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Frontoparietal cortical thickness mediates the effect of COMT *Val*^{158}*Met* polymorphism on age-associated executive function

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ABSTRACT

Proper dopamine (DA) signaling is likely necessary for maintaining optimal cognitive performance as we age, particularly in prefrontal-parietal networks and in fronto-striatal networks. Thus, reduced DA availability is a salient risk factor for accelerated cognitive aging. A common polymorphism that affects DA D1 receptor dopamine availability, COMT *Val*^{158}*Met* (rs4680), influences enzymatic breakdown of DA, with COMT Val carriers having a 3- to 4-fold reduction in synaptic DA compared to COMT Met carriers. Furthermore, dopamine receptors and postsynaptic availability are drastically reduced with aging, as is executive function performance that ostensibly relies on these pathways. Here, we investigated in 176 individuals aged 20–94 years whether: (1) COMT Val carriers differ from their Met counterparts in thickness of regional cortices receiving D1 receptor pathways: prefrontal, parietal, cingulate cortices; (2) this gene-brain association differs across the adult lifespan; and (3) COMT-related regional thinning evidences cognitive consequences. We found that COMT Val carriers evidenced thinner cortex in prefrontal, parietal, and posterior cingulate cortices than COMT Met carriers and this effect was not age-dependent. Further, we demonstrate that thickness of these regions significantly mediates the effect of COMT genotype on an executive function composite measure. These results suggest that poorer executive function performance is due partly to thinner association cortex in dopaminergic-rich regions, and particularly so in individuals who are genetically predisposed to lower postsynaptic dopamine availability, regardless of age.

1. Introduction

The human brain undergoes many alterations as a result of the normal aging process, with notable tissue reduction observed (Kennedy and Raz, 2015). This brain shrinkage is regionally specific, with relative age-related preservation of primary cortices, and pronounced reductions to volume and thickness in heteromodal association cortices (Fjell et al., 2009; Rast et al., 2018; Raz et al., 2010; Salat et al., 2004). This reduction in thickness and volume is highly variable across persons, and this variability likely is driven by individual differences in health, lifestyle/environmental, and genetic factors. Indeed, brain morphometry is highly heritable (Kochunov et al., 2015) and partly under genetic control (Thompson et al., 2001).

In complement to heritability estimates, single nucleotide polymorphisms have been identified that exert influence on brain and cognitive aging, and the identification of these candidate genes has allowed for investigation of brain properties not readily available for in vivo study in human cognitive aging. Perhaps the best studied of these is a common polymorphism (COMT *Val*^{158}*Met*, rs4680) in COMT, a gene that codes for the enzyme catechol-O-methyltransferase (Axelrod and Tomchick, 1958) that breaks down and eliminates dopamine (DA) in the synapse (predominately in D1 receptors: Hirvonen et al., 2010; Slifstein et al., 2008). Widely expressed in the neocortex, COMT regulates dopamine levels in prefrontal D1 receptors through degradation of extracellular dopamine. Individuals with less active enzymatic properties have 3-4 times greater levels of DA in the synapse, thus a progressive reduction in enzymatic activity among the genotypes has been identified to occur in a dose-response manner: Val/Val > Val/Met > Met/Met (Bäckman et al., 2006; Lotta et al., 1995; Weinshilboum et al., 1999). This increased enzymatic activity in the Val variant of COMT results in lower synaptic dopamine relative to COMT Met carriers (Chen et al., 2004; Papenberg et al., 2015).

Dopamine is a neurotransmitter highly associated with cognitive function, and its D1 receptors are densely concentrated in neocortical areas, primarily in prefrontal and parietal association cortex (Hall et al., 1994; Lidow et al., 1991; Palomeroa-Gallahger, Amunts, & Zilles, 2015). Synthesized in the midbrain,

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dopamine densely innervates the striatum and is distributed throughout the brain via multiple pathways: projections from the substantia nigra to the striatum (the nigrostriatal pathway), and projections from the ventral tegmental area to limbic regions (mesolimbic pathway) and to the neocortex (mesocortical pathway) (Lewis and Sesack, 1997; Li et al., 2010; Stoof and Kebabian, 1984). Neocortical regions receiving these dopaminergic projections are of interest not only because of their high concentrations of D1 receptors (Hall et al., 1994; Lidow et al., 1991) but also because of their vulnerability to age-related reductions in volume and thickness, and their associations with cognition, particularly executive functions (Buchsbaum et al., 2005; Laird et al., 2005; Middleton and Strick, 2000; Yuan and Raz, 2014). Furthermore, the neocortex in particular, unlike the striatum, lacks dopamine transporters and thus depends on COMT locally for regulating dopamine in the synapse (Slifstein et al., 2008; Tunbridge et al., 2004). COMT activity is particularly important in the prefrontal cortex, which is richest in dopaminergic pathways in the brain (Chen et al., 2004; Egan et al., 2001; Lidow et al., 1991; Matsumoto et al., 2003; Slifstein et al., 2008).

Inopportunely, normal aging brings about decreases in frontal D1 receptor densities and a gradual decline in postsynaptic markers of dopamine in striatal, neocortical, and limbic areas of the brain (Bäckman et al., 2006; de Keyser et al., 1990; Karrer et al., 2017; Suhara et al., 1991; Wang et al., 1998). Dopaminergic cell bodies in the substantia nigra are also negatively influenced by age, with a 3% reduction per decade (Bäckman et al., 2006; Fearnley and Lees, 1991). Because heritability of cognitive function (McClearn et al., 1997; Raz and Lustig, 2014) and brain structural properties (Kochunov et al., 2015) increase with age, and because it is also quite likely that gene expression differs with age across individuals (because of epigenetic factors), there may be important gene x age interactions on the effect of the gene on brain and cognitive function. The resource modulation hypothesis (Lindenberger et al., 2008) postulates that the effects of genes on cognitive performance are magnified in older adults because the neural systems are now degraded; however, this association is nonlinear as the neural system becomes further degraded, and the gene effects begin to diminish.

Given that the prefrontal circuitry is widely believed to support executive functions and because aging is associated with DA reduction, the role of DA and the COMT *Val*^{158}*Met* polymorphism have been examined for their effects on cognitive aging (Barnett et al., 2007; Papenberg et al., 2015; Raz et al., 2009; Witte and Flöel, 2012). Previous research indicates that the D1 receptor system plays a role in executive function and working memory, with lower DA receptor density and binding being associated with poorer performance on various cognitive tasks (Ito et al., 2008; Karlsson et al., 2009; McNab et al., 2009; Müller et al., 1998; Rieckmann et al., 2011; Salami et al., 2018; Wang et al., 1998). Studies examining the COMT *Val*^{158}*Met* polymorphism in healthy adults demonstrated that individuals with the lower enzymatic activity Met allele(s) evidence better cognitive performance compared to their Val counterparts, likely because of the greater synaptic DA in the Met carriers (Barnett et al., 2007; Caldú et al., 2007; Egan et al., 2001; Joober et al., 2002; Malhotra et al., 2002; Raz et al., 2009; Rosa et al., 2004; Witte and Flöel, 2012), but these effects are expected to be small (Barnett et al., 2008). In addition, according to the resource modulation hypothesis, COMT genotype may modulate the effects of age on cognitive performance (Li et al., 2010; Lindenberger et al., 2008; Nagel et al., 2008; Papenberg et al., 2015).

Given these considerations, the present study aimed to take advantage of the natural Mendelian randomization of biological characteristics, here dopamine availability at D1 receptors, that influence the aging process, in situations that cannot be easily or ethically experimentally randomized or manipulated (Mattay et al., 2008; Raz and Lustig, 2014). We do so by examining the effects of a candidate gene polymorphism, COMT *Val*^{158}*Met*, on cortical thickness in regions receiving projections from the mesocortical dopaminergic pathways. We chose to investigate cortical thickness as our measure of brain morphometry because it is a reasonably specific measure of brain structure (a proxy for laminar thickness) compared to tissue volume and because cortical thickness studies in rodents (Sannino et al., 2015) and children (Shaw et al., 2009) suggest that this metric of morphometry may be particularly influenced by COMT. Indeed, Cerasa et al. (2010) found small, local, but promising effects of COMT on thickness in a lifespan sample. We also investigate whether this association is age-dependent (i.e., age x gene interactions on regional thickness) and whether these COMT-brain associations have cognitive consequences. Specifically, we hypothesize that (1) regional cortical thickness of frontal, parietal, and cingulate cortex will be reduced in individuals genetically predisposed to lower dopamine availability (COMT Val carriers), (2) that COMT-thickness associations may magnify with increasing age, and (3) that COMT-related reductions in cortical thickness will be associated with poorer performance on executive function tasks.

2. Method

2.1. Participants

Participants included 176 healthy adult volunteers (70 men, 106 women), aged 20-94 years ($M = 53.49 \pm 19.28$ *SD* years of age) from the Dallas/Fort Worth metro community, recruited by posted flyers and media ads and were compensated for their participation. Participants were right-handed, native English speakers, with a minimum of high school education or equivalent ($M = 15.49 \pm 2.51$ *SD* years of education). Participants were screened to be free from history of cardiovascular problems (except controlled hypertension $n = 42$), neurological or psychiatric disorders, substance abuse, or head injury with loss of consciousness greater than 5 minutes. Participants tested at normal or corrected-to-normal vision and had no metallic implants or other contraindications for an MRI scan (e.g., claustrophobia). Participants were screened for both depression and dementia using the Center for Epidemiological Study Depression ([CESD], Radloff, 1977) scale and the mini mental state exam ([MMSE], Folstein, Folsteinet al, 1975) and were excluded if scoring at or above 16 or below 26, respectively. For inclusion in this study, participants were required to have complete data for COMT *Val*^{158}*Met* polymorphism genotype (COMT), T1-weighted MRI, and cognitive battery. Demographic characteristics of the sample, by genotype group, are provided in Table 1. All participants provided written informed consent in accord with local institutional review board guidelines.

Table 1
Sample demographic characteristics by COMT *Val*^{158}*Met* allele group

Variable	Met/Met	Val/Met	Val/Val	Total
N	41	89	46	176
Sex *N*, M/F	16/25	34/55	20/26	70/106
Age range	22–89	20–94	20–86	20–94
Mean age (SD)	59.20 (19.31)	52.04 (19.46)	51.22 (18.32)	53.49 (19.28)
Education (SD)	15.71 (2.59)	15.25 (2.50)	15.78 (2.47)	15.49 (2.51)
MMSE (SD)	28.95 (0.95)	28.98 (0.88)	29.07 (0.85)	28.99 (0.88)
CESD (SD)	4.29 (3.55)	4.17 (3.96)	3.67 (3.20)	4.09 (3.67)

Note. *N* = sample size; CESD, Center for Epidemiological Study-Depression; MMSE, mini mental state exam.
Groups did not differ significantly on these demographic characteristics (p's > 0.05).

2.2. DNA genotyping

Participants provided a saliva sample during a cognitive testing visit to the lab via Oragene kit (DNA Genotek, Ottawa, ON, Canada). DNA extraction and genotyping assays were performed at the University of Texas Southwestern Medical Center Microarray Core Facility. Ten percent direct repeats and DNA sequencing for verification were performed for genotyping quality control. DNA and no-template controls were used and ran 5′-nuclease assays with Applied Biosystem's 7900HT Fast Real-Time PCR System. DNA was extracted from the saliva samples using the prepIT-L2P purifier reagent (DNA Genotek, Ottawa, ON, Canada) while following the procedure in the manual purification protocol handbook. DNA integrity was determined by subjecting the samples to electrophoresis with 1% agarose gels. The polymorphism for rs4680 (COMT *Val*^{158}*Met*) was ascertained using Taqman SNP Genotyping assays (Applied Biosystems) with DNA sequencing reactions carried out using the 0.5x protocol for ABI PRISM BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems). COMT genotype for the sample included 46 Val homozygotes (26%), 89 heterozygotes (51%), and 41 Met homozygotes (23%), which was in Hardy-Weinberg equilibrium ($\chi^2 = 0.026$, $p = 0.872$). There were no significant differences among COMT genotypes in age ($p = 0.094$), education ($p = 0.42$), CESD ($p = 0.64$), or MMSE ($p = 0.81$). Twenty-two participants reported their ethnicity as other than only Caucasian: Met/Met ($n = 1$ Asian); Val/Met ($n = 5$ African-American, $n = 2$ Asian, $n = 3$ other); Val/Val ($n = 8$ African-American, $n = 1$ Asian, $n = 2$ other).

2.3. Magnetic resonance imaging (MRI) protocol

All participants were imaged on a single 3T Philips Achieva scanner with a 32-channel head coil. A high-resolution T1-weighted MP-RAGE pulse sequence was acquired with 160 sagittal slices at 1 x 1 x 1 mm^3 resolution with the following parameters: 204 x 256 x 160 matrix, TR = 8.1 ms, TE = 3.7 ms, flip-angle = 12°. This scan was used for estimating cortical thickness.

2.3.1. Cortical thickness measurements

Each participant's T1-weighted image was processed using the FreeSurfer v5.3.0 pipeline (Dale et al., 1999; Fischl, 2012; Fischl and Dale, 2000; Fischl et al., 1999) to obtain pial and white matter surfaces and for parcelation into cortical regions of interest (ROIs) using the Desikan atlas (Desikan et al., 2006). The quality of the resulting parcelation and segmentation was visually inspected by trained operators, and manual edits were made when necessary and processes reiterated to ensure proper regional demarcation.

For the present study, we selected a priori cortical regions for their association with mesocortical dopaminergic pathways and greater D1 dopamine receptor density (Egan et al., 2001; Hall et al., 1994; Karoum et al., 1994; Lewis and Sesack, 1997; Matsumoto et al., 2003; Palomero-Gallagher et al., 2015). These include 10 parcelation areas from prefrontal, parietal, and cingulate cortex. To gauge the relative specificity of our findings to the mesocortical pathway targets, 4 control regions where we did not expect to find a relationship were selected: pericalcarine cortex thickness as a control measure of cortical thickness with minimal dopaminergic innervation (Lewis et al., 2001); cerebellum and thalamus volumes as regions with minimal dopaminergic innervation, but also age-sensitive and cognitively relevant; and a limbic target as a dopamine-related, but extramesocortical pathway control region, hippocampus volume. Cortical thickness was measured (in mm) from these regions bilaterally and averaged across hemisphere, as we had no laterality driven hypotheses and to facilitate data reduction. Individual parcels were then averaged to form larger ROIs for use in statistical models, which included 5 frontal regions (superior, middle, inferior frontal gyri, orbitofrontal, and anterior cingulate cortices) and 5 parietal regions (precuneus, supramarginal and angular gyri, superior parietal, posterior cingulate), as illustrated in Fig. 1. Control region volumes (mm^3) were generated from FreeSurfer, averaged across hemisphere and adjusted for intracranial volume.

2.4. Cognitive tests

Participants were administered a battery of cognitive and neuropsychological tests across two approximately 2-hour visits to our laboratory. For this study, we utilize multiple tests that measure executive function:

Wisconsin Card Sorting Task ([WCST]; Heaton, 2008). A computerized version of the WCST was administered where participants received feedback (correct or incorrect) after each trial of matching a card to a choice of 4 cards by color, form, or number. Several indices of performance are computed from this task, and for this study, the index of performance is the percent of perseverative errors, including only incorrect responses. This index serves as a measure of cognitive flexibility or the ability to discontinue a previously valid strategy to adopt a new strategy.

Delis-Kaplan Executive Function Scales ([D-KEFS]; Delis et al., 2001). All tests of the D-KEFS were administered including the Stroop color word interference (Stroop; a verbal test of inhibition and cognitive switching ability), the trail making test (Trails; a visual-motor test of sequencing and switching ability), and verbal fluency (an oral word production test by category, and by switching between categories). Participants perform several subtests of these tasks, and for this study we use as the index of performance the switching trial indices. Specifically, the Stroop measure is computed as the average of total time taken in seconds for color naming and total time taken in seconds for word reading, subtracted from total time taken in seconds for switching and inhibition trials; the trails measure is computed as the average of the time taken to complete number sequencing condition in seconds and the time taken to complete letter sequencing condition in seconds, subtracted from the time taken to complete number letter switching in seconds; the verbal fluency measure is computed as the total category switching accuracy score.

To create a reliable construct of executive function, we computed standardized *z*-scores from the 4 indices described above (multiplying the verbal fluency by -1 to scale all scores in the same direction) and averaged the 4 *z*-scores to create an executive function composite. Cronbach's $\alpha = 0.71$ across the 4 measures.

2.5. Data analysis approach

Potential outlying data points were identified using the outlier labeling technique (Hoaglin and Iglewicz, 1987; Hoaglin et al., 1986; Tukey, 1977). For each ROI, the 25th percentile mean (*Q*1) and the 75th percentile mean (*Q*3) were identified. The interquartile range was multiplied by a factor (*g*) of 2.2 to yield *g*'. Any values outside the lower (*LL* = *Q*1+*g*') and upper limits (*UL* = *Q*3-*g*') were considered an outlier for each ROI and were excluded listwise from the data set. Four ROIs from 3 participants were excluded using this criterion, all from the Val/Met group ($n = 5$ data points).

Hypotheses 1 and 2 were tested in the general linear model framework. The models were specified with the region of interest as the dependent variable, and the independent variables for these models were the COMT *Val*^{158}*Met* polymorphism as a three-level categorical variable (Met/Met, Val/Met, Val/Val), mean-centered age as a continuous variable, and sex as a categorical variable, as well as the interaction term age*COMT to test whether the effect of

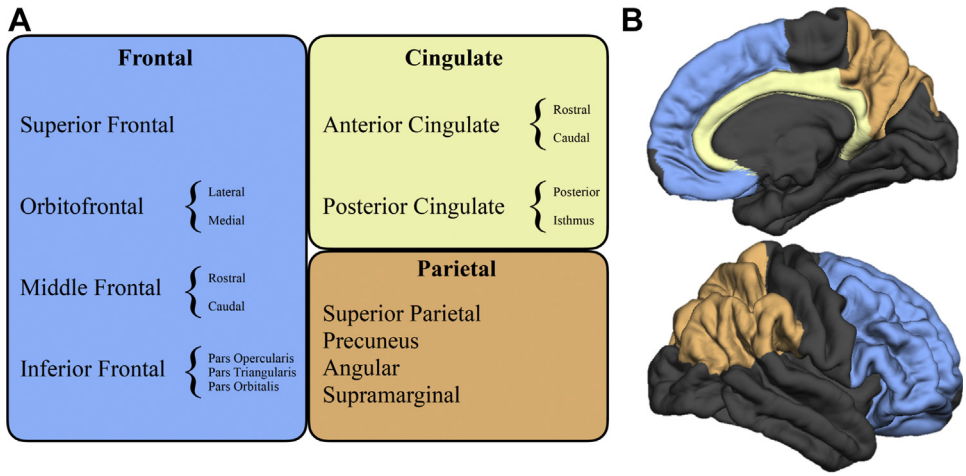

Fig. 1. Cortical regions of interest (ROIs) aggregates from FreeSurfer parcelations. (A) Thickness measures from the parcels encompassed within a brace were averaged to create the larger ROI to the left of the brace. (B) Lateral surface and medial wall views of mesocortical ROIs.

COMT on brain structure depends on age. Nonsignificant interactions were removed and the models re-estimated to conserve statistical power. As a conservative measure of effect size, ω^2 was reported for significant main effects. Post hoc comparisons using Tukey highly significant differences were conducted to determine the nature of group differences after identifying significant main effects of COMT; reported *p*-values are Tukey highly significant differences-corrected.

Hypothesis 3 was then tested in a moderated-mediation model framework using the PROCESS macro for SPSS (Hayes, 2013) to determine whether the genetic effect *(X)* on cortical thickness *(M)* makes a significant contribution to executive function performance *(Y)* and whether this mediation is moderated by age (as a continuous variable) *(W)*. See Fig. 4A for model specification illustration. To test this, a mean cortical thickness variable was created that incorporated regions with a significant ($p < 0.05$) or marginally significant ($p < 0.10$) main effect of COMT *Val*^{158}*Met* on cortical thickness from the univariate results. The presence of a significant indirect effect of COMT on executive function through cortical thickness would indicate a significant mediation effect of cortical thickness, and a significant effect of age (*W*) on path *"a"* (i.e., the effect of COMT on thickness) would indicate moderated mediation of this effect. Sex served as a covariate in the model.

3. Results

3.1. Age and COMT as modifiers of cortical thickness

The first objective of this study was to examine the role of COMT *Val*^{158}*Met* polymorphism on brain morphometry as a function of age. General linear models were specified as previously described.

3.1.1. Thickness construct

As an omnibus examination, we first test for effects on the mean thickness composite consisting of the 10 hypothesized ROIs. There was a significant negative effect of age on the thickness composite [$F(1,170) = 172.743$, $p < 0.001$, $\omega^2 = 0.493$], with older adults having thinner cortices, and a trend effect of sex [$F(1,170) = 3.042$, $p = 0.083$, $\omega^2 = 0.0002$], with women ($M = 2.416$, $SE = 0.011$) having marginally thicker cortices than men ($M = 2.386$, $SE = 0.014$). A significant main effect of COMT group on thickness [$F(2,170) = 3.062$, $p = 0.049$, $\omega^2 = 0.009$] was found where Met homozygotes ($M = 2.437$, $SE = 0.017$) had marginally thicker cortices than Val homozygotes ($M = 2.385$, $SE = 0.016$), $p = 0.077$. Met/Met individuals also had marginally thicker cortices than Val/Met individuals ($M = 2.389$, $SE = 0.012$), $p = 0.065$. There were no significant interactions. As a follow-up to this significant omnibus examination of COMT effects on the mean thickness construct, regional univariate analyses were conducted to determine the spatial specificity across these ROIs, with general linear models specified as before. Results are organized below by variable and then by region.

3.1.1.1. Age effects. There was a significant negative effect of age on all regions examined (all *p*'s < 0.001, see Fig. 2). To additionally test for nonlinear relationships, we added age^2 (while retaining age) to the model to test for quadratic effects of age on each region. See scatterplots in Fig. 1, where panel A displays the hypothesized regions and panel B displays the control regions. Three of the parietal cortex regions (superior parietal lobule, angular gyrus, precuneus) and hippocampus evidenced significant nonlinear accelerated age-related thinning (or volume loss for hippocampus), denoted with an asterisk in Fig. 2.

3.1.2. COMT effects

Of the 10 a priori ROI's examined, all 4 frontal ROIs displayed either a significant or marginally significant main effect of COMT on cortical thickness, where Met/Met individuals had thicker cortex than Val carriers. In contrast, 2 of 4 parietal, and 1 of 2 cingulate ROIs thickness differed by COMT group. See Fig. 3 for summary of regional COMT effects. Detailed model parameters and effect sizes are as follows by lobe:

3.1.2.1. Frontal. Middle frontal gyrus [$F(2,170) = 4.232$, $p = 0.016$, $\omega^2 = 0.018$] showed a significant difference between Met/Met ($M = 2.423$, $SE = 0.020$) and Val/Val ($M = 2.343$, $SE = 0.019$), where the Met/Met genotype had significantly thicker cortex compared to the Val/Val individuals ($p = 0.013$). Met/Met also showed marginally significant thicker cortex than Val/Met ($M = 2.370$, $SE = 0.013$; $p = 0.078$). Middle frontal gyrus [$F(1,170) = 6.363$, $p = 0.013$, $\omega^2 = 0.011$] showed a significant difference between men ($M = 2.350$, $SE = 0.015$) and women ($M = 2.399$, $SE = 0.013$), where women had significantly thicker cortex. Inferior frontal gyrus [$F(2,170) = 2.856$, $p = 0.060$, $\omega^2 = 0.008$] showed differences between Met/Met ($M = 2.520$, $SE = 0.025$) and Val/Val ($M = 2.438$, $SE = 0.024$), where the Met/Met genotype had marginally significantly thicker cortex compared to their Val/Val counterparts ($p = 0.056$). There were no

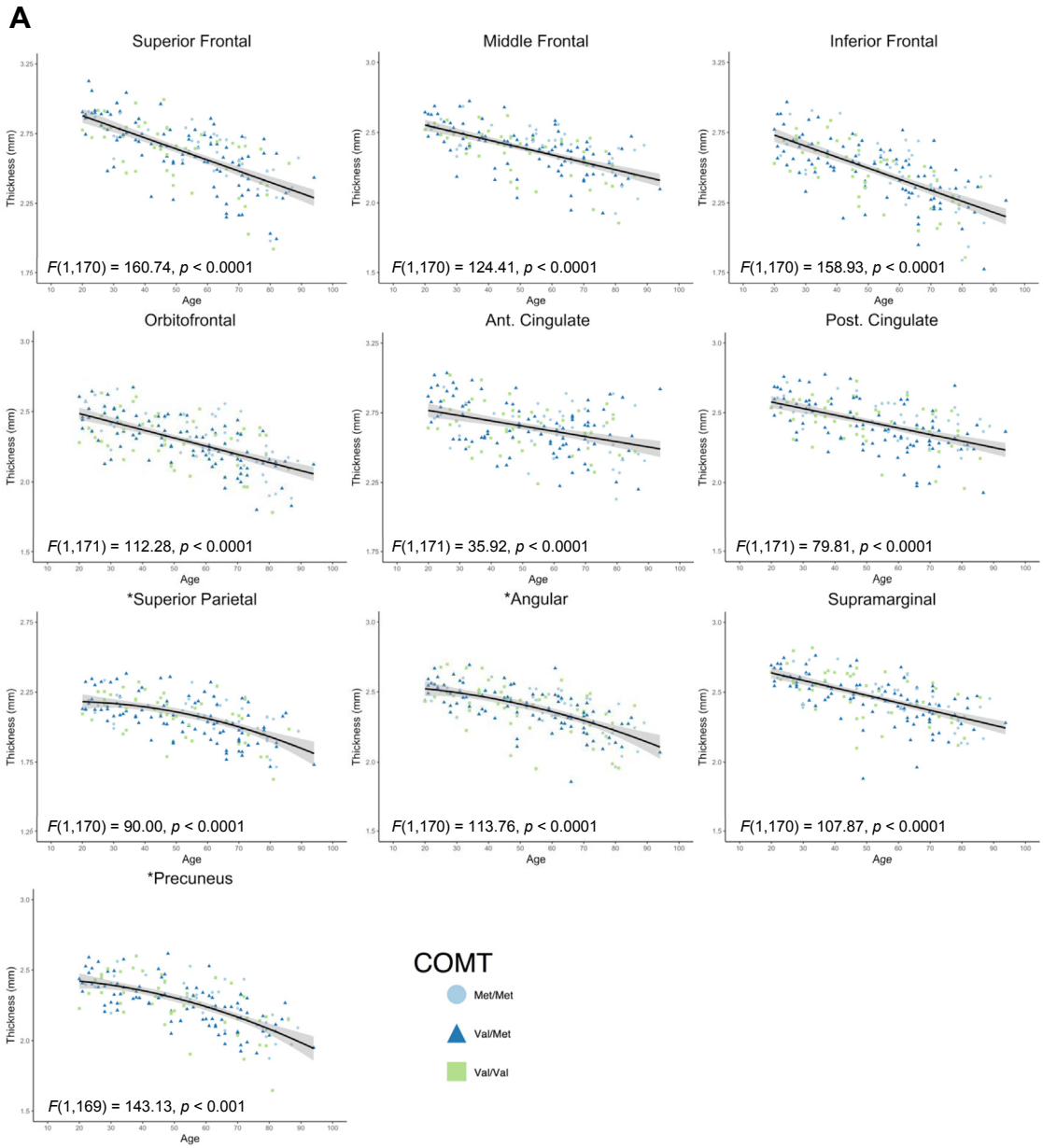

Fig. 2. Effects of aging on regional cortical thickness. Panel A displays the hypothesized COMT-related regions and Panel B displays the control regions. All regions examined demonstrated significant age-related reduction in thickness across the adult lifespan ($p < 0.001$). Three of the parietal regions and the hippocampus evidenced significant nonlinear (accelerated decline) age trajectories, identified with an asterisk. To visualize the distribution of COMT genotype across the lifespan in this sample, scatterdots are coded for genotype group. Note that there is not a significant age × COMT interaction for any region.

significant main effects of sex on cortical thickness in the inferior frontal gyrus [$F(1,170) = 0.338$, $p = 0.562$]. Superior frontal gyrus [$F(2,170) = 2.418$, $p = 0.092$, $\omega^2 = 0.020$] showed a nonsignificant trend toward a difference between Met/Met ($M = 2.662$, $SE = 0.026$) and Val/Val ($M = 2.588$, $SE = 0.024$), where the Met/Met genotype had marginally significantly thicker cortex compared to the Val/Val group ($p = 0.096$). Superior frontal gyrus [$F(1,170) = 6.917$, $p = 0.009$, $\omega^2 = 0.012$] also significantly differed between men ($M = 2.577$, $SE = 0.020$) and women ($M = 2.644$, $SE = 0.017$), where women had thicker cortex. Orbitofrontal cortex showed a nonsignificant trend [$F(2,171) = 2.373$, $p = 0.097$, $\omega^2 = 0.006$] for differences among COMT genotypes: Met/Met ($M = 2.335$, $SE = 0.023$), Val/Met ($M = 2.280$, $SE = 0.015$), Val/Val ($M = 2.276$, $SE = 0.021$). No significant effects of sex on orbitofrontal cortex thickness were observed, $F(1,171) = 0.163$, $p = 0.687$.

3.1.2.2. Parietal. There were 2 parietal regions with a marginally significant main effect of COMT. Precuneus [$F(2,169) = 2.457$ $p = 0.089$, $\omega^2 = 0.006$], where Met/Met ($M = 2.302$, $SE = 0.020$) had marginally significantly thicker cortex than Val/Met ($M = 2.251$, $SE = 0.014$; $p = 0.095$). There was no sex difference in precuneus thickness [$F(1,169) = 0.015$, $p = 0.903$]. Superior parietal lobule [$F(2,170) = 2.359$, $p = 0.098$, $\omega^2 = 0.006$] also showed a nonsignificant trend toward thicker cortex in Met/Met ($M = 2.110$, $SE = 0.020$) than Val/Met ($M = 2.059$, $SE = 0.013$) individuals ($p = 0.091$). There was no significant effect of sex on superior parietal lobule thickness [$F(1,170) = 2.598$, $p = 0.109$]. Supramarginal [$F(2,170) = 1.582$, $p = 0.209$] and angular gyri [$F(2,170) = 0.735$, $p = 0.481$] showed no significant main effect of COMT, nor sex differences: supramarginal [$F(1,170) = 0.002$, $p = 0.965$]; angular gyrus [$F(1,170) = 2.113$, $p = 0.148$].

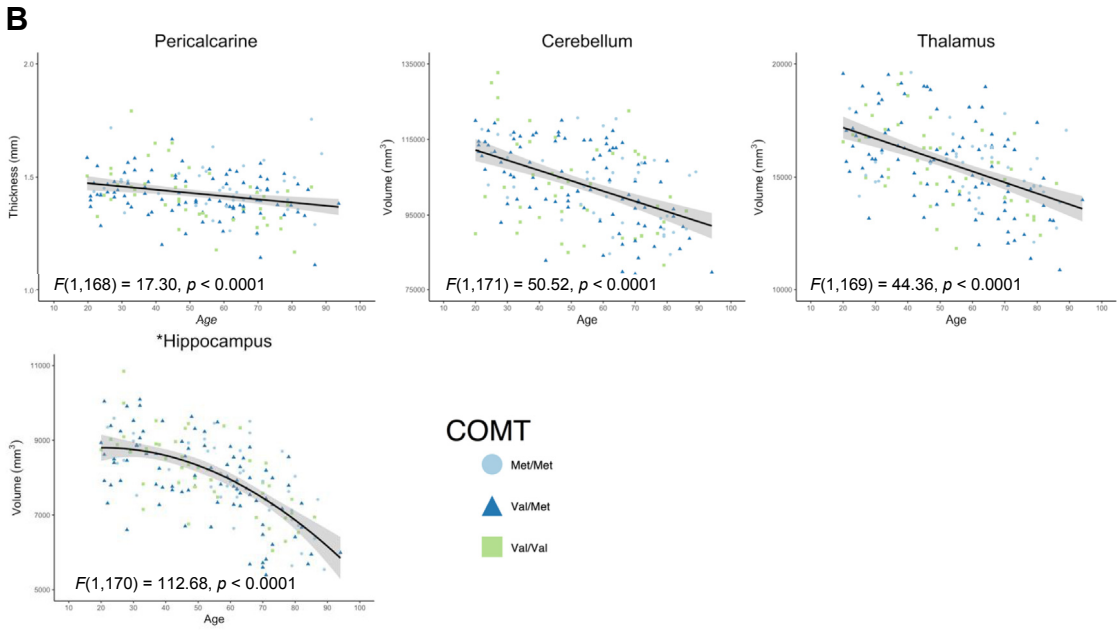

Fig. 2. (*continued*).

3.1.2.3. Cingulate gyrus. There was no significant main effect of genotype on anterior cingulate thickness [$F(2,171) = 0.133$, $p = 0.876$], but women ($M = 2.666$, $SE = 0.017$) had significantly thicker cortex than men ($M = 2.605$, $SE = 0.020$), $F(1,171) = 5.762$, $p = 0.017$, $\omega^2 = 0.013$. There was, however, a significant main effect of COMT for the posterior cingulate (pCing) [$F(2,171) = 4.623$, $p = 0.011$, $\omega^2 = 0.024$], where Met/Met ($M = 2.481$, $SE = 0.022$) group was thicker than Val/Val group ($M = 2.406$, $SE = 0.021$; $p = 0.043$). Met/Met genotype also evidenced significantly thicker cortex compared to Val/Met ($M = 2.402$, $SE = 0.015$; $p = 0.011$). Women ($M = 2.447$, $SE = 0.014$) also had thicker pCing than men ($M = 2.403$, $SE = 0.017$), $F(1,171) = 4.054$, $p = 0.046$, $\omega^2 = 0.004$.

3.1.2.4. Control regions. As expected, there were no significant main effects of COMT on pericalcarine cortex thickness [$F(2,168) = 2.129$, $p = 0.122$], or cerebellar [$F(2,171) = 0.685$, $p = 0.506$], hippocampal [$F(2,170) = 2.183$, $p = 0.116$], or thalamus volume [$F(2,169) = 0.347$, $p = 0.708$]. There was also no significant main effect of sex on pericalcarine thickness [$F(2,168) = 0.241$, $p = 0.624$], hippocampus [$F(2,170) = 0.056$, $p = 0.813$], or thalamus volume [$F(2,169) = 1.069$, $p = 0.303$]. Cerebellar volume was significantly larger in men ($M = 105{,}301.254$, $SE = 1206.087$) than women ($M = 101{,}760.940$, $SE = 1002.173$), $F(2,171) = 5.364$, $p = 0.022$, $\omega^2 = 0.0102$. These control region analyses suggest evidence of a relatively selective effect of COMT genotype on mesocortical pathway targets.

3.2. Interactive effects of COMT on cortical thickness

Second, we note that as a test of the resource modulation hypothesis, there were no significant or marginally significant age*COMT interactions for any of the 10 a priori cortical regions tested (p's > 0.387), suggesting that the effects of COMT on cortical thickness are not magnified with older age in this lifespan sample. For the 4 control regions, there were no significant age*COMT interactions for pericalcarine, cerebellum, or hippocampus (all F's < 1.3), but the thalamus displayed a marginally significant interaction [$F(2,169) = 5.364$, $p = 0.086$, $\omega^2 = 0.008$] where Met heterozygotes showed the least age-related volume reduction.

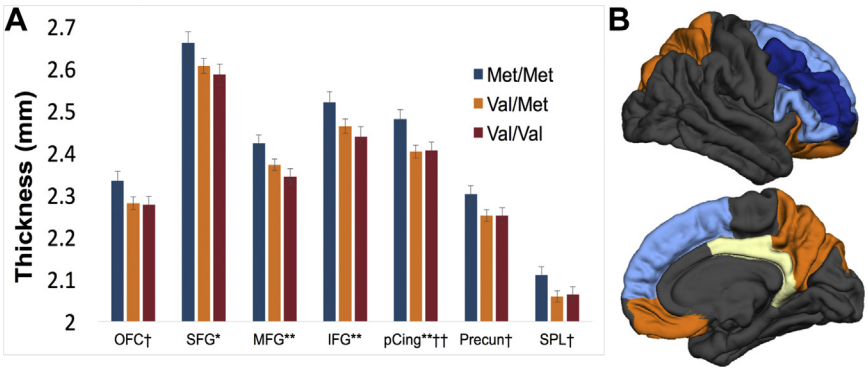

Fig. 3. Effects of COMT polymorphism on regional cortical thickness. (A) Regions where COMT Met homozygotes have thicker regional cortices compared with Val homozygotes and/or heterozygotes, beyond the effects of age. (B) Regions in blue were thicker in Met/Met individuals than Val/Val individuals. In orange regions, Met/Met evidenced thicker cortex than Val/Met. Yellow indicates region with Met/Met having thicker cortex than both Val/Met and Val/Val. ** $p < 0.05$, Met/Met > Val/Val, * $p < 0.10$, Met/Met > Val/Val, †† $p < 0.05$, Met/Met > Val/Met, † $p < 0.10$, Met/Met > Val/Met. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

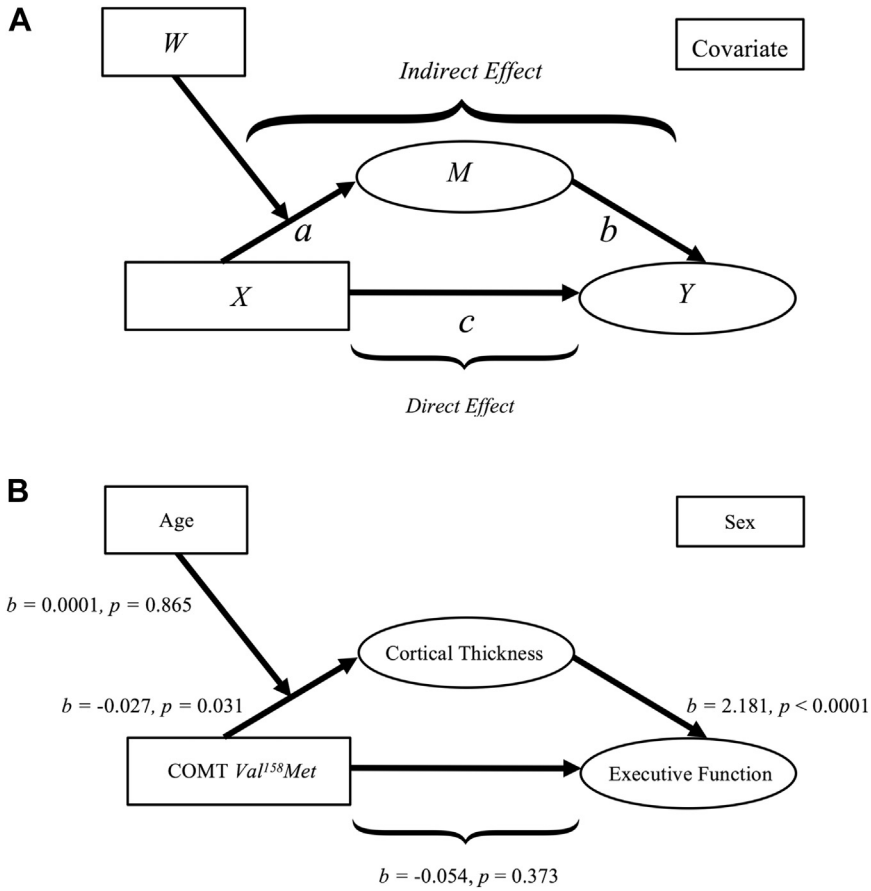

Fig. 4. Regional mesocortical thickness mediates the association between COMT and executive function performance across the adult lifespan. Panel A details the conceptual model specification and Panel B illustrates the model results. The indirect effect of COMT Val^{158}Met on executive function through cortical thickness was significant, b = −0.060, BCa 95% CI [−0.122, −0.010]. This mediation was not moderated by age, index of moderated-mediation = 0.0002, BCa 95% CI [−0.0023, 0.0030]. Direct effect of COMT on EF is not significant, b = −0.054, $p = 0.373$, BCa [−0.173, 0.065] suggesting full mediation of COMT effect on executive function by cortical thickness. Parameter estimates shown are unstandardized beta weights.

3.3. Moderated-mediation analysis: associations among age, COMT *Val^{158}Met*, cortical thickness, and executive function

After establishing the effects of COMT genotype on regional cortical thickness, the third objective was to determine if the effect of COMT polymorphism on cortical thickness significantly contributed to executive function performance. This was accomplished by conducting a moderated-mediation analysis via the PROCESS macro for SPSS (Hayes, 2013) employing bias corrected and accelerated (BCa) 95% confidence intervals bootstrap estimation approach with 10,000 samples. A mean thickness variable (Cronbach's $\alpha = 0.951$) was created by averaging the regions illustrated in Fig. 3. A moderated-mediation model was specified where executive function *(Y)* was regressed on COMT genotype *(X)* with cortical thickness *(M)* as a mediator and age *(W)* as a potential moderator of the mediation effect (as illustrated in Fig. 4A). The zero-order Pearson correlation between age and EF construct was $r = -0.544$, $p < 0.0001$. The mean (±standard error) EF *z*-score by COMT group was Met/Met = 0.014 (±0.101), Val/Met = 0.122 (±0.072), Val/Val = -0.104 (±0.0.099).

As illustrated in Fig. 4B, the model results indicated that COMT *Val^{158}Met* was a significant predictor of cortical thickness (*a*), ($b = -0.027$, $SE = 0.013$, $p = 0.031$, BCa 95% CI [−0.052, −0.003]) and that cortical thickness was a significant predictor of executive function (*b*), ($b = 2.181$, $SE = 0.280$, $p = 0.0001$, BCa 95% CI [1.630, 2.733]). Age (*W*) was not a significant predictor of the relationship between COMT and cortical thickness *(a)*, ($b = 0.0001$, $SE = 0.0006$, $p = 0.865$, BCa 95% CI [−0.001, 0.001]). As hypothesized, the indirect effect of COMT on executive function through cortical thickness ($X \rightarrow M \rightarrow Y$) was significant, ($b = -0.060$, $SE = 0.028$, BCa 95% CI [−0.122, −0.010]), indicating significant mediation. The model also indicated that COMT did not significantly predict executive function as a direct effect *(c)*, ($b = -0.05$, $SE = 0.061$, $p = 0.373$, BCa 95% CI [−0.1734, 0.0653]), suggesting full mediation of cortical thickness on EF. There was no significant moderation of this mediation by age (index of moderated-mediation = 0.0002, $SE = 0.001$, BCa 95% CI [−0.0023, 0.0030]).

4. Discussion

In this cross-sectional study, we investigated the relationship between the COMT *Val^{158}Met* polymorphism and age on regional cortical thickness in healthy adults across the lifespan. The mesocortical pathway was of primary interest because of its projections from the ventral tegmental area to the prefrontal cortex and throughout the neocortex (Li et al., 2010). We found that several target cortical regions of the mesocortical system were thinner in individuals who were predisposed to lower dopamine via carrying the COMT Val allele(s). Specifically, beyond the effects of age, we found thinner cortex in COMT Val carriers than in Met carriers in the frontal, parietal, and cingulate regions, most predominantly in frontal regions, which are highly populated with dopamine D1

receptors (Lidow et al., 1991; Matsumoto et al., 2003). Given the known role of COMT in the regulation of dopamine in the prefrontal cortex (Hong et al., 1998), these results suggest that genotypic differences influencing dopamine regulation also play a role in mesocortical target thickness differences among genetic variants. Further, in this lifespan sample, these differences were not modulated by age, suggesting that COMT-related effects are apparent throughout the adult lifespan and not only as a magnification of older age. Finally, we sought to examine whether these COMT-related reductions in cortical thickness were related to cognitive performance. Past research provides evidence that COMT plays an influential role in cognition (e.g., Barnett et al., 2007; Caldú et al., 2007; Egan et al., 2001; Joober et al., 2002; Malhotra et al., 2002; Raz et al., 2009; Rosa et al., 2004), and we sought to evaluate whether thickness measures in dopamine-rich cortex mediated the association between COMT and executive function. Results indicated that, indeed, COMT Val carriers performed more poorly on executive function tasks, but also that mesocortical thickness completely mediated this COMT-EF association.

4.1. COMT $Val^{158}Met$ and regional brain structure

There was a significant influence of COMT genotype on regional cortical thickness in this lifespan sample, with Val carriage associated with thinner cortex in regions that receive dopaminergic innervation. These regions include not only prefrontal areas (superior, middle, and inferior gyri and orbitofrontal cortex) but also regions with strong connectivity to prefrontal cortex: the posterior cingulate, precuneus, and superior parietal lobule. Although COMT has traditionally been thought to primarily regulate dopamine levels in the prefrontal cortex (Matsumoto et al., 2003), the precuneus, superior, and inferior parietal lobules are also relatively rich in DA D1 receptors (Palomeroa-Gallahger et al., 2015) and therefore would also be influenced by COMT. Furthermore, there is abundant connectivity across these regions, with the posterior cingulate making strong reciprocal connections to the prefrontal cortex (PFC) (Parvizi et al., 2006), and the precuneus is extensively connected to higher cognitive processing areas within the prefrontal cortex (Margulies et al., 2009). The abundant connectivity among these regions and the prefrontal cortex may facilitate the shared influence of COMT on these ROIs.

The current findings are interesting in light of what is known from previous animal and human studies. Dopamine exerts its effects on prefrontal cortex by modulation of synaptic inputs. COMT has the greatest mRNA expression in neurons (as compared to glia) and is higher in the PFC than in striatum or midbrain in both rats and humans (Matsumoto et al., 2003), manifesting its effects at the postsynaptic neuron dendrites. In COMT-knockout mice, the knockout of the COMT gene reduces COMT enzyme extracellular dopamine degrading activity, leading to an increase in dopamine levels in the synapse. This phenotype can be roughly correlated to Met/Met (complete knockout) or Val/Met (partial). Male mice with either level of this COMT gene knockout have been shown to have increased gray matter volume in the frontal and postero-parieto-temporal cortex compared to wild-type (roughly Val/Val equivalent) mice (Sannino et al., 2015). It has been long demonstrated that PFC cortical thickness is related to dopaminergic innervation in rodents (Kalsbeek et al., 1989), and more recently established that the COMT enzyme reduces neuronal density in mice (Sannino et al., 2015), suggesting a potential cellular substrate for the regional effect of COMT that would suggest a developmental origin. In humans, Shaw et al. (2010) found that COMT Met carriers had thicker temporal and parietal cortices in children and adolescents, further suggesting a developmental effect of COMT. In adult samples, Cerasa et al. (2010) also found thicker cortices in temporal and prefrontal gyri in Met carriers, whereas Sannino et al. (2015) in their adult human sample found thicker cortices in cingulate gyrus, posterior parietal, and medial PFC, but also frontal and temporal cortex in a sexually dimorphic manner (i.e., exclusively in men). In the current sample, we did not detect such sex effects.

The other studies addressing the impact of COMT $Val^{158}Met$ genotype on brain structure (mostly voxel-based morphometry studies of density/volume) have been quite mixed, with the direction of COMT influence varying among studies including null findings (Cerasa et al., 2008; Honea et al., 2009; Zinkstok et al., 2006). This inconsistency using voxel-based morphometry estimates of brain structure is most likely because of lesser reliability of that method (Kennedy et al., 2009), differently aged samples, limited sample sizes in some studies, reduced genotype specificity by combining allelic groups, and sample demographic differences (Lee and Qiu, 2016; Wang et al., 2013). Specifically, Lee and Qiu (2016) investigated the influences of the COMT haplotypes and aging on brain structure and found that COMT genetic variants modulate the association with age and brain structure in certain subcortical regions of high dopaminergic concentration. However, the direction of these findings (Val>Met) in their predominantly Asian population are inconsistent with what one would expect in a predominantly Caucasian population (Met>Val), which may be because of demographic differences previously identified in Chinese participants (Wang et al., 2013). The influence of COMT likely also works through alterations in white matter connectivity (e.g., Papenberg et al., 2014, 2015), at least in very old adults.

4.2. Magnification of COMT effects by age

A secondary goal of this study was to examine the sample for evidence of a magnification of COMT effects on cortical thickness with increasing age. According to the resource modulation hypothesis, common genetic variations that influence cognitive functioning are modulated in normal aging by losses of anatomical and neurochemical brain resources, with genetic differences exerting larger influence as resources move from high to medium levels (Lindenberger et al., 2008; Nagel et al., 2008; Papenberg et al., 2015). As a result, genotype differences should, then, not yield significant changes in anatomical and neurochemical brain resources among younger adults. Rather, the disparity between genotypes would become pronounced in later adulthood, with older adults who carry a more beneficial genotype (e.g., Met) retaining their anatomical and neurochemical brain resources to a greater extent than those with a less beneficial genotype (e.g., Val).

However, these exacerbated genetic effects with age are not universally found. In this lifespan sample of healthy adults, we find that the COMT effect on cortical thickness is not age-dependent. This could be because of several reasons. It may be that those age by COMT effects are more likely influencing cognition, rather than influencing a mediating property of brain structure. Sampling characteristics across previous studies may also explain the disparity between the results of this study and other prior research that has identified significant age by COMT interactions. In the present study, an even distribution of participants across decades of the adult lifespan was evaluated, whereas other studies evaluated age categorically with much of middle adulthood not addressed (e.g., Nagel et al., 2008). In the current sample, however, the Met homozygotes were slightly (but not significantly) older than the Val group, which may have decreased the likelihood of detecting an interaction. Another possibility is that the effect of the COMT polymorphism is more robust in brain structure compared to cognitive functioning; specifically, while there is an overall main effect of COMT with Met homozygotes having thicker cortices than Val carriers consistently across the lifespan, cognitive functions for

the Val carriers may be well maintained in early adulthood via some other supporting or moderating factor. Finally, one intriguing possibility, while speculative, is that age by COMT effects may not be robustly found because the genetic effects may be largely influencing brain morphometry during gestation. Support for this notion comes from rodent studies that demonstrate not only thicker regional cortex in COMT-knockout mice but also greater neuronal density (Sannino et al., 2015), suggesting a developmental origin for the COMT effects, at least in rodents.

4.3. COMT-reduced cortical thickness effects on executive function

Executive functions rely on a functioning network among prefrontal, parietal, and cingulate cortices, which are highly vulnerable to age-related alterations to their structure (Raz et al., 2005). Previous research has indicated that dopamine is involved in age-related decline of executive functioning and working memory (Bäckman et al., 2011). Furthermore, the COMT *Val*^{158}*Met* polymorphism has been shown to influence cognitive performance. Although the effects are expected to be small (Barnett et al., 2008), previous research has indicated that lower enzymatic activity Met carriers have better cognitive performance compared to their Val carrying counterparts (Barnett et al., 2007; Caldú et al., 2007; Egan et al., 2001; Joober et al., 2002; Malhotra et al., 2002; Raz et al., 2009; Rosa et al., 2004; Witte and Flöel, 2012). The present study adds evidence to this literature that cortical thickness mediates the relationship between COMT and executive function across the lifespan, identifying one mechanism by which COMT exerts its effects on executive function via influencing regional cortical thickness in dopamine areas rich in dopaminergic innervation.

4.4. Limitations

The results of this study should be interpreted in the context of its limitations and strengths. First, this was a cross-sectional and not a longitudinal study, so any findings, or lack thereof, regarding interactions between COMT and age, should be considered in terms of age relation estimates rather than changes due to the aging process per se. Relatedly, mediation analyses using cross-sectional data may yield biased approximations of longitudinal change, as well (Maxwell and Cole, 2007; Salthouse, 2011). We did, however, sample from the entire adult lifespan, which is a strength of the study given that the extant literature is based on extreme age groups comparison. Second, because of the nature of population genotype frequencies, group sizes for variants of the COMT *Val*^{158}*Met* polymorphism were uneven, although they were in Hardy-Weinberg equilibrium. We chose the strength of keeping all 3 allelic groups intact over removing participants to match sample size or collapse across homozygote and heterozygote groups, allowing for more specificity in the estimation of effects. The sample was also multiracial, and genetic stratification can confound polymorphism effects. We were underpowered to test these effects in the current sample. Third, to evaluate regional cortical thickness, we preferred an a priori ROI approach to target pathways of the mesocortical system over an exploratory whole-brain approach. We combined these ROIs for data reduction to further limit the number of statistical comparisons. Although this is an acceptable method when having a priori hypotheses, a vertex-wise analysis may have revealed regions of significance that were not investigated via the hypothesized and control ROI approach. Finally, larger sample sizes are always desirable in polymorphism studies; however, this was a respectable sample size that still allowed for collection of rich cognitive data. Longitudinal studies to be able to examine genetic influences on within-person change in brain structure and cognitive decline or maintenance over time (e.g., Josefsson et al., 2012) are highly valuable, and we are currently collecting follow-up waves of data on this sample.

4.5. Conclusions

In summary, to our knowledge, this is the first study to evaluate the effect of both COMT genotype and aging on cortical thickness across the lifespan, while also evaluating the mediating effects of brain structure between COMT group and cognition. This study provides evidence for an overall effect of COMT genotype above and beyond age on various cortical targets of the mesocortical pathway, which are rich in dopamine receptors. Those individuals predisposed to lower postsynaptic dopamine (Val carriers) demonstrated thinner cortex than their Met carrying counterparts. Furthermore, this association was not age-dependent. In addition, thickness of mesocortical regions fully mediated the effects of COMT polymorphism on executive function performance across the adult lifespan. These findings highlight the impact that genetic factors can have on shaping human brain structure, specifically that differences in dopamine degradation may influence cortical structure in regions rich in dopaminergic activity, and that these structural differences, in turn, can influence cognitive performance.

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References

Axelrod, J., Tomchick, R., 1958. Enzymatic O-methylation of epinephrine and other catechols. J. Biol. Chem. 233, 702–705.
Bäckman, L., Karlsson, S., Fischer, H., Karlsson, P., Brehmer, Y., Rieckmann, A., Nyberg, L., 2011. Dopamine D 1 receptors and age differences in brain activation during working memory. Neurobiol. Aging 32, 1849–1856.
Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.-C., Farde, L., 2006. The correlative triad among aging, dopamine, and cognition: current status and future prospects. Neurosci. Biobehav. Rev. 30, 791–807.
Barnett, J., Jones, P., Robbins, T., Müller, U., 2007. Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. Mol. Psychiatry 12, 502–509.
Barnett, J.H., Scoriels, L., Munafò, M.R., 2008. Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. Biol. Psychiatry 64, 137–144.
Buchsbaum, B.R., Greer, S., Chang, W.L., Berman, K.F., 2005. Meta-analysis of neuroimaging studies of the Wisconsin Card-Sorting task and component processes. Hum. Brain Mapp. 25, 35–45.
Caldú, X., Vendrell, P., Bartrés-Faz, D., Clemente, I., Bargalló, N., Jurado, M.Á., Junqué, C., 2007. Impact of the COMT Val 108/158 Met and DAT genotypes on prefrontal function in healthy subjects. Neuroimage 37, 1437–1444.
Cerasa, A., Cherubini, A., Quattrone, A., Gioia, M., Tarantino, P., Annesi, G., Spalletta, G., 2010. Met 158 variant of the catechol-O-methyltransferase genotype is associated with thicker cortex in adult brain. Neuroscience 167, 809–814.
Cerasa, A., Gioia, M.C., Labate, A., Liguori, M., Lanza, P., Quattrone, A., 2008. Impact of catechol-O-methyltransferase Val108/158 Met genotype on hippocampal and prefrontal gray matter volume. Neuroreport 19, 405–408.
Chen, J., Lipska, B.K., Halim, N., Ma, Q.D., Matsumoto, M., Melhem, S., Apud, J., 2004. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am. J. Hum. Genet. 75, 807–821.
Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis: I. Segmentation and surface reconstruction. Neuroimage 9, 179–194.
de Keyser, J., De Backer, J.-P., Vauquelin, G., Ebinger, G., 1990. The effect of aging on the D 1 dopamine receptors in human frontal cortex. Brain Res. 528, 308–310.
Delis, D.C., Kaplan, E., Kramer, J.H., 2001. Delis-Kaplan Executive Function System (D-KEFS). The Psychological Corporation, San Antonio.
Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Albert, M.S., 2006. An automated labeling system for subdividing the human

cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980.
Egan, M.F., Goldberg, T.E., Kolachana, B.S., Callicott, J.H., Mazzanti, C.M., Straub, R.E., Weinberger, D.R., 2001. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc. Natl. Acad. Sci. 98, 6917–6922.
Fearnley, J.M., Lees, A.J., 1991. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 114, 2283–2301.
Fischl, B., 2012. FreeSurfer. Neuroimage 62, 774–781.
Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. 97, 11050–11055.
Fischl, B., Sereno, M.I., Dale, A.M., 1999. Cortical surface-based analysis: II: inflation, flattening, and a surface-based coordinate system. Neuroimage 9, 195–207.
Fjell, A.M., Walhovd, K.B., Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Holland, D., Dale, A.M., 2009. One-year brain atrophy evident in healthy aging. J. Neurosci. 29, 15223–15231.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.
Hall, H., Sedvall, G., Magnusson, O., Kopp, J., Halldin, C., Farde, L., 1994. Distribution of D1-and D2-dopamine receptors, and dopamine and its metabolites in the human brain. Neuropsychopharmacology 11, 245–256.
Hayes, A.F., 2013. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-based Approach. The Guilford Press, New York, NY.
Heaton, R.K., 2008. Wisconsin Card Sorting Test: Computer Version 4. Psychological Assessment Resources, Odessa, FL.
Hirvonen, M.M., Någren, K., Rinne, J.O., Pesonen, U., Vahlberg, T., Hagelberg, N., Hietala, J., 2010. COMT Val158Met genotype does not alter cortical or striatal dopamine D2 receptor availability in vivo. Mol. Imaging Biol. 12, 192–197.
Hoaglin, D.C., Iglewicz, B., 1987. Fine-tuning some resistant rules for outlier labeling. J. Am. Stat. Assoc. 82, 1147–1149.
Hoaglin, D.C., Iglewicz, B., Tukey, J.W., 1986. Performance of some resistant rules for outlier labeling. J. Am. Stat. Assoc. 81, 991–999.
Honea, R., Verchinski, B.A., Pezawas, L., Kolachana, B.S., Callicott, J.H., Mattay, V.S., Meyer-Lindenberg, A., 2009. Impact of interacting functional variants in COMT on regional gray matter volume in human brain. Neuroimage 45, 44–51.
Hong, J., Shu-Leong, H., Tao, X., Lap-Ping, Y., 1998. Distribution of catechol-O-methyltransferase expression in human central nervous system. Neuroreport 9, 2861–2864.
Ito, H., Takahashi, H., Arakawa, R., Takano, H., Suhara, T., 2008. Normal database of dopaminergic neurotransmission system in human brain measured by positron emission tomography. Neuroimage 39, 555–565.
Joober, R., Gauthier, J., Lal, S., Bloom, D., Lalonde, P., Rouleau, G., Labelle, A., 2002. Catechol-O-methyltransferase val-108/158-met gene variants associated with performance on the Wisconsin card Sorting test. Arch. Gen. Psychiatry 59, 662–663.
Josefsson, M., de Luna, X., Pudas, S., Nilsson, L.G., Nyberg, L., 2012. Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. J. Am. Geriatr. Soc. 60, 2308–2312.
Kalsbeek, A., Matthijssen, M.A.H., Uylings, H.B.M., 1989. Morphometric analysis of prefrontal cortical development following neonatal lesioning of the dopaminergic mesocortical projection. Exp. Brain Res. 78, 279–289.
Karlsson, S., Nyberg, L., Karlsson, P., Fischer, H., Thilers, P., MacDonald, S., Farde, L., 2009. Modulation of striatal dopamine D1 binding by cognitive processing. Neuroimage 48, 398–404.
Karoum, F., Chrapusta, S.J., Egan, M.F., 1994. 3-Methoxytyramine is the major metabolite of released dopamine in the rat frontal cortex: reassessment of the effects of antipsychotics on the dynamics of dopamine release and metabolism in the frontal cortex, nucleus accumbens, and striatum by a simple two pool model. J. Neurochem. 63, 972–979.
Karrer, T.M., Josef, A.K., Mata, R., Morris, E.D., Samanez-Larkin, G.R., 2017. Reduced dopamine receptors and transporters but not synthesis capacity in normal aging adults: a meta-analysis. Neurobiol. Aging 57, 36–46.
Kennedy, K.M., Erickson, K.I., Rodrigue, K.M., Voss, M.W., Colcombe, S.J., Kramer, A.F., Raz, N., 2009. Age-related differences in regional brain volumes: a comparison of optimized voxel-based morphometry to manual volumetry. Neurobiol. Aging 30, 1657–1676.
Kennedy, K.M., Raz, N., 2015. Normal Aging of the Brain. In Social Cognitive Neuroscience, Cognitive Neuroscience, Clinical Brain Mapping, 3. Elsevier Inc, London, pp. 603–617.
Kochunov, P., Jahanshad, N., Marcus, D., Winkler, A., Sprooten, E., Nichols, T.E., Jbabdi, S., 2015. Heritability of fractional anisotropy in human white matter: a comparison of Human Connectome Project and ENIGMA-DTI data. Neuroimage 111, 300–311.
Laird, A.R., McMillan, K.M., Lancaster, J.L., Kochunov, P., Turkeltaub, P.E., Pardo, J.V., Fox, P.T., 2005. A comparison of label-based review and ALE meta-analysis in the Stroop task. Hum. Brain Mapp. 25, 6–21.
Lee, A., Qiu, A., 2016. Modulative effects of COMT haplotype on age-related associations with brain morphology. Hum. Brain Mapp. 37, 2068–2082.
Lewis, D.A., Melchitzky, D.S., Sesack, S.R., Whitehead, R.E., Sampson, A., 2001. Dopamine transporter immunoreactivity in monkey cerebral cortex: regional, laminar, and ultrastructural localization. J. Comp. Neurol. 432, 119–136.
Lewis, D.A., Sesack, S.R., 1997. Chapter VI dopamine systems in the primate brain. Handbook Chem. Neuroanat. 13, 263–375.
Li, S.-C., Lindenberger, U., Bäckman, L., 2010. Dopaminergic modulation of cognition across the life span: Editorial. Neurosci. Biobehav. Rev. 34, 625–630.
Lidow, M., Goldman-Rakic, P., Gallager, D., Rakic, P., 1991. Distribution of dopaminergic receptors in the primate cerebral cortex: quantitative autoradiographic analysis using [3 H] raclopride,[3 H] spiperone and [3 H] SCH23390. Neuroscience 40, 657–671.
Lindenberger, U., Nagel, I.E., Chicherio, C., Li, S.-C., Heekeren, H.R., Bäckman, L., 2008. Age-related decline in brain resources modulates genetic effects on cognitive functioning. Front. Neurosci. 2, 234–244.
Lotta, T., Vidgren, J., Tilgmann, C., Ulmanen, I., Melen, K., Julkunen, I., Taskinen, J., 1995. Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. Biochemistry 34, 4202–4210.
Malhotra, A.K., Kestler, L.J., Mazzanti, C., Bates, J.A., Goldberg, T., Goldman, D., 2002. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am. J. Psychiatry 159, 652–654.
Margulies, D.S., Vincent, J.L., Kelly, C., Lohmann, G., Uddin, L.Q., Biswal, B.B., Petrides, M., 2009. Precuneus shares intrinsic functional architecture in humans and monkeys. Proc. Natl. Acad. Sci. 106, 20069–20074.
Matsumoto, M., Weickert, C.S., Akil, M., Lipska, B., Hyde, T., Herman, M., Weinberger, D., 2003. Catechol O-methyltransferase mRNA expression in human and rat brain: evidence for a role in cortical neuronal function. Neuroscience 116, 127–137.
Mattay, V.S., Goldberg, T.E., Sambataro, F., Weinberger, D.R., 2008. Neurobiology of cognitive aging: insights from imaging genetics. Biol. Psychol. 79, 9–22.
Maxwell, S.E., Cole, D.A., 2007. Bias in cross-sectional analyses of longitudinal mediation. Psychol. Methods 12, 23.
McClearn, G.E., Johansson, B., Berg, S., Pedersen, N.L., Ahern, F., Petrill, S.A., Plomin, R., 1997. Substantial genetic influence on cognitive abilities in twins 80 or more years old. Science 276, 1560–1563.
McNab, F., Varrone, A., Farde, L., Jucaite, A., Bystritsky, P., Forssberg, H., Klingberg, T., 2009. Changes in cortical dopamine D1 receptor binding associated with cognitive training. Science 323, 800–802.
Middleton, F.A., Strick, P.L., 2000. Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. Brain Cogn. 42, 183–200.
Müller, U., von Cramon, D.Y., Pollmann, S., 1998. D1-versus D2-receptor modulation of visuospatial working memory in humans. J. Neurosci. 18, 2720–2728.
Nagel, I.E., Chicherio, C., Li, S.-C., Von Oertzen, T., Sander, T., Villringer, A., Lindenberger, U., 2008. Human aging magnifies genetic effects on executive functioning and working memory. Front. Hum. Neurosci. 2, 1–8.
Palomero-Gallagher, N., Amunts, K., Zilles, K., 2015. Myeloarchitecture and Maps of the Cerebral Cortex. In: Brain Mapping: An Encyclopedic Reference, pp. 137–156.
Papenberg, G., Bäckman, L., Nagel, I.E., Nietfeld, W., Schröder, J., Bertram, L., Heekeren, H.R., Lindenberger, U., Li, S.C., 2014. COMT polymorphism and memory dedifferentiation in old age. Psychol. Aging 29, 374.
Papenberg, G., Lindenberger, U., Bäckman, L., 2015. Aging-related magnification of genetic effects on cognitive and brain integrity. Trends Cogn. Sci. 19, 506–514.
Parvizi, J., Van Hoesen, G.W., Buckwalter, J., Damasio, A., 2006. Neural connections of the posteromedial cortex in the macaque. Proc. Natl. Acad. Sci. 103, 1563–1568.
Radloff, L.S., 1977. The CES-D scale: a self-report depression scale for research in the general population. Appl. Psychol. Meas. 1, 385–401.
Rast, P., Kennedy, K.M., Rodrigue, K.M., Robinson, P.R., Gross, A.L., McLaren, D.G., Willis, S.L., 2018. APOEε4 Genotype and Hypertension Modify 8-year Cortical Thinning: Five Occasion Evidence from the Seattle Longitudinal Study. Cereb. Cortex 28, 1934–1945.
Raz, N., Ghisletta, P., Rodrigue, K.M., Kennedy, K.M., Lindenberger, U., 2010. Trajectories of brain aging in middle-aged and older adults: regional and individual differences. Neuroimage 51, 501–511.
Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex 15, 1676–1689.
Raz, N., Lustig, C., 2014. Genetic variants and cognitive aging: destiny or a nudge? Psychol. Aging 29, 359.
Raz, N., Rodrigue, K.M., Kennedy, K.M., Land, S., 2009. Genetic and vascular modifiers of age-sensitive cognitive skills: effects of COMT, BDNF, ApoE, and hypertension. Neuropsychology 23, 105–116.
Rieckmann, A., Karlsson, S., Karlsson, P., Brehmer, Y., Fischer, H., Farde, L., Bäckman, L., 2011. Dopamine D1 receptor associations within and between dopaminergic pathways in younger and elderly adults: links to cognitive performance. Cereb. Cortex 21, 2023–2032.
Rosa, A., Peralta, V., Cuesta, M.J., Zarzuela, A., Serrano, F., Martínez-Larrea, A., Fañanás, L., 2004. New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. Am. J. Psychiatry 161, 1110–1112.
Salami, A., Rieckmann, A., Karalija, N., Avelar-Pereira, B., Andersson, M., Wåhlin, A., Lindenberger, U., 2018. Neurocognitive profiles of older adults with working-memory dysfunction. Cereb. Cortex 28, 2525–2539.
Salat, D.H., Buckner, R.L., Snyder, A.Z., Greve, D.N., Desikan, R.S., Busa, E., Fischl, B., 2004. Thinning of the cerebral cortex in aging. Cereb. Cortex 14, 721–730.
Salthouse, T.A., 2011. Neuroanatomical substrates of age-related cognitive decline. Psychol. Bull. 137, 753.
Sannino, S., Gozzi, A., Cerasa, A., Piras, F., Scheggia, D., Managò, F., Tonelli, D.D.P., 2015. COMT genetic reduction produces sexually divergent effects on cortical anatomy and working memory in mice and humans. Cereb. Cortex 25, 2529–2541.

Shaw, P., Wallace, G., Addington, A., Evans, A., Rapoport, J., Giedd, J., 2009. Effects of the Val158Met catechol-O-methyltransferase polymorphism on cortical structure in children and adolescents. Mol. Psychiatry 14, 348–349.
Slifstein, M., Kolachana, B., Simpson, E., Tabares, P., Cheng, B., Duvall, M., Abi-Dargham, A., 2008. COMT genotype predicts cortical-limbic D1 receptor availability measured with [11C] NNC112 and PET. Mol. Psychiatry 13, 821–827.
Stoof, J., Kebabian, J., 1984. Two dopamine receptors: biochemistry, physiology and pharmacology. Life Sci. 35, 2281–2296.
Suhara, T., Fukuda, H., Inoue, O., Itoh, T., Suzuki, K., Yamasaki, T., Tateno, Y., 1991. Age-related changes in human D1 dopamine receptors measured by positron emission tomography. Psychopharmacology 103, 41–45.
Thompson, P.M., Cannon, T.D., Narr, K.L., Van Erp, T., Poutanen, V.-P., Huttunen, M., Khaledy, M., 2001. Genetic influences on brain structure. Nat. Neurosci. 4, 1253–1258.
Tukey, J.W., 1977. Exploratory Data Analysis. Addison-Wesley Publishing Company, Reading, PA.
Tunbridge, E.M., Bannerman, D.M., Sharp, T., Harrison, P.J., 2004. Catechol-o-methyltransferase inhibition improves set-shifting performance and elevates stimulated dopamine release in the rat prefrontal cortex. J. Neurosci. 24, 5331–5335.
Wang, Y., Chan, G.L., Holden, J.E., Dobko, T., Mak, E., Schulzer, M., Calne, D.B., 1998. Age-dependent decline of dopamine D1 receptors in human brain: a PET study. Synapse 30, 56–61.
Wang, Y., Li, J., Chen, C., Zhu, B., Moysis, R., Lei, X., Liu, B., 2013. COMT rs4680 Met is not always the 'smart allele': val allele is associated with better working memory and larger hippocampal volume in healthy Chinese. Genes, Brain Behav. 12, 323–329.
Weinshilboum, R.M., Otterness, D.M., Szumlanski, C.L., 1999. Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. Annu. Rev. Pharmacol. Toxicol. 39, 19–52.
Witte, A.V., Flöel, A., 2012. Effects of COMT polymorphisms on brain function and behavior in health and disease. Brain Res. Bull. 88, 418–428.
Yuan, P., Raz, N., 2014. Prefrontal cortex and executive functions in healthy adults: a meta-analysis of structural neuroimaging studies. Neurosci. Biobehav. Rev. 42, 180–192.
Zinkstok, J., Schmitz, N., van Amelsvoort, T., de Win, M., van den Brink, W., Baas, F., Linszen, D., 2006. The COMT val 158 met polymorphism and brain morphometry in healthy young adults. Neurosci. Lett. 405, 34–39.