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The COMT Val108/158Met Polymorphism and Medial Temporal Lobe Volumetry in Patients with Schizophrenia and Healthy Adults

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Abstract

Abnormalities of the medial temporal lobe have been consistently demonstrated in schizophrenia. A common functional polymorphism, Val108/158Met, in the putative schizophrenia susceptibility gene, catechol-O-methyltransferase (COMT) has been shown to influence medial temporal lobe function. However, the effects of this polymorphism on volumes of medial temporal lobe structures, particularly in patients with schizophrenia, are less clear. Here we measured the effects of COMT Val108/158Met genotype on the volume of two regions within the medial temporal lobe, the amygdala and hippocampus, in patients with schizophrenia and healthy control subjects.

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We obtained MRI and genotype data for 98 schizophrenic patients and 114 matched controls. An automated atlas-based segmentation algorithm was used to generate volumetric measures of the amygdala and hippocampus. Regression analyses included COMT met allele load as an additive effect, and also controlled for age, intracranial volume, gender and acquisition site.

Across patients and controls, each copy of the COMT met allele was associated on average with a 2.6% increase in right amygdala volume, a 3.8% increase in left amygdala volume and a 2.2% increase in right hippocampus volume. There were no effects of COMT genotype on volumes of the whole brain and prefrontal regions.

Therefore, the COMT Val108/158Met polymorphism was shown to influence medial temporal lobe volumes in a linear-additive manner, mirroring its effect on dopamine catabolism. Taken together with previous work, our data support a model in which lower COMT activity, and a resulting elevation in extracellular dopamine levels, stimulates growth of medial temporal lobe structures.

Keywords

COMT Val108/158Met Polymorphism; Amygdala; Hippocampus; structural MRI; Schizophrenia; Dopamine

Introduction

Catechol-O-methyltransferase (COMT) is an enzyme found throughout the mammalian central nervous system which degrades the catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine. A common G-to-A transition in exon 4 of the COMT gene, resulting in a valine (val)-to-methionine (met) substitution at amino acid position 108 or 158 (depending on the splice variant), leads to a four-fold decrease in enzyme activity in met homozygotes, while heterozygotes demonstrate intermediate activity (Lachman et al., 1996). Because schizophrenia is associated with dysregulation of dopaminergic neurotransmission, the relationship between the COMT Val108/158Met polymorphism and schizophrenia has been studied intensively. A small association between the val allele and schizophrenia has been found in family-based studies, but not in overall meta-analyses (Glatt et al., 2003; Munafo et al., 2005). However, one recent study found that the risk contributed by COMT genotype may be more evident when evaluated within a high risk sample (McIntosh et al., 2007), in which other schizophrenia susceptibility genes are presumably also playing a role.

The low activity COMT met allele has been associated with higher extracellular dopamine levels (Lotta et al., 1995) and more efficient activation of the dorsolateral prefrontal cortex (DLPFC) in tests of executive functioning and working memory (Bertolino et al., 2006; Egan et al., 2001; Ho et al., 2005). In addition, the Val108/158Met polymorphism has been found to influence the physiology of regions within the medial temporal lobe, including the amygdala (Smolka et al., 2005) and hippocampus (Drabant et al., 2006).

The effect of COMT Val108/158Met genotype on brain structure is less clear. Several studies have found no direct effect of this polymorphism on measures of brain structural integrity, including total frontal gray matter volume (Ho et al., 2005) and regional gray matter density (Zinkstok et al., 2006). However, a recent large study of healthy subjects which used voxel-based morphometry found that participants with higher numbers of met alleles had increased hippocampal grey matter intensity (Honea et al., 2008). Also, a study of patients with velocardiofacial syndrome, who have only one copy of the COMT gene, found that these patients have larger amygdala volumes compared to healthy control subjects (Kates et al., 2006). Taken together, these studies suggest that less COMT activity

and higher extracellular dopamine levels may be associated with elevated responsiveness and larger volumes of medial temporal lobe structures.

Morphometric investigations have consistently found a small reduction in medial temporal lobe volume in schizophrenia, with approximately 4–6% reductions in the volume of the hippocampus and a 6% reduction in the volume of the amygdala (Honea et al., 2005; Wright et al., 2000). Abnormalities of the structure and function of the amygdala and hippocampus in schizophrenia have been associated with deficits in memory and executive function (Antonova et al., 2004) and emotional processing (Exner et al., 2004; Holt and Phillips, 2009; Namiki et al., 2007), suggesting that these structural changes could reflect a central pathophysiological process associated with the illness (Heckers, 2001).

Given the evidence for an effect of COMT Val108/158Met genotype on the function and structure of the medial temporal lobe and its putative contribution to risk for schizophrenia, in the current study we sought to measure the influence of this polymorphism on amygdala and hippocampus volumes in patients with schizophrenia and healthy control subjects. An automated atlas-based segmentation technique, which estimates volumes objectively in the original (untransformed) MR images (Fischl et al., 2002), was used to measure amygdala and hippocampal volumes. We tested the prediction that COMT Val108/158Met genotype influences amygdala and hippocampal volumes in a linear-additive manner, i.e. each copy of the met allele is associated with a proportionate increase in amygdala and hippocampal volume. Measurement of total brain volume served as a control in this analysis. Because of evidence for effects of COMT genotype on frontal lobe function (Bertolino et al., 2006; Egan et al., 2001; Ho et al., 2005), exploratory analyses of the effect of this genotype on volumes of frontal lobe regions were also conducted.

Methods and Materials

Participants

The Mind Clinical Imaging Consortium (MCIC) study of schizophrenia(Roffman et al., 2008a) obtained baseline structural MRI scans on a total of 328 subjects (160 individuals with schizophrenia, 168 healthy controls) from four participating sites: Universities of Iowa (UI), Minnesota (UMN), and New Mexico (UNM) and Massachusetts General Hospital in Boston (MGH). The schizophrenic patient group (SCZ) consisted of individuals with a DSM-IV diagnosis of schizophrenia, established using structured clinical interviews and review of case files by trained clinicians. Healthy controls (HC) were included if they had no history of a medical or Axis I psychiatric diagnosis. All participants were required to be at least 18 and no older than 60, and to be fluent in English. Participants were excluded if they had a history of neurologic disease, or psychiatric disease other than schizophrenia, history of a head injury, history of substance abuse or dependence within the past month, severe or disabling medical conditions, contraindication to MR scanning or IQ less than 70 (based on the reading subtest from the WRAT-IIIRT). After complete description of the study to the participants, written informed consent was obtained. The human subjects research committees at each of the four sites approved the study protocol.

Genotype data were available for 222 subjects of the initial sample. After excluding 10 additional subjects due to poor structural MRI quality (see below), the final sample consisted of 98 patients with schizophrenia and 114 healthy controls. The distribution of gender, race, premorbid cognitive functioning, parental SES, handedness, length of illness, positive and negative symptoms were similar in the included (n=212) and excluded (n=116) subjects. Excluded subjects were on average 3.1 years older than included subjects (t=2.48, df=326, p=0.014).

Instruments

Before starting the study, clinicians from all four sites participated in a two-day training session, during which cross-site inter-rater reliability for the primary diagnostic and symptom-rating scales was established (>85% concordance with videotaped training materials). All study participants underwent an extensive clinical diagnostic assessment that included either the SCID-I/P or NP (First et al., 2002) or the Comprehensive Assessment of Symptoms and History (CASH)(Andreasen et al., 1992). To further characterize our sample, the severity of positive and negative symptoms was assessed using the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983; Andreasen, 1984). Premorbid cognitive achievement was estimated by the Wide Range Achievement Test (WRAT-IIIRT (Wilkinson, 1993)); parental socioeconomic status (SES) was determined using the Hollingshead index (Hollingshead, 1965) and handedness was determined using the Annett Scale of Hand Preference (Annett, 1970).

Antipsychotic history was collected as part of the psychiatric assessment using the PSYCH instrument (Andreasen, 1987), and cumulative and current antipsychotic exposure was calculated using the chlorpromazine (CPZ) conversion factors of Woods et al (Woods, 2003). To calculate cumulative dose years, the following formulas were applied:

$$\text{Cumulative dose years} = [(\text{Dose in mg/day}) * (\text{Days on dose})] / [\text{conversion factor}^{*}(365.25 \text{ days})]$$

For current antipsychotic exposure, we converted all current doses into chlorpromazine units, using the formula below:

$$\text{Chlorpromazine units} = [\text{Dose drug (mg/day)}/(\text{Conversion factor}] * [100 \text{ CPZ units/mg}]$$

Genotyping

Genotyping for the COMT Val108/158Met polymorphism was conducted with the Taqman platform (Applied Biosystems, Foster City, CA) using primers previously described (Roffman et al., 2008b).

Image Acquisition and Processing

Cross site MRI acquisition calibration and reliability were established in a preceding study using human phantoms, following guidelines developed by the Biomedical Informatics Research Network (BIRN) test bed for morphometry (Jovicich et al., 2006; Jovicich et al., 2009). The MRI acquisition protocol for high-resolution coronal T1-weighted images were matched across the four different sites (UMN: Siemens 3T Trio, UI: Siemens 1.5T Sonata, MGH and UNM: Siemens 1.5T Avanto): 3T Trio: TR/TE/flip angle = 2.53s/3.79ms/7°, 1.5T Sonata: TR/TE/flip angle = 20ms/6 ms/20°, 1.5T Avanto TR/TE/flip angle 12ms/4.76ms/20°, FOV = 16×16 cm, 128 contiguous slices (imaging matrix = 256×256, in plane resolution = 0.625 × 0.625 mm, slice thickness = 1.5 mm), NEX = 3. Acquisition time for this Gradient Echo sequence was approximately 20 minutes.

MR data were analyzed in an automated manner with atlas-based FreeSurfer segmentation software (http://surfer.nmr.mgh.harvard.edu, Version 4.0.1) to generate volumetric measures of regions of interest (Figure 1) (Fischl et al., 2002). According to standard FreeSurfer procedures three consecutively-acquired, T1-weighted 3D gradient-echo MR images were corrected for motion artefacts, realigned and averaged to generate a single volume with

higher signal-to-noise ratio for each subject. Volumes of the amygdala, hippocampus and frontal lobe regions are a standard output of the FreeSurfer segmentation (Fischl et al., 2002) and parcellation (Desikan et al., 2006) procedures. These procedures rely upon variations in voxel signal intensities, probabilistic atlas location and local spatial relationships between the structures (Fischl et al., 2002). Total intracranial volume (ICV) was estimated with the FreeSurfer standard procedure that uses the determinant of the transform matrix used to align the image with the atlas (Buckner et al., 2004). Whole brain volume, which includes the cerebellum but not CSF-containing spaces, was calculated by subtracting the volumes of the ventricles from the brain segmentation volume. DLPFC volumes (Figure 1) were derived from FreeSurfer cortical parcellations and conservative Talairach coordinates as detailed in (Rajkowska and Goldman-Rakic, 1995).

Image and segmentation quality were assured by manual inspection of all raw MRI volumes, segmented volumes in three planes, and three-dimensional cortical surface models. The automated segmentation procedure failed in 10 subjects of the subsample that had complete structural MRI and genotype data (n=222) due to excessive motion artifact. Furthermore, 5 participants' MRI data failed the aforementioned quality assurance. These subjects were then recovered with minor manual intervention.

Statistical Analyses

First, the primary aim of the study was to test the prediction that COMT Val108/158Met genotype accounts for a significant portion of variance in amygdala and hippocampal volumes, in a linear-additive manner. Therefore, four regions of interest were studied: the right and left amygdala and right and left hippocampus. Second, measurements of whole brain volume served as a control; we did not expect to find an effect of genotype on total brain volume. Lastly, exploratory analyses were conducted for 12 frontal lobe regions in each hemisphere: rostral middle frontal gyrus, superior frontal gyrus, caudal middle frontal gyrus, lateral orbitofrontal gyrus, medial orbitofrontal gyrus, pars opercularis, pars orbitalis, pars triangularis, precentral gyrus, rostral anterior cingulate cortex, caudal anterior cingulate cortex and the DLPFC.

To test our prediction, linear regression models of the COMT polymorphism controlling for age, ICV, gender and site were fit for the ROIs. We first tested whether the effect of COMT on the volume of each ROI could be adequately modelled as a linear-additive effect: i.e., we hypothesized that the difference between having one and zero copies of the met allele was half of the difference between having two and zero copies. Since the null hypothesis was not rejected for any region examined, we included COMT genotype as an additive effect (met allele load) in all subsequent models. The overall effect of site was significant for the right amygdala, whole brain volume and most of the frontal brain regions (Table 3). Subsequently site was included into all models to control for those differences (Segall et al., 2009;Stonnington et al., 2008). In additional models we controlled for the effects of race, antipsychotic medication, handedness, premorbid cognitive functioning and a history of alcohol dependence, as well as for all two-way and three-way interactions of the main models using a forward stepwise model selection procedure.

To control for the number of comparisons (four main ROIs) we applied a modified Sidak correction which accounts for the high correlation among these four ROI volumes (mean r=0.744); was set to .0353 (Sankoh et al., 1997). To investigate the association between volumetric brain measures and measures of psychiatric symptomatology, standardized residuals of amygdala and hippocampal volumes were initially computed by correcting for COMT genotype, gender, ICV and site. Pearson correlations between the residualized ROI volumes, and SANS and SAPS were conducted for the outcome ROIs.

Means are shown with standard deviations (SD) unless otherwise indicated, and all statistical tests were two-tailed. All analyses were carried out with SPSS 16.0.

Results

Sample characteristics

Patients and healthy control subjects did not differ in age, parental SES or handedness score. Patients had a significantly lower premorbid IQ than controls, and there were slightly more male and more non-white participants in the patient group as compared to the control group (Table 1). COMT genotype frequency was in Hardy-Weinberg equilibrium and there was no significant association between genotype and diagnosis (Armitage's trend test χ^2=0.09, p=0.770). A series of linear or logistic regression analysis with COMT genotype, diagnostic group, race and acquisition site as predictors as well as interactions between genotype and the other variables showed no significant differences in age, parental SES, premorbid IQ, handedness score, sex, race, length of illness, positive, or negative symptoms, cumulative or current antipsychotic drug dose (for additional details, see Table 1, Supplementary Table 1 and 2).

Region of interest volumes

Pooled across site, gender and hemisphere, mean amygdala volumes were 1810±237 mm^3 for the controls and 1750±239 mm^3 for the patients with schizophrenia. Hippocampus volumes were 4410±435 mm^3 for the controls and 4151±489 mm^3 for the patients with schizophrenia. The volumes of the amygdala, hippocampus, as well as whole brain (Figure 2), were significantly lower in the patients with schizophrenia compared to the controls (for both raw and corrected volumes, see Table 3). Also, across groups, females had significantly smaller bilateral amygdala volumes and smaller whole brain volumes than males (Table 3), and the volume of all regions measured decreased with age (Table 3).

Significant main effects of genotype were found for amygdala and hippocampal volumes; each copy of the COMT met allele was associated with a 44 mm^3 increase in right (t=−2.54, p=0.012) and a 64 mm^3 increase in left amygdala volume (t=−3.34, p=0.001, Table 3, Figure 3), as well as a 93 mm^3 increase in right hippocampus volume (t=−2.43, p=0.016, Table 3, Figure 3). Neither the volume of the left hippocampus (t=1.59, p=0.114) or the volumes of whole brain were significantly affected by the COMT Val108/158Met polymorphism (Table 3). The effect of genotype did not differ between schizophrenic patients and controls; i.e., interactions between diagnosis and genotype were not significant (right amygdala t=−0.36, p=0.716; left amygdala t=−1.64, p=0.103; right hippocampus t=−0.99, p=0.321; left hippocampus t=−0.50, p=0.618) and thus were not included in the final models (Table 3). Furthermore, none of the additional control variables (see Methods) or interactions, including all interactions with site, increased the model fit.

In addition, we conducted tests for the potentially confounding effects of cumulative antipsychotic medication exposure (cumulative exposure to typical, atypical and clozapine antipsychotic medication) within the schizophrenia group. Neither the single effects of the aforementioned variables nor the change in model fit for all three variables together (adjusted R^2) reached significance in any of the models. Also, the linear-additive effect of met allele load remained significant for the right amygdala (t=2.20, p=0.031), left amygdala (t=3.71, p<0.001) and right hippocampus (t=2.02, p=0.046) within the patient group. Another set of regression models controlling for current antipsychotic exposure yielded similar results.

We tested for the presence of population and group stratification effects by performing the same regression models with race as a factor and in a sample limited to the majority

ethnicity (Caucasian). Race did not explain any variance of our outcome variables, and the effects of COMT remained present in the models which included race, as well as in the Caucasian subsample, although the effect in the right amygdala was slightly weaker ($p = 0.063$) in the Caucasian subsample (Supplementary Table 3).

Finally, we found no significant main effects of COMT genotype or genotype by group interactions on grey matter volume in 12 regions of the frontal lobe, including the DLPFC (all p values > 0.1). This negative result was not altered in the patient group when we controlled for the effects of cumulative or current doses of typical, atypical and clozapine antipsychotic medication.

Clinical associations

Pearson correlations between the residualized region of interest volumes and the Total SANS score were significant for the right amygdala ($r = -0.215$, $p = 0.034$) and right hippocampus ($r = -0.272$, $p = 0.007$). There were no significant correlations for the left amygdala and hippocampus, or for the Total SAPS score.

Discussion

Using an automated segmentation procedure to measure regional brain volumes in a large number of healthy and schizophrenic subjects, we detected a significant effect of the COMT Val108/158Met polymorphism on medial temporal lobe volumes. Across patients and controls, each copy of the COMT met allele was associated with a 2.6% increase in right amygdala volume, a 3.8% increase in left amygdala volume and a 2.2% increase in right hippocampus volume. These dose-dependent effects are consistent with the results of both in vitro thermostability studies indicating that the alleles act codominantly (Weinshilboum, 2006) and in vivo functional imaging studies in humans (Egan et al., 2001; Smolka et al., 2005). However, despite the known influence of COMT Val108/158Met genotype on the function of the frontal lobe, in particular the dorsolateral prefrontal cortex (DLPFC) (Egan et al., 2001), we found no effect of genotype on the volume of frontal lobe regions (or on whole brain volume) in either group. Lastly, consistent with a large body of previous work (Honea et al., 2005; Nelson et al., 1998; Wright et al., 2000), we found an approximately 3.4% reduction in amygdala and a 4.6% reduction in hippocampal volumes in the patients with schizophrenia compared to the controls.

Several previous investigations of the effects of the Val108/158Met COMT polymorphism on brain morphometry (although not all (Zinkstok et al., 2006)) have found associations in healthy controls. Using a semi-automated segmentation method, Taylor et al. (Taylor et al., 2007) found evidence for a relationship between the number of COMT met alleles and hippocampal and temporal lobe volumes (with a trend in the amygdala) in 31 healthy subjects. Also, a well-powered voxel-based morphometry (VBM) study (n=151) showed significant increases in gray matter density in a cluster of voxels in the hippocampus and parahippocampal gyrus in healthy met homozygotes relative to healthy val allele carriers (Honea et al., 2008). In contrast, using a voxel-wise deformation based method (tensor based morphometry), Ohnishi et al. (Ohnishi et al., 2006) did not detect a main effect of genotype (met carriers vs. val homozygotes) in a cohort of 47 patients with schizophrenia and 76 healthy controls in the medial temporal lobe, although they did find, within the patient group alone, a significant reduction in left amygdala-uncus volumes in val homozygotes compared to met carriers. Here we confirm and extend these previous findings by demonstrating a main (linear) effect of COMT genotype in our sample of 114 healthy subjects and 98 patients with schizophrenia, using a measure of each individual subject's hippocampal and amygdala volume.

Previous studies which used indirect measures of DLPFC volume have not found an effect of the Val108/158Met COMT genotype on the volume of the DLPFC (Ho et al., 2005; McIntosh et al., 2007; Taylor et al., 2007; Zinkstok et al., 2006), consistent with the current results. However, previous findings of statistical trends towards COMT genotype effects on the DLPFC (Honea et al., 2008; Ohnishi et al., 2006) suggest that effects on DLPFC volume may be evident under certain circumstances (e.g. in the presence of other genetic variants) but are more subtle than the effects of this genotype on the volume of medial temporal lobe structures. The methodological challenges inherent in identifying borders of frontal cortical areas such as the DLPFC, which have fewer objectively-defined borders than medial temporal lobe structures, could also account in part for these negative findings.

Diminished medial temporal lobe volume is one of the most consistently replicated abnormalities found in schizophrenia (Heckers, 2001; Honea et al., 2005; Nelson et al., 1998; Wright et al., 2000), and it may represent a stable endophenotype of the disorder (Goldman et al., 2008; Seidman et al., 2002). In the present study, the COMT met allele was associated with higher, and the val allele with lower, medial temporal lobe volumes. Given that it is the val allele of the Val108/158Met COMT polymorphism that has been most frequently associated with risk for schizophrenia (Glatt et al., 2003; Munafo et al., 2005), the present results suggest that the val allele may also contribute to lower medial temporal lobe volumes in schizophrenic patients. However, the results of the current study, taken together with previous findings (Honea et al., 2008; Taylor et al., 2007), indicate that the effect of this genotype on medial temporal lobe volume is not limited to, or greater in, patients with schizophrenia. The absence of a COMT Val108/158Met genotype by group interaction observed here is in in line with evidence for a weak or absent association of this polymorphism with schizophrenia (Munafo et al., 2005) and the failure to find a greater effect of this genotype on working memory and prefrontal function in schizophrenic patients (Bertolino et al., 2006; Egan et al., 2001; Ho et al., 2005). It has been suggested that other polymorphisms in the COMT gene (Chen et al., 2004; Handoko et al., 2005; Sanders et al., 2005), interactions with risk alleles of other genes (Lawrie et al., 2008; Nicodemus et al., 2007; Roffman et al., 2008a; Tan et al., 2008) and environmental influences (Caspi et al., 2005) may constitute a background of risk factors that could interact with the COMT Val108/158Met polymorphism to increase schizophrenia susceptibility, which could be manifested, in part, as a structural change in the medial temporal lobe (Job et al., 2005).

Consistent with the present results is a report of abnormally elevated amygdala volume in patients with velocardiofacial syndrome (VCFS) (Kates et al., 2006). This and the current findings suggest that lower COMT activity (associated with the low-activity met allele, or deletion of one COMT gene copy as in the case of VCFS), and the resulting higher levels of extracellular dopamine, is associated with increased amygdala volume, while higher COMT activity (seen with the high-activity val allele) is associated with decreased amygdala volumes. It is also noteworthy that D1 dopamine receptor binding in the amygdala and hippocampus is lower in met carriers compared to val homozygotes (Slifstein et al., 2008). Thus, increased dopamine signalling in met carriers may lead to down-regulation of D1 receptors in medial temporal lobe structures.

These findings have led to the proposal that COMT Val108/158Met genotype may influence neuronal growth in the medial temporal lobe, and its size in adults, via neurotrophic effects of dopamine on the amygdala and hippocampus during development. Evidence for this is provided by in vitro and knock-out experiments: Dopamine has been shown to regulate brain-derived neurotrophic factor expression in neuronal cell cultures (Kuppers and Beyer, 2001), and dopamine D1 receptor knock-out mice show disrupted cellular and neurochemical architecture in cortex (Stanwood et al., 2005). Dopaminergic projections from the midbrain influence amygdala and hippocampal activity in adult rodents (Laviolette,

2007), and thus are likely to modulate neuronal firing in these regions during development as well.

Dopaminergic neurotransmission plays a critical role in both affective regulation and emotional learning (Laviolette, 2007). For example, the ventral hippocampus may exert control over fear responses by modulating dopaminergic transmission in the orbitofrontal cortex (Peleg-Raibstein et al., 2005). Furthermore, dopamine modulates inhibitory and excitatory neurotransmission between the basolateral amygdala and the medial prefrontal cortex (Floresco and Tse, 2007). In the current study, the severity of negative symptoms (which include impairments in emotional function such as anhedonia and flattened affect) were inversely correlated with right amygdala and hippocampal volumes. Because negative symptoms have been associated with low dopamine states, and can be ameliorated by D1 agonists (Abi-Dargham and Moore, 2003; Burton, 2006), we speculate that reduced amygdala volume and negative symptoms in schizophrenia may arise from impaired dopaminergic neurotransmission. Reports of associations between smaller amygdala size in schizophrenia and impaired emotional learning (Exner et al., 2004), and impaired emotion recognition (Namiki et al., 2007), suggest that amygdala volume may serve as a proxy measure for some aspects of affective processing.

The approach used here of conducting quantitative, automated morphometric analyses, of data collected at multiple acquisition sites, is associated with both advantages and disadvantages. It allowed rapid collection and analysis of data from a large cohort of subjects; combining these datasets increased reliability and power, while permitting inclusion of appropriate corrections for common confounds such as antipsychotic medication. It also enabled us to test for met allele load as an additive effect and build appropriate statistical models. Although we followed the best practice guidelines for multi-site MR acquisition by the Biomedical Informatics Research Network (http://www.nbirn.net), small effects of acquisition site were found. However, previous multi-site studies have found that scanner-related effects, regardless of magnitude, are not likely to influence final morphometric measurements, as long as these effects are adequately accounted for in the analyses (Segall et al., 2009; Stonnington et al., 2008).

In summary, in this mult-site study we detected a dose-dependent effect of the COMT Val108/158Met polymorphism on bilateral amygdala and right hippocampal volumes. Our finding provides further in-vivo evidence for the importance of heritable variation in dopamine neurotransmission in regional brain structure. Future studies of the interactions between other genes and COMT, and their joint effects on the structure and function of limbic brain regions, may shed further light on the causes of medial temporal lobe abnormalities in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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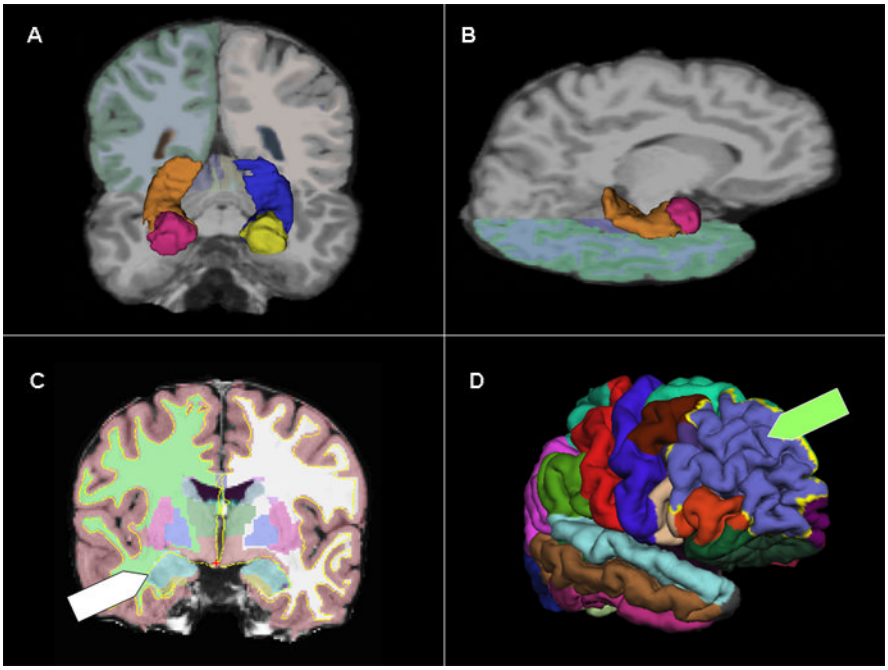

Figure 1.
Freesurfer subcortical segmentation of the hippocampus and amygdala (white arrow in C) and cortical parcellations with the DLPFC (green arrow in D). Models are displayed overlaid on one randomly chosen female patient. Images A and B constructed using Slicer 3.0 (www.slicer.org), C using tkmedit and D using tksurfer (http://surfer.nmr.mgh.harvard.edu/). The DLPFC parcellations were generated by: (A) Merging the standard Freesurfer parcellation labels of the superior frontal gyrus, the rostral middle frontal gyrus and caudal middle frontal gyrus. (B) Making a cut along the vertex on the inflated cortical surface to divide medial and lateral components and (C) Introducing a coronal cut of the lateral component at Talairach coordinate y=26 to separate DLPFC from premotor cortex.

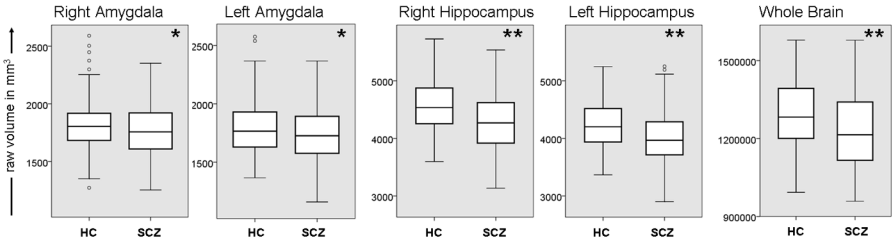

Figure 2.

Boxplots of the raw volumes of the four brain regions of interest and the control regions in mm^3 for 98 schizophrenic patients (SCZ) and 114 healthy controls (HC). The differences between patients and controls (while controlling for the effect of COMT, gender, age and ICV) were significant for all regions (*p<0.03; **p<0.001).

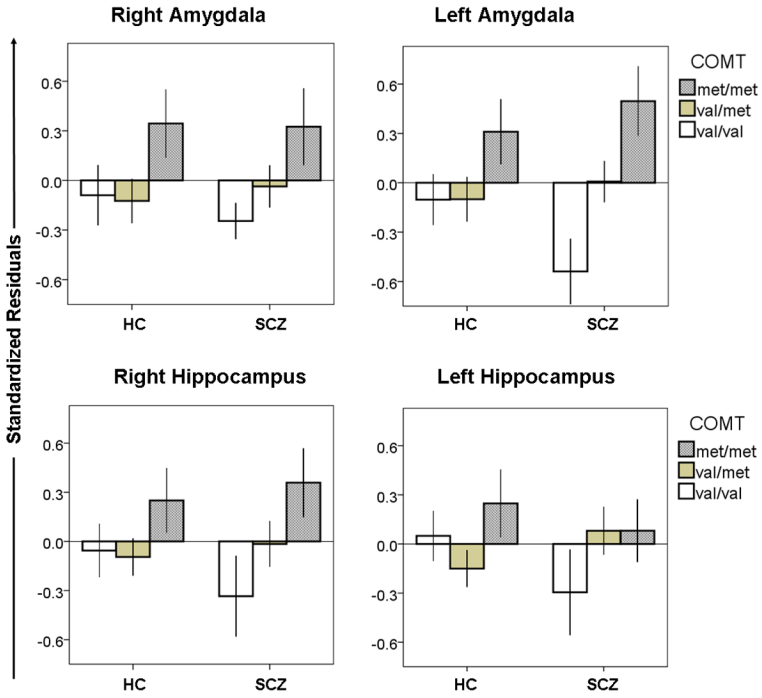

Figure 3.

Barcharts showing mean and standard errors of the standardized residuals for the effects of COMT on amygdala and hippocampus volumes in healthy controls (HC) and patients with schizophrenia (SCZ) controlled for intracranial volume, age and gender. The additive effect of COMT is significant for right and left amygdala as well as right hippocampus.

Table 1

Demographic results.

			N	Gender		Race		Age		WRAT Score		Parental SES		Handedness		COMT Genotype					
				female		Caucasian		Mean	SD	Mean	SD	Mean	SD	Mean	SD	met/met		val/met		val/val	
				N	%	N	%									N	%	N	%	N	%
Site	UI	HC	60	26	43.3[b]	56	93.3	30.18	10.05	50.40[a]	4.13	2.85	0.44	0.87	2.84	13	21.7	30	50.0	17	28.3
		SCZ	27	6	22.2[b]	25	92.6	33.56	10.83	48.00[a]	5.27	2.58	0.81	1.56	3.94	4	14.8	14	51.9	9	33.3
	MGH	HC	20	10	50.0	12	60.0	38.85	9.38	51.95[a]	4.12	3.05	0.89	0.60	1.82	2	10.0	11	55.0	7	35.0
		SCZ	26	7	26.9	15	57.7	39.50	7.50	44.38[a]	7.25	3.48	1.16	1.71	3.84	7	26.9	15	57.7	4	15.4
	UMN	HC	17	5	29.4	17	100.0[b]	31.59	11.77	50.47[a]	3.79	2.47	0.80	0.47	0.80	8	47.1	7	41.2	2	11.8
		SCZ	25	7	28.0	16	64.0[b]	31.92	10.11	45.16[a]	5.63	2.72	0.84	1.32	3.29	8	32.0	13	52.0	4	16.0
	UNM	HC	17	4	23.5	15	88.2	32.06	13.75	51.47[a]	3.57	2.00	0.79	1.00	2.42	5	29.4	8	47.1	4	23.5
		SCZ	20	5	25.0	18	90.0	35.80	13.92	46.65[a]	5.76	2.61	1.04	1.25	2.99	3	15.0	13	65.0	4	20.0
Total		HC	114	45	39.5[b]	100	87.7[b]	32.19	11.13	50.84[a]	4.00	2.70	0.73	0.78	2.39	28	24.6	56	49.1	30	26.3
		SCZ	98	25	25.5[b]	74	75.5[b]	35.17	10.85	46.05[a]	6.09	2.86	1.02	1.47	3.52	22	22.4	55	56.1	21	21.4

Linear or logistic regression analysis with COMT genotype, diagnostic group and the interaction of the two indicated no significant differences in age, parental SES, premorbid IQ, handedness score, sex or race between the genotype groups, or between the genotype groups by diagnostic group. HC=healthy controls, SCZ=patient with schizophrenia. Cognitive achievement was measured by the Wide Range Achievement Test (WRAT-IIIRT), parental SES (socioeconomic status) classified according to Hollingshead and handedness determined using the Annett Scale of Hand Preference.

[a] significantly differed between SCZ patients and HN Controls on the basis of Student's t tests($p>0.05$).

[b] significantly differed between SCZ patients and HN Controls on the basis of $\chi 2$ tests ($p>0.05$).

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Table 2

Clinical variables for patients with schizophrenia.

		Length of Illness		SAPS		SANS		Cumulative typical antipsychotics		Cumulative atypical antipsychotics		Cumulative Clozapine		Current typical antipsychotics		Current atypical antipsychotics		Current Clozapine	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Site	UI	11.87	7.73	4.70	3.29	8.48	3.61	24.27	49.51	28.59	35.93	8.01	25.69	116.35	347.63	349.04	410.46	123.08	349.06
	MGH	16.55	10.47	4.38	3.21	6.12	4.01	61.37	203.83	15.06	23.68	22.88	40.86	97.00	241.99	234.00	315.89	221.60	470.28
	UMN	9.97	8.82	5.12	2.49	7.76	2.95	24.45	67.77	22.29	80.02	3.57	17.50	262.68	819.80	320.83	356.67	32.00	160.00
	UNM	11.98	12.25	5.15	2.78	7.90	3.63	5.67	12.51	8.96	9.03	12.48	32.25	106.25	475.16	274.38	326.38	215.00	405.59
Total		12.61	9.94	4.82	2.95	7.55	3.63	30.10	112.74	19.39	46.30	11.71	30.63	147.31	516.07	295.92	353.55	144.17	365.20

SANS, Scale for the Assessment of Negative Symptoms. SAPS, Scale for the Assessment of Positive Symptoms. Cumulative antipsychotic drug exposures are given as dose years (1 dose year = 100 chlorpromazine equivalents per day for one year). Current antipsychotic drug dosages are given in chlorpomazine units.

Table 3

Multiple regression models for main outcome and control ROIs.

	Right-Amygdala			Left-Amygdala			Right-Hippocampus			Left-Hippocampus			Whole brain		
Variables	**Beta**	**t**	**p**	**beta**	**t**	**p**	**beta**	**t**	**p**	**beta**	**t**	**p**	**beta**	**t**	**p**
Diagnosis (SCZ)	−59.6	−2.3	0.020	−61.8	−2.2	0.029	−231.5	−4.1	0.000	−167.1	−3.2	0.001	−42412.1	−4.8	0.000
COMT (met load)	44.4	2.5	0.012	64.6	3.3	0.001	93.0	2.4	0.016	56.2	1.6	0.114	7033.2	1.1	0.254
Gender (female)	−104.3	−3.2	0.002	−132.5	−3.7	0.000	−56.8	−0.8	0.426	−38.0	−0.6	0.564	−25400.4	−2.2	0.027
age centered	−3.7	−3.2	0.001	−3.7	−3.0	0.003	−7.6	−3.1	0.002	−6.1	−2.7	0.008	−3127.7	−7.9	0.000
	R2			R2			R2			R2			R2		
Summary statistics	change		p	change		p	change		p	change		p	change		p
Effect of Site	0.025		0.021	0.002		0.844	0.019		0.067	0.019		0.090	0.093		<0.001
Total adjusted R2	0.472			0.383			0.453			0.387			0.829		

The intercept as well the effect of ICV are not shown.