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MET^{158} VARIANT OF THE CATECHOL-O-METHYLTRANSFERASE GENOTYPE IS ASSOCIATED WITH THICKER CORTEX IN ADULT BRAIN

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Abstract—Cortical thickness has been proposed as a new promising brain imaging endophenotype in elucidating the nature of gene–brain relationships. Here, we define the morphological impact of the *Val*^{158}Met polymorphism in the catechol-O-methyltransferase (COMT) gene on human brain anatomy. One hundred and forty-nine adult healthy subjects (mean age: 40.7±16.1; ranging from 19 to 76 years) were genotyped (38 in the homozygous *Val*^{158} group; 80 in the *Val*^{158}*Met* group; 31 in the homozygous *Met*^{158} group) for the COMT polymorphism and underwent morphological examination. Surface-based analysis of the cortical mantle showed that the COMT genotype was associated with structural differences in the right superior temporal sulcus and inferior prefrontal sulcus, where the individuals carrying the *Met*^{158} allele had a thicker cortex with respect to their *Val*^{158} counterparts. Our study extends the previous evidence found on pediatric population to the adult population, demonstrating that the higher synaptic dopamine levels associated with the presence of the *Met*^{158} allele may influence neuronal architecture in brain structures important for executive and emotional processing.

Key words: COMT *Val*^{158}*Met* polymorphism, cortical thickness, superior temporal sulcus, inferior prefrontal sulcus, imaging genetics.

Imaging genetics is an emerging area of neuroscience that is proving to be effective in delineating genetic effects on individual differences in brain function/structure and on human behavior. There are few genetic polymorphisms that have demonstrated having an effect either at an intermediate phenotypic level (brain function and structure) and at a phenotypic level (gene-cognitive function or gene-behavioral disorder relationships). One of the most important genotypes investigated in the imaging genetics field is the *Val*^{158}*Met* polymorphism (known as rs4680) of the catechol-O-methyltransferase (COMT) gene. Regulation of dopamine signaling and neurotransmission in the cortex is critically affected by COMT (Matsumoto et al., 2003), which inactivates via methylation dopamine and other catecholamines. COMT is widely expressed in the hippocampus and the prefrontal cortex (PFC) (Matsumoto et al., 2003). Of particular interest is a functional single nucleotide polymorphism (SNP) of the COMT gene that produces an amino acid substitution of methionine (*Met*) to valine (*Val*) at codon 158 (*Val*^{158}*Met*) (Mannisto and Kaakkola, 1999), which affects dopamine regulation in the PFC (Palmatier et al., 1999). This polymorphism alters the stability of the enzyme activity. The *Met*^{158} allele has been associated with decreased COMT activity, resulting in higher extracellular dopamine levels, whereas the *Val*^{158} allele has been associated with increased COMT activity, resulting in lower synaptic levels (Lotta et al., 1995; Weinberger et al., 2001; Chen et al., 2004). Several studies have demonstrated that the *Met*^{158} allele improves cognitive performance, compared to the *Val*^{158} allele (Bruder et al., 2005; Egan et al., 2001; Mattay et al., 2003; Goldberg et al., 2003), resulting in a better cortical efficiency of prefrontal activity as assessed by functional magnetic resonance technique (fMRI) (Egan et al., 2001; Mattay et al., 2003).

However, despite this polymorphism being consistently linked with the measurement of brain activity, earlier data on its association with brain morphology have been conflicting (Ohnishi et al., 2006; Taylor et al., 2007; Cerasa et al., 2008; Honea et al., 2009; Mechelli et al., 2009). Recently, by using an *in vivo* measurement of cortical thickness to define possible genetic factors that influence anatomy in the human pediatric brain, Shaw et al. (2009) showed that the *Val*^{158}Met polymorphism has a specific impact on the temporal and prefrontal cortices. In particular, these authors demonstrated that the carriers of the *Met*^{158} allele had thicker cortex with respect to their *Val*^{158} counterparts.

The aim of this study is to define, by using cortical thickness measurement, the morphological effect of the COMT genotype on a large cohort of healthy adults, in order to extend the work from Shaw et al. (2009) by adding new evidence on the genetically driven morphological variations in the brain throughout the course of a human lifetime.

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Abbreviations: BDNF, brain derived neurotrophic factor; COMT, catechol-O-methyltransferase; fMRI, functional magnetic resonance imaging; GLM, general linear model; Met, methionine; MMSE, Mini Mental State Examination; PCR, polymerase chain reaction; PET, positron emission tomography; SNP, single nucleotide polymorphism; Val, valine.

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EXPERIMENTAL PROCEDURES

Subjects

One hundred and fifty-five healthy individuals (Caucasian, age-range 18–70) were recruited by local advertisements. Exclusion criteria were: (1) major medical illnesses and/or known or suspected history of alcoholism or drug dependence and abuse; (2) mental disorders (i.e., mood, anxiety, personality and/or any other significant mental disorders) according to the DSM-IV criteria assessed by the Structured Clinical Interviews for DSM-IV Axis I (SCID-I) (First et al., 1997a) and Axis II (SCID-II) (First et al., 1997b) and/or neurological disorders diagnosed by an accurate clinical neurological examination; (3) presence of vascular brain lesions, brain tumor and/or marked cortical and/or subcortical atrophy on MRI scan and (4) dementia. Subjects screened positive for dementia if they scored <27 points on the 37-item version of the Mini Mental State Examination (MMSE; Folstein et al., 1975) or if they presented a dementia diagnosis according to DSM-IV criteria.

After a careful evaluation of these exclusion criteria, six subjects were excluded from the sample because they were diagnosed with dementia or because they had previous traumatic brain injury. Written, informed consent was obtained from all subjects participating to the study, which was approved by the local ethics committee at Santa Lucia Foundation of Rome, in accordance with the guidelines of the Helsinki Declaration (1983).

The final sample of 149 were classified on the basis of COMT *Val*^{158}*Met* polymorphism as *Val*/*Val* (n=38), *Val*/*Met* (n=80) and *Met*/*Met* (n=31). To check for known potentially confounding variables, since cortical gray matter volume has been previously associated with a functional polymorphism in the targeting region of the brain derived neurotrophic factor (BDNF) gene (*Val*^{66}*Met*) (Pezawas et al., 2004), we genotyped our group according to this polymorphism to account for potential confounds in interpreting COMT effects on brain morphology (detailed demographics and statistics are summarized in Table 1).

Genotyping

Genomic DNA was extracted from peripheral blood samples using standard procedures (Liguori et al., 2007; Cerasa et al., 2008, 2010). The *Val*^{158}*Met* COMT polymorphism was assayed by polymerase chain reaction (PCR) amplification using primers 5′-TCGTGGACGCCGTGATTCAGG-3′ and 5′-AGGTCTGACAACGGGTCAGGC-3′. The amplification conditions were initiated at 95 °C for 2 min, followed by 30 cycles consisting of denaturation at 95 °C for 30 s, annealing at 55 °C for 30 s with an extension at 72 °C for 1 min, with a final extension step of 10 min at 72 °C. Enzymatic digestion with the NlaIII restriction enzyme (Yim et al., 2001) was then performed on the PCR products, followed by 3.0% metaphor gel-electrophoresis. Restriction fragments of 114, 83 and 20 bp revealed the Val-allele, those of 96, 83, 20 and 18 bp identified the Met-allele.

Within the BDNF gene, a SNP located at nucleotide 196 (dbSNP rs6265), resulted in a valine to methionine (*Val*^{66}*Met*) substitution in the pro-peptide of the BDNF molecule. The nucleotide substitution, identifying the BDNF *Val*^{66}*Met* amino acid change, was assayed by PCR amplification using primers 5′-ACTCTGGAGAGCGTGAATGG-3′ and 5′-ACTACTGAGCATCACCCTGGA-3′. The amplification conditions were initiated at 95 °C for 5 min, followed by 35 cycles consisting of denaturation at 95 °C for 1 min, annealing at 60 °C for 30 s with an extension of 72 °C for 1 min, with a final extension step of 10 min at 72 °C. Enzymatic digestion with the Eco72I restriction enzyme was then performed on the PCR products, followed by 3.0% agarose gel-electrophoresis. The uncut A-allele (*Met*) was 171 base-pairs (bp) long, while the G-allele (*Val*) comprised cut bands of 99 bp and 72 bp (Nakata et al., 2003).

Magnetic resonance imaging

Each of the 149 participants underwent the same imaging protocol with a whole-brain T1-weighted scan using a 3-T Allegra MR imager (Siemens, Erlangen, Germany) with a standard quadrature head coil. Whole-brain T1-weighted images were obtained in the sagittal plane using a modified driven equilibrium Fourier transform (MDEFT) (Deichmann et al., 2004) sequence (TE/TR=2.4/7.92 ms, flip angle 15°, voxel-size 1×1×1 mm^3).

Cortical thickness

MRI-based quantification of cortical thickness was performed using *Freesurfer* (vs. 4.05) software package (http://surfer.nmr.mgh.harvard.edu). This method has been previously described in detail (Dale et al., 1999; Fischl et al., 1999; Fischl and Dale, 2000). The procedure involves segmentation of white matter, tessellation of the gray/white matter junction, inflation of the folded surface, tessellation patterns and automatic correction of topological defects in the resulting mainfold. Cortical thickness measurements were obtained by reconstructing representations of the gray/white matter boundary and the cortical surface. The distance between these two surfaces was calculated individually at each point across the cortical mantle. This method uses both intensity and continuity information from the entire 3D MRI volume in segmentation and deformation procedures to construct representations of cortical thickness. The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The entire cortex in each individual subject was then visually inspected, and any inaccuracies in Talairach-transformed, skull stripped and segmentation were manually corrected and re-inspected. Thickness measurements

Table 1. Group demographics for cortical thickness analysis

Demographic data	COMT$^{108/158}$ Val/Val	COMT$^{108/158}$ Val/Met	COMT$^{108/158}$ Met/Met	P
N[a]	38	80	31	
Age (y)	41.4±17.1	40.6±15.8	37.6±16.1	0.31[b]
Gender (f/m)	20/18	49/31	21/10	0.51[a]
Educational level (y)	14 (5–21)	13 (5–19)	16 (8–19)	0.43[c]
MMSE	29.3±1	29.4±1	29.4±1.2	0.23[b]
BDNF Val^{66}Val (%) group	63.3%	67.5%	51.7%	
BDNF Val^{66}Met (%) group	31.5%	27.5%	45.1%	
BDNF Met^{66}Met (%) group	5.2%	5%	3.2%	

Data are given as mean values (SD) or median values (range) when appropriate.
[a] Chi-square-test.
[b] One-way ANOVA.
[c] Mann–Whitney test.

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can be mapped onto the "inflated" surface of each participant's reconstructed brain, thus allowing visualization without interference from cortical folding. Maps were smoothed using a circularly symmetric Gaussian kernel across the brain/cortical surface with a standard deviation of 12.6 mm and averaged across participants using a non-rigid high-dimensional spherical averaging method to align cortical folding patterns. This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortions, resulting in a mean measure of cortical thickness for each group at each point on the reconstructed surface. This spherical morphing procedure was used to construct the cortical thickness difference brain maps.

For each hemisphere, estimation of statistical effects was generated by computing a general linear model (GLM) of the effects of the COMT genotype on cortical thickness at each vertex. We modeled cortical thickness data using a linear regression analysis with genotype group treated as a linear ordered factor (that is, Val^{158}=0, $Val^{158}Met$=1, Met^{158}=2). Overall, morphological analyses showed no significant interaction between genotype and sex, nor between genotype and age, implying that genotype effects were stable across the age range. However, we included age and gender as covariates of no-interest in our model.

Statistical analyses were performed with the Statistical Package for Social Sciences software-SPSS (version 12.0, Chicago, IL, USA) for Windows. Assumptions for normality were tested for all cognitive and demographic variables. Normality was tested using the Kolmogorov–Smirnov test. All variables were normally distributed, except for the number of years of formal education. ANOVAs, Mann–Whitney U-test (educational level) and χ^2 (gender and BDNF $Val^{66}Met$ genotype distribution) were used to assess potential differences between the genotype groups for all demographic variables.

RESULTS

There were no significant differences in demographic and cognitive variables between the three groups (Table 1). The allelic distribution of BDNF genotype was in Hardy–Weinberg equilibrium in both COMT genotype groups (Met^{158}: χ^2=0.07, P>0.7; $Val^{158}Met$: χ^2=0.36, P>0.5; Val^{158}: χ^2=0.46, P>0.5).

The number of Met^{158} alleles in the COMT gene was positively associated ($Met^{158}Met$>$Val^{158}Met$>$Val^{158}Val$) with increased thickness of the right inferior prefrontal sulcus ($F_{2,141}$=9.94; P-level<0.0001) and right superior temporal sulcus ($F_{2,141}$=9.83; P-level<0.0001). In particular, the $Met^{158}Met$ homozygous showed the highest value of thickness (2.245±0.28 mm; 2.442±0.34 mm, for the temporal and prefrontal structures respectively), while the $Val^{158}Val$ individuals had the lowest (1.991±0.24 mm; 2.151±0.2 mm, for the posterior and anterior structures respectively) (Fig. 1). All morphological results survived adjustment for multiple comparisons using the false discovery rate (FDR) procedure with P<0.05. No significant inverse correlation was detected ($Val^{158}Val$>$Val^{158}Met$>$Met^{158}Met$).

DISCUSSION

Using cortical thickness analysis, we demonstrated that the effect of the $Val^{158}Met$ COMT genotype on brain morphology in the adult brain is restricted to defined brain regions, with particular involvement of the inferior prefrontal sulcus and the superior temporal sulcus. Our data confirm and extend previous evidence (Shaw et al., 2009) on the impact of the COMT genotype on brain anatomy.

COMT has attracted considerable attention as a promising candidate gene for both cognitive function and affective psychopathology (Mier et al., in press). The most abundant expression of COMT is found in the prefrontal cortex (Matsumoto et al., 2003; Palmatier et al., 1999). Previous fMRI studies reported that the $Val^{158}Met$ polymorphism specifically impacts prefrontal-related cognitive performance as well as the efficiency of prefrontal function during the execution of working memory and attentional tasks (Bruder et al., 2005; Egan et al., 2001; Mattay et al., 2003; Goldberg et al., 2003). In particular, the low-activity Met^{158} allele predicted enhanced cognitive performance associated with a more efficient physiological response in the prefrontal cortex (i.e., decreased magnitude and extent of activation for a given level of task performance). The underlying mechanism of such behavioral differences may be related to higher prefrontal dopamine levels arising from lower dopamine catabolism mediated by the Met^{158} allele that may finally result in optimal dopamine receptor stimulation for proper prefrontal function (Chen et al., 2004; Mattay et al., 2003). Our structural data are consistent with the reported influence of the COMT genotype on function of the prefrontal cortex. In particular, the presence of thicker cortex in the carriers of the Met^{158} allele with respect to their Val^{158} counterparts would seem to provide a neuroanatomical basis for the hypothesized dopamine-related prefrontal efficiency.

As concerns morphological effects on the temporal cortex, several imaging genetics studies provided evidence that the COMT $Val^{158}Met$ genotype impacts the function and structure of this brain area and has a putative contribution to an increased risk for anxiety and mental disorders (Kempton et al., 2009; Taylor et al., 2007; Shaw et al., 2009; Domschke and Dannlowski, in press; Mier et al., in press). In particular, two recent works confirmed increased gray matter in the temporal cortex of healthy carriers of the Met^{158} allele (Taylor et al., 2007; Shaw et al., 2009), although some methodological differences with respect to our findings need to be argued. In fact, Taylor et al. (2007) provided evidence that the COMT genotype impacts the entire volume of the temporal cortex. By definition, volume is the product of surface and thickness, therefore measurements of gray matter volume combine structural properties that are unique to both cortical surface area and cortical thickness, and it has been demonstrated that thickness and surface area are biologically independent and differently influenced by genetic factors (Winkler et al., in press; Panizzon et al., 2009). Therefore in certain situations it can be difficult to disentangle the relative contribution of these physical alterations to observed results (Panizzon et al., 2009). On the other hand, the thicker temporal cortex detected by Shaw et al. (2009) in adolescents carrying the Met^{158} allele partially overlapped with our data. Whereas, the peak of difference detected by Shaw et al. (2009) involved middle/superior temporal gyrus, our data reported COMT-related morphological changes that

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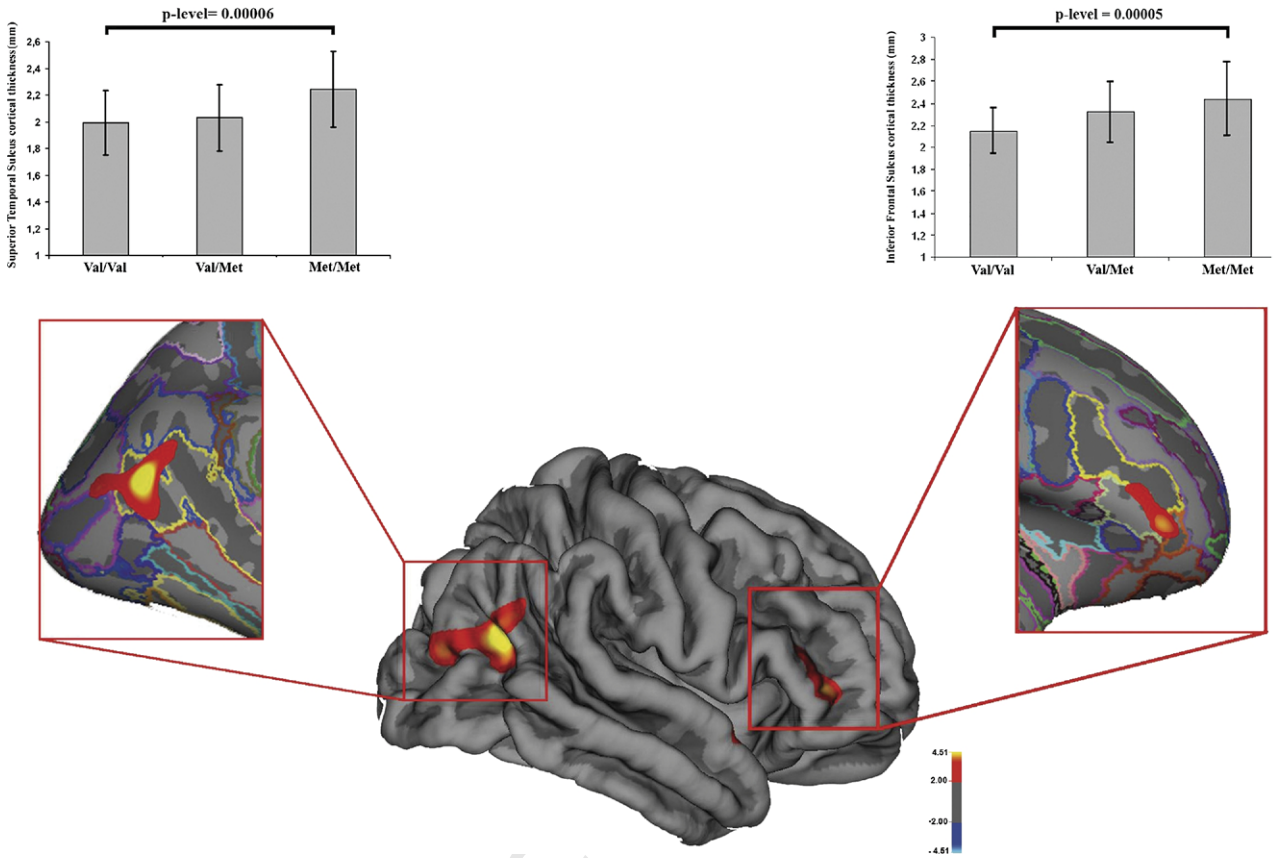

COLOR

Fig. 1. Whole brain vertex-wise analysis of cortical thickness for genotype groups. Mean difference maps were generated by aligning and averaging brain MRIs across participants in spherical space to demonstrate the main cortical thickness differences between the three groups at each point on the cortex. Maps are presented on the pial cortical surface (right lateral view) that shows the regions with a linear increase in cortical thickness where $Val^{158}Val < Val^{158}Met < Met^{158}Met$. Red ($t$-value=2.00) and yellow (t-value=4.51) represent areas where $Met^{158}Met$ individuals had significantly thicker cortices than their $Val^{158}Val$ counterparts, with peak differences of almost 0.3 mm. FDR-determined $P<0.05$ significance threshold was at t-value=4.51. To better describe morphological changes we used an inflated cerebral mantle with a superimposed parcelated cortex (*aparc.a2005s.annot*) derived from an probabilistic labeling algorithm (Fischl et al., 2004) that was applied for defining cortical regions of interest (Destrieux et al., 1998). Whereas the effect of COMT genotype on anatomy of the prefrontal cortex was clearly localized on the inferior frontal sulcus (right side), the effect on the posterior cortex was widespread. In fact, the detected cortical thickness alterations involved a large region encompassing both posterior temporal cortex and inferior parietal cortex, with the local maxima detected in the superior temporal sulcus (left side). The graphs show the mean thickness (±SD) by genotype of the regions showing the maximum COMT effect.

were relatively more posterior in location, involving a wide region at the borderline between the temporal and parietal cortices. This difference could be related to methodological aspects, such as the different population employed (adolescent vs. adult) or the influence of other functional polymorphisms known to affect brain anatomy (such as $Val^{66}Met$ BDNF, Pezawas et al., 2004). However, the peak of difference detected in our study specifically included the superior temporal sulcus (Fig. 1). The activity of this cortical area has been widely demonstrated as playing a key role in the emotional processing and anxiety disorders (Bishop et al., 2007; Sander et al., 2005; Haxby et al., 2000). Therefore, given the well-reported role of the COMT $Val^{158}Met$ genotype on the pathogenesis of anxiety disorders (Domschke and Dannlowski, in press; Mier et al., in press), further studies are warranted to define whether the detected altered brain anatomy of the superior temporal sulcus could be a new promising endophenotype in elucidating genotype–phenotype relationships.

Otherwise, neuroimaging measures of the COMT $Val^{158}Met$ effect has already shown promise in studying the neurobiology of mental illness. In fact, using positron emission tomography (PET) to define the functional correlates of resting state in schizophrenic patients, Eisenberg et al. (2010) found that the Val^{158} allele predicted lower regional cerebral blood flow in both the right temporal and prefrontal cortex with respect to that in the Met^{158} counterparts. The same detrimental effect of the Val^{158} allele on the temporal and prefrontal cortex was also detected in schizophrenic patients by analyzing regional gray matter volume (Ohnishi et al., 2006). Overall, all these studies confirmed both that specific brain regions are under considerable COMT-related influence and that the $Val^{158}Met$ polymorphism emerges as a possible risk gene, by affecting the function and morphology of specific neocortical areas that play key roles in the neuropathology of schizophrenia (Ohnishi et al., 2006).

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Another challenging finding of our study is the right hemisphere lateralization effect found in association with the COMT genotype. Although the similar morphological effect has been detected in a pediatric population (Shaw et al., 2009), previous morphological and functional studies reported a bilateral effect (Ohnishi et al., 2006; Cerasa et al., 2008; Honea et al., 2009; Mier et al., in press). This remains an open question that could be addressed in future studies, although the detected COMT-related morphological lateralization is plausible because it is consistent with the right-specialization of working memory-related cognitive function (Nelson et al., 2000).

CONCLUSION

In conclusion, our study demonstrates that the presence of the *Met*^{158} allele in a large healthy people is associated with significant increases of cortical thickness in the right superior temporal sulcus and the inferior prefrontal sulcus, two important areas involved in executive functions and relevant to the pathophysiology of mental illness. A similar morphological effect is present in pediatric (Shaw et al., 2009) and adult populations, confirming the role of this genotype in affecting human brain morphology independent of age.

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