computed by analysis of covariance identifying brain HF functional connectivity for each subject separately (first level). Finally, comparison between COMT groups to identify regions showing a significant across-task change in functional connectivity with the HF was performed using a random effects approach. For this, we entered the subject-specific maps into a second-level analysis (Friston et al 1999). To detect the association between COMT genotype and functional connectivity of the HF to the VLPFC and to the parietal cortex (as a control region), the contrast images of all subjects (both for encoding and retrieval) were included in a regression analysis with SPM. Genotype was coded as a covariate by the number of *Met* alleles (*Val/Val* = 0, *Val/Met* = 1, and *Met/Met* = 2). Because of our strong a priori hypothesis regarding the differential functional connectivity with the VLPFC and our use of a rigorous random effects statistical model, we used a statistical threshold of $p < .005$, $k = 3$, with a further FWE small-volume correction for multiple comparisons (using a 10-mm radius sphere centered around the coordinates in VLPFC published in previous studies, $p = .05$ (Wagner et al 1998a, 1998c; see also Buckner et al 1995; Fernandez and Tendolkar 2001; Gabrieli et al 1998; Kelley et al 1998; Passingham et al 2000; Poldrack et al 1999). The same statistical threshold was used to investigate the connectivity of the HF to the parietal cortex (control region). Because we had no a priori hypotheses regarding the functional connectivity between the HF and regions outside of the inferior prefrontal and parietal cortex, we used a statistical threshold of $p = .05$, corrected for multiple comparisons across all suprathreshold voxels, for whole-brain comparisons.

Statistical Analysis for Demographics and Declarative Memory Performance

ANOVAs and $\chi 2$ were used to assess potential differences between the three COMT genotype groups (Met/Met, Val/Met, Val/Val) for all demographic variables. Repeated-measures analysis of variance was used to evaluate the effect of COMT genotype both on encoding and retrieval accuracy and reaction time.

Results

Genotype Determination

Nine subjects were COMT Met/Met (3 men, mean age ± SD 26.2 ± 3.8), nine were Val/Met (4 men, mean age ± SD 24.7 ± 7.7), and nine were Val/Val (4 men, mean age ± SD 22.7 ± 4.5). As for BDNF val66met genotype, eight subjects were Val/Val and one was Val/Met in each of the three COMT groups. In terms of ApoE genotype, two subjects in the COMT Val/Val group were carriers of the e 4 allele, and one subject in the Met/Met group (and none in the Val/Met group). The three COMT genotype subgroups of subjects did not differ on any demographic variable [all Fs$(2,24) < 1.3$, all ps $> .2$, gender $\chi 2 = .9$, df 2, $p > .6$).

Recognition Memory Performance

The ANOVA of performance accuracy indicated a main effect of genotype [$F(2,24) = 4.1$, $p < .02$], a main effect of condition [encoding vs. retrieval, $F(2,24) = 29.6$, $p < .001$), and an interaction between genotype and performance [$F(2,24) = 4.2$, $p < .02$]. Post hoc analysis of the interaction term with Tukey Honest Significant Difference (HSD) indicated that accuracy at retrieval was significantly reduced in Val/Val subjects compared with both Val/Met subjects ($p < .04$) and Met/Met subjects ($p < .02$), whereas no significant difference was evident between Val/Met and Met/Met (Figure 1). No significant difference was evident at encoding (Figure 1). A similar analysis for reaction time indicated a main effect of memory condition [$F(2,24) = 29.7$, $p < .001$] but no main effect of genotype and no interaction between genotype and memory condition (all ps $> .2$). As expected, post hoc analysis with Tukey HSD indicated that subjects respond faster at encoding than at retrieval (mean ± SD, 1214.8 ± 174.5 msec vs. 1392.3 ± 205.5 msec, respectively, $p < .001$).

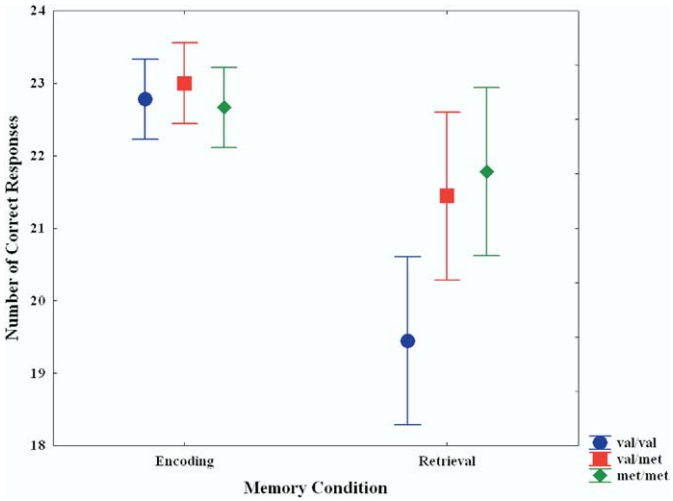

Figure 1. Behavioral performance (mean ± 95% confidence intervals) at encoding and at retrieval for the three COMT val158met genotypes. Val/Val subjects have reduced performance at retrieval compared with the other two genotype groups. See text for statistics. VV, Val/Val; VM, Val/Met; MM, Met/Met.

Neuroimaging Results

Main Effect of Task. Consistent with prior reports (Hariri et al 2003), we found significant bilateral activation of the HF (hippocampus and parahippocampal gyrus) during both encoding and retrieval in all subjects. In addition, both encoding and retrieval were associated with significant bilateral activations in the inferior temporal and parietal cortex as well as frontal cortices (including dorsolateral prefrontal and ventrolateral prefrontal cortex), a distributed network critical for visuospatial information processing.

Effect of COMT Genotype—Encoding. In the HF, the number of Met alleles was positively correlated with the peak BOLD signal changes elicited by encoding (x –29, y –40, z –3, $Z = 3.23$, $k = 7$, $p = .006$ after FWE small volume correction (SVC); x –26, y –48, z 4, $Z = 23.17$, $k = 3$, $p = .02$ after FWE SVC; x –29, y –29, z –14, $Z = 2.68$, $k = 3$, $p = .08$ after FWE correction; Figure 2). On the other hand, the number of Met alleles was negatively correlated with the peak BOLD signal changes elicited by encoding in VLPFC (BA 44, x 44, y 15, z 10, $Z = 2.87$ $k = 4$, $p = .05$ after FWE SVC). No other region survived the correction for multiple comparisons.

Effect of COMT Genotype—Retrieval. In the HF, the number of Met alleles was positively correlated with the peak BOLD signal changes elicited by retrieval (x –25, y –36, z 7, $Z = 3.11$, $k = 8$, $p = .03$ after FWE SVC; Figure 3). On the other hand, the number of Met alleles was negatively correlated with the peak BOLD signal changes elicited by retrieval in VLPFC (BA 44/45, x 49, y 19, z 16, Z = 3.24, $k = 8$, $p = .02$ after FWE SVC; Figure 3). No other region survived correction for multiple comparisons.

Correlations Between Performance and fMRI Signal Change. To evaluate the relationship between performance accuracy and activation in the brain areas that differentiated the

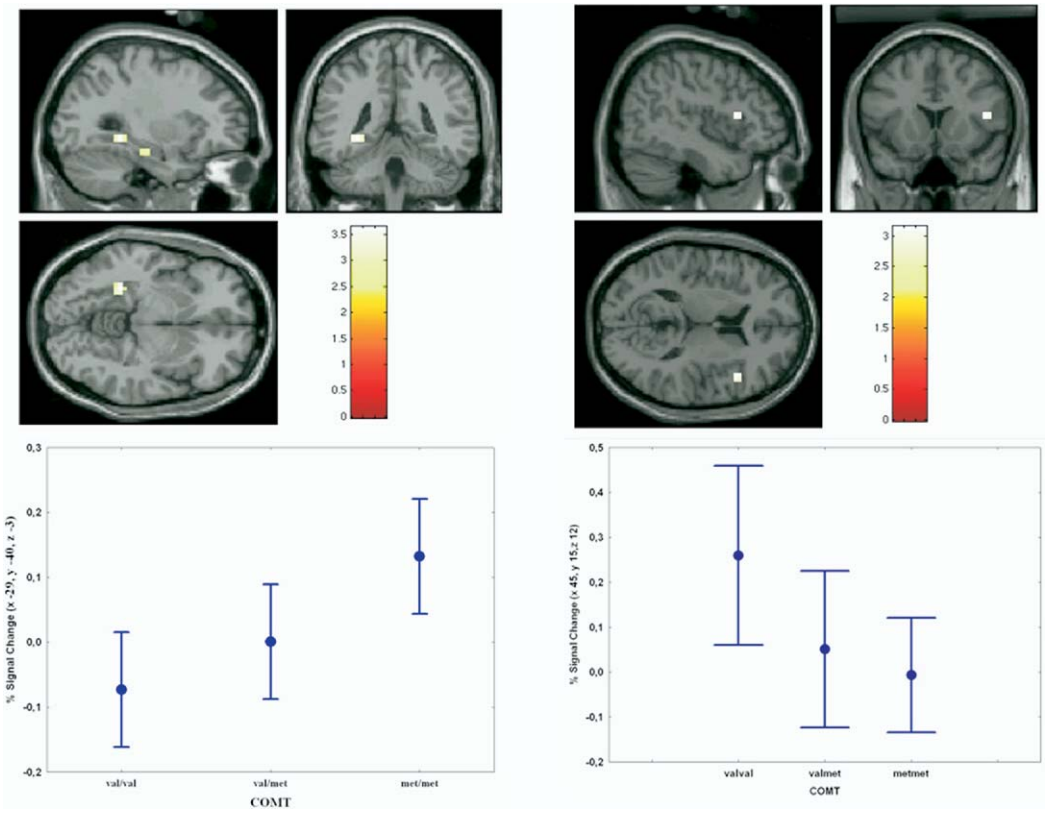

Figure 2. Effect of COMT genotype on functional magnetic resonance imaging (fMRI) activation during encoding. Upper section: regions showing a significant relationship between number of Met alleles and activation are in yellow and shown in the three orthogonal planes. In hippocampal formation (HF; x –29, y – 40, z –3; x –29, y –29, z –14), there was a positive correlation between number of Met alleles and blood oxygen level–dependent (BOLD) activation (left). In ventrolateral prefrontal cortex (VLPFC; Brodmann's area 44, x 44, y 15, z 10), there was a negative correlation between number of Met alleles and BOLD activation (right). Lower section: plots of the mean fMRI signal change in HF (left) and in VLPFC (right).

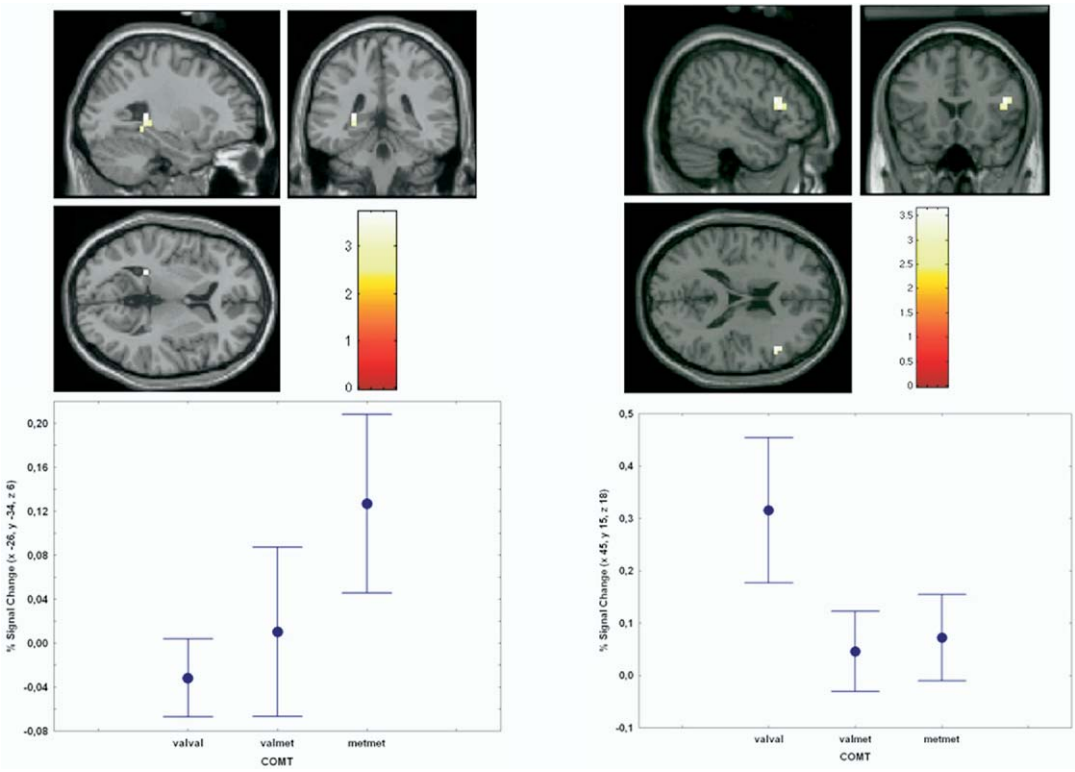

Figure 3. Effect of COMT genotype on functional magnetic resonance imaging (fMRI) activation during retrieval. Upper section: regions showing a significant relationship between number of Met alleles and activation are in yellow and shown in the three orthogonal planes. In hippocampal formation (x –25, y –36, z 7), there was a positive correlation between number of Met alleles and blood oxygen level–dependent (BOLD) activation (left). In ventrolateral prefrontal cortex (VLPFC; Brodmann's area 44/45 x 49, y 19, z 16), there was a negative correlation between number of Met alleles and BOLD activation (right). Lower section: plots of the mean fMRI signal change in HF (left) and in VLPFC (right).

groups, we performed Spearman correlations between accuracy at encoding and at retrieval with BOLD signal change extracted from the clusters in HF and in VLPFC determined in the previous statistical analyses. Including all subjects in these analyses, we found correlations between accuracy at retrieval with signal change at encoding in HF ($n = 27$, rho = .38, $p = .04$) as well as with signal change at retrieval in right and left VLPFC (respectively, $n = 27$, rho = –.47, $p = .01$, Figure 4).

Functional Connectivity—Encoding. The BOLD responses in the HF covaried highly with those in VLPFC and in parietal cortex at encoding. Furthermore, coupling of the HF to VLPFC, which was negative in sign, was positively correlated with the number of Met alleles (indicating decreased coupling for Met carriers) even though these results did not survive small-volume correction for multiple comparisons (Brodmann's area 44, x 55, y 11, z 16, $Z = 2.61$, $k = 3$, $p = .004$, $p = .1$ after FWE SVC). No cluster crossed the statistical threshold when evaluating the connectivity between HF to the parietal cortex (control region). The negative correlation did not show any cluster crossing the statistical threshold. No brain region

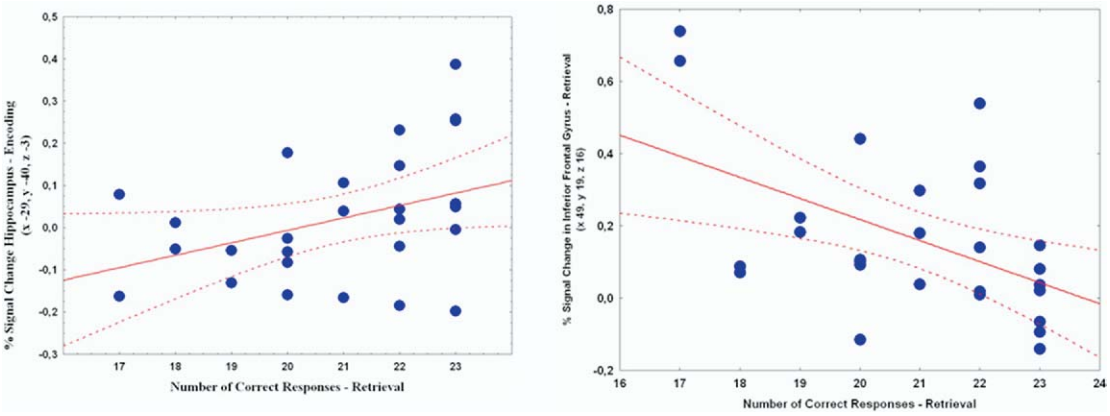

Figure 4. Scatterplots of the correlation between behavioral performance (number of correct responses) at retrieval and functional magnetic resonance imaging (fMRI) signal change in hippocampal formation (HF; left) at encoding and fMRI signal change in ventrolateral prefrontal cortex at retrieval (right). See text for statistics.

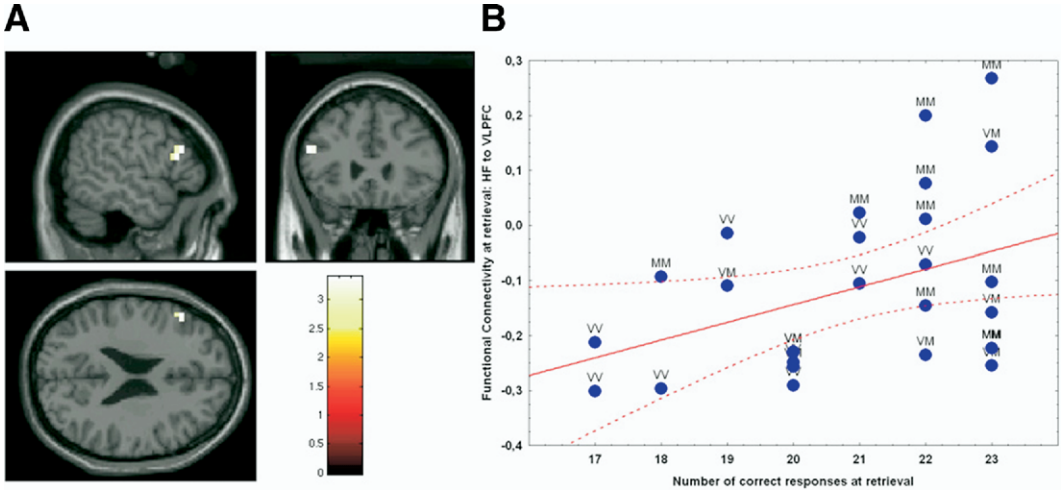

Figure 5. (A) Effect of COMT genotype on functional connectivity of hippocampal formation (HF) to ventrolateral prefrontal cortex (VLPFC) at retrieval: regions showing a significant relationship between number of Met alleles and functional connectivity are in yellow and shown in the three orthogonal planes. Coupling of the HF to VLPFC was positively correlated with the number of Met alleles (BA 45, x –51, y 26, z 20). **(B)** Scatterplot showing a significant positive correlation between HF-VLPFC connectivity at retrieval and number of correct responses at retrieval across the whole sample. VV, Val/Val; VM, Val/Met; MM, Met/Met; rho = .36, $p = .05$.

crossed the statistical threshold used for whole-brain comparisons.

Functional Connectivity—Retrieval. The BOLD responses in the HF covaried highly with BOLD responses in VLPFC and in parietal cortex at retrieval. Furthermore, coupling of the HF to VLPFC, which was negative in sign, was positively correlated with the number of Met alleles (BA 45, x –51, y 26, z 20, $Z = 3.17$, $k = 4$, $p = .03$ after FWE SVC, Figure 5), indicating that connection strength decreased with the number of Met alleles. Furthermore, coupling between HF and VLPFC (at x –51, y 26, z 20) positively predicted behavioral accuracy at retrieval ($n = 27$, Spearman rho = .36, $p = .05$). Because the directionality of the connection was negative, the strength of coupling was less for subjects performing better, suggesting that the more uncoupled two brain regions were, the better the behavioral performance and vice versa (Figure 5). No cluster crossed the statistical threshold when evaluating the connectivity between HF to the parietal cortex (control region). The negative correlation did not show any cluster crossing the statistical threshold. No brain region crossed the statistical threshold used for whole-brain comparisons.

Discussion

Consistent with earlier studies, our data demonstrate a role for COMT val158met genotype in the modulation of recognition memory performance, its associated cortical circuitry as well as the functional connectivity between specific anatomic regions within this network. More specifically, individuals homozygous for the Val allele had reduced behavioral performance accuracy at retrieval, reduced HF activation at encoding and at retrieval and increased activation of VLPFC at encoding and at retrieval. These differential patterns of activation were also behaviorally meaningful because HF activation at encoding and VLPFC activation at retrieval were significantly correlated with performance accuracy at retrieval: greater HF activation correlated with better performance, lower VLPFC activation correlated with better performance. Moreover, a functional connectivity analysis showed that the relationship between the HF and VLPFC was modulated by COMT genotype mostly at retrieval (with trend levels at encoding), with the number of Met alleles predicting decreased coupling. The three COMT subjects groups were matched for a number of demographic variables that could affect memory performance and also for BDNF val66met genotype and for the number of Apoϵ4 alleles, which have previously been associated with declarative memory performance as well as HF activation (Bookheimer et al 2000; Egan et al 2003; Hariri et al 2003).

Consistent with earlier data (de Frias et al 2004), we found that Val/Val subjects have reduced performance accuracy at retrieval, without deficits in accuracy at encoding or in prolonged reaction times during encoding and retrieval. Therefore, the COMT effect on accuracy at retrieval does not seem to be dependent on differential ability of the subjects to encode the stimuli accurately or on simple speed of processing. Activity in HF and in VLPFC reflected this performance difference. Neuropsychological data show that hippocampal and parahippocampal damage selectively causes a profound anterograde amnesia (Wagner et al 1999), suggesting that activity within these structures is a direct correlate of mnemonic operations. These neuropsychological data are consistent with functional imaging studies indicating that activity in these anatomic regions at encoding correlates with successful behavioral performance at retrieval (Wagner et al 1998b). A similar picture emerges for retrieval of memories (Ranganath et al 2004).

Even though patients with prefrontal damage do not have a general mnemonic impairment, they nevertheless exhibit impairments in certain declarative memory tasks, especially those that require association of the study items with appropriate context or in tests that allow interference from prior learning episodes (Adolphs et al 1997; Markowitsch and Kessler 2000). Therefore, neuropsychological data suggest that the role played by prefrontal cortex in declarative and recognition memory formation is to support effortful associative processing and to suppress irrelevant information. This processing might reflect the contribution of working memory operations to declarative memory formation. These working-memory contributions likely include the monitoring of single-item information by integrating this information in the context of previously seen stimuli or in the context of existing semantic or visuospatial knowledge (Wagner et al

1998b). This proposal is supported by studies in animals that are consistent with a model (Petrides 1995) in which the ventrolateral PFC yields working memory processes depending on the context of the material, whereas the middle PFC appears to be engaged in data manipulation, integrating different aspects across time and modalities. Consistent with these data, functional imaging studies have indicated that activity in the ventrolateral PFC during encoding is associated with better behavioral performance at retrieval (Wagner et al 1998b). Similarly, during retrieval, ventrolateral PFC is thought to subserve mechanisms that support both the formation and controlled retrieval of associations between representations (Passingham et al 2000; Petrides 2002; Wagner et al 2001). It has long been known that dopamine modulates the hippocampal formation and the prefrontal cortex in different processes associated with cognition (for review, see Thierry et al 2000). Dopamine levels in the cortex determine the relative balance of D1 and D2 activation (Seamans and Yang 2004), and this balance has implications for cortical memory processing (Bilder et al 2004; Winterer and Weinberger 2004). Both in vivo and in vitro studies have demonstrated that D1 receptor activation enhances hippocampal long term potentiation (LTP) (Frey et al 1990), whereas D2 receptor activation inhibits LTP (Manahan-Vaughan and Kulla 2003). These studies suggest that activation of D1 transmission in the hippocampus is preferentially associated with increased capacity for mnemonic storage (Frey et al 1990), whereas D2 transmission is preferentially associated with flexibility and the capacity to switch from one context or behavior to another (Lena et al 2001). Consistent with these earlier studies and with recent proposals that the Met allele is associated with greater D1 signaling (Bilder et al 2004; Seamans and Yang 2004), we demonstrate that the Met allele is associated with increased hippocampal recruitment both at encoding and at retrieval, which would lead to greater capacity for mnemonic storage. In fact, greater hippocampal activity at encoding is associated with better behavioral accuracy at retrieval.

The effect of dopamine release in prefrontal cortex may modulate different cellular mechanisms during memory. Via activation of D1 receptors, dopamine enhances task-related neural activity by enhancing response-related firing much more than background activity (Sawaguchi and Goldman-Rakic 1994a, 1994b) to sharpen the tuning of pyramidal cells and to focus activity on task-relevant items. This D1 effect is preceded by a D2-mediated decrease in inhibition (Seamans et al 2001). This effect would allow multiple representations to be activated closely in time, so that even weak representations could pop easily into the delay-active state (Durstewitz et al 2000). Conversely, in a mode dominated by the D1-mediated enhancement in inhibition, weakly active representations fail to be maintained, and a single or limited number of strongly active representations become very stable to subsequent interfering inputs and noise (Durstewitz et al 2000), thus requiring lesser recruitment of neuronal resources. Again, consistent with these previous studies and with the recent proposals mentioned earlier (Bilder et al 2004; Seamans and Yang 2004), we demonstrate that the Met allele is associated with more efficient prefrontal recruitment at both encoding and retrieval. These COMT genotype results in prefrontal cortex are similar to the effects of this genotype on other prefrontal processes, including attentional control (Blasi et al 2005) and working memory (Bertolino et al 2004; Egan et al 2001).

Based on these notions, a network of brain regions closely acting together has been proposed in which hippocampal–parahippocampal cortex and prefrontal cortex cooperate to form and retrieve memories. Several studies in humans have indicated that memory processes within the mesial temporal lobe are modulated by the prefrontal cortex and vice versa (Kirchhoff et al 2000; Wagner et al 1998a). As seen in earlier reports (Meyer-Lindenberg et al 2005), interaction between HF and DLPFC was negative in sign in our study, suggesting a reciprocal relationship between these regions during recognition memory. Studies in animals confirm the plausibility of these data. The two brain regions are reciprocally connected (Rosene and Van Hoesen 1977), neonatal lesions of the hippocampal formation affect prefrontal neuronal integrity (Bertolino et al 1997, 2002), and single-cell extracellular recordings indicate a complex electrophysiologic relationship. Activation of the hippocampal–prefrontal pathway exerts a complex synaptic influence on the majority of pyramidal cells in prefrontal cortex: a monosynaptic excitation is followed by a series of synaptic events [late excitatory post synaptic potential (EPSPs) as well as fast and slow inhibitory post synaptic potential (IPSPs)] likely associated with subsequent activation of local circuits (Jay et al 1995; Mulder et al 1997). Further studies have also demonstrated a role for dopamine in the modulation of hippocampal–prefrontal circuits. Ultrastructural studies have demonstrated that dopamine and hippocampal terminals are frequently in direct apposition to one another (Carr and Sesack 1996). Blockade of excitatory responses evoked in prefrontal neurons by hippocampal stimulation is observed following activation of the mesocortical dopamine system (Jay et al 1995). Furthermore, hippocampal-evoked activity in prefrontal neurons is gated by inputs from the ventral tegmental area (Floresco and Grace 2003), and D1 dopamine receptors modulate this circuitry during the integration of spatial memory with executive functions (Seamans et al 1998). Consistent with these studies in humans and animals, we demonstrate a role for COMT Val158Met genotype in the modulation of this circuitry. Coupling of the HF to VLPFC was positively correlated with the number of Met alleles, indicating that connection strength decreased with the number of Met alleles. Furthermore, coupling between HF and VLPFC positively predicted behavioral accuracy at retrieval. Because the directionality of the connection was negative in sign, the strength of coupling was less for subjects performing better, suggesting that the more uncoupled two brain regions were, the better the behavioral performance and vice versa. These data are consistent with the electrophysiologic complexity of the relationship between hippocampal and prefrontal neurons described earlier and further suggest that genetically determined dopamine inactivation may explain at least in part the variability of this relationship. The finding that COMT genotype predicts the tightness of these cross-regional correlations further suggests that these functional relationships are lawful manifestations of the efficacy of information processing.

Although our study included only healthy subjects, it is possible to speculate about its potential implications for the pathophysiology of schizophrenia. Patients with this disorder suffer from several cognitive deficits involving recognition memory. It has also been repeatedly reported that altered neuronal integrity and function of the HF are associated with schizophrenia (Bertolino et al 1996; Heckers et al 1998). Moreover, several linkage and association studies as well as meta-analyses have reported results consistent with the COMT Val allele contributing by itself a very small increase in genetic risk for schizophrenia (for review, see Harrison and Weinberger 2005). Other evidence also indicates that variation in COMT is linked more strongly with cognitive intermediate phenotypes rather than with the schizo-

phrenia syndrome itself, suggesting that the small increase in risk for schizophrenia may be conferred by its role in modulating dopamine signaling in prefrontal cortex and in the HF (for review, see Harrison and Weinberger 2005). In this regard, it is also important to note the Val158Met allele alone may not capture the complexity of the genetic regulation of COMT activity. Recently, other single nucleotide polymorphisms (SNPs) across the COMT gene have emerged as possible risk alleles for schizophrenia, although little is known about whether they affect prefrontal and hippocampal cognition. Preliminary evidence suggests a modest role for a SNP in the 5′ region of the gene on select tests of attention and target detection. Haplotype effects also may account for a modest percentage of the variance in test performance and are an important area for future study (for review see, Diaz-Asper et al 2006). Variation in other genes implicated in modulating dopamine signaling may also interact and add further effect in conferring risk for altered prefrontal and hippocampal information processing (Bertolino et al 2006).

Limitations

There are several limitations to this study. First, we used a block design fMRI paradigm, which does not allow for distinction between neural activity during correct and incorrect responses. Therefore, further examination using more temporally sensitive measures (event-related fMRI or magneto encephalography [MEG]) are desirable to disambiguate the time course of activation of specific brain structures during encoding and retrieval; however, we believe this limitation is softened by the fact that performance at encoding was well above 90%, and at retrieval it varied between 80% and 90%. Moreover, it is unlikely that the difference in behavioral performance between the Val/Val subjects and the other two groups represents a major confound of the data because it is difficult to imagine that the difference in performance would be manifest at the same time in two qualitatively opposite responses in the HF and in VLPFC.

To control for potential confounders of the COMT effect, we matched the COMT groups for a series of demographic variables and for BDNF Val66Met and the number of ApoE e4 alleles. Furthermore, the memory task used in this study is fairly easy and does not provide a parametric cognitive load. Previous studies have demonstrated that the COMT effect on cortical activation is more evident at the highest cognitive load in parametric tasks (Bertolino et al 2004; Blasi et al 2005; Egan et al 2001). These factors together may have significantly contributed to the subtlety of some of the differences between the groups in terms of spatial extent. Nonetheless, we believe that the strong hypotheses, the behavioral significance of these differences (correlations with performance accuracy), and the stringent statistical approach we have used speak to the robustness of the findings. In fact, the effect sizes of the differences in signal change and in functional connectivity (Cohen's *d*) are large, ranging from 1.3 to 1.8. Furthermore, although sample homogeneity facilitated the investigation of subtle contributions of genetic effects to corticolimbic information processing, it limits the generalizability of the findings to diverse populations.

We also acknowledge the possibility that the effects of COMT Val158Met genotype on recognition memory and its associated neuronal engagement may be more general because various components of cognition may not be independent of each other. For example, it has recently been demonstrated that genetic variation within the dysbindin gene is associated with general intelligence, *g* (Burdick et al 2006); however, our study used a rather specific approach with evaluation of the effect of COMT Val158Met genotype on brain activity during a recognition memory task, rather than evaluation of a purely cognitive statistical phenotype such as *g*. Moreover, we matched the groups for IQ scores; however, we cannot exclude definitively that genetic variation having an effect on *g* may also affect brain regions underlying recognition memory as modulated by COMT Val158Met genotype. Moreover, investigation of interactions between additional functional gene variants in biasing the response dynamics of mnemonic brain circuits is necessary. These limitations withstanding, our results shed new light on differences in responsivity and connectivity between HF and VLPFC, probably reflecting genetic modulation of dopamine in terms of predisposition for inefficient processing of recognition memory, a mechanism that may account for aspects of individual differences in memory performance.

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