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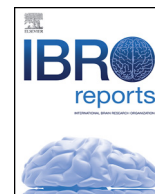
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Research Paper

COMT val158met is not associated with A β -amyloid and APOE ϵ 4 related cognitive decline in cognitively normal older adults



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ABSTRACT

The non-synonymous single nucleotide polymorphism (SNP), Val158Met within the Catechol-O-methyltransferase (*COMT*) gene has been associated with altered levels of cognition and memory performance in cognitively normal adults. This study aimed to investigate the independent and interactional effects of *COMT* Val158Met on cognitive performance. In particular, it was hypothesised that *COMT* Val158Met would modify the effect of neocortical A β -amyloid (A β) accumulation and carriage of the apolipoprotein E (*APOE*) ϵ 4 allele on cognition in preclinical Alzheimer's disease (AD). In 598 cognitively normal older adults with known neocortical A β levels, linear mixed modelling revealed no significant independent or interactional associations between *COMT* Val158Met and cognitive decline. These findings do not support previous associations between *COMT* Val158Met and cognitive performance and suggest this variant does not influence A β -amyloid or *APOE* ϵ 4 driven cognitive decline in a well characterised cohort of cognitively normal older adults.

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1. Introduction

Catechol-*O*-methyltransferase (COMT) is an enzyme with an important role in the regulation of dopamine availability in the central nervous system (CNS). The enzyme is encoded by the *COMT* gene (Chromosome 22q11.21, (Grossman et al., 1992)) and allelic variation in this gene plays an important role in enzymatic function. In particular, the non-synonymous single nucleotide polymorphism (SNP) in exon 3, rs4680 (NG_011526.1:g.27009G > A), results in a valine (Val) to methionine (Met; Val158Met; henceforth referred to as *COMT*) substitution. Consequently, carriage of Met (*COMT*^{Met}) confers a 3 to 4-fold reduction in enzymatic activity resulting in higher levels of CNS dopamine, compared to carriage of Val (*COMT*^{Val}) (Chen et al., 2004; Lachman et al., 1996; Lotta et al., 1995).

Normal dopamine neurotransmission is essential for optimal human cognition, mood and behaviour. Disruption to dopamine neurotransmission is associated with brain disease and mental illness. Consequently, allelic variation in the *COMT* gene has been associated with levels of cognition in cohorts of healthy individuals (Bellander et al., 2015; Degen et al., 2016; Diamond et al., 2004; Dumontheil et al., 2011; Egan et al., 2001; Goldberg et al., 2003; Malhotra et al., 2002; Nagel et al., 2008; Rosa et al., 2004, 2010; Sheldrick et al., 2008; Starr et al., 2007; Stefanis et al., 2005) and schizophrenia patients (Bilder et al., 2002; Egan et al., 2001; Goldberg et al., 2003; Nolan et al., 2004; Rosa et al., 2010), with carriage of *COMT*^{Val} associated with poorer performance. However, several studies and a meta-analysis (Barnett et al., 2008) investigating healthy (Blanchard et al., 2011; de Frias et al., 2010; Ho et al., 2005; Liu et al., 2014; O'Hara et al., 2006; Papenberg et al., 2014; Potter et al., 2009; Stefanis et al., 2004; Stuart et al., 2014; Wardle et al., 2013) and diseased individuals (e.g., with schizophrenia (Dickerson et al., 2007; Ho et al., 2005; Zilles et al., 2012), depression (Opmeer et al., 2013; Potter et al., 2009; Wang et al., 2014), traumatic brain injury (Willmott et al., 2014), Parkinson's disease (Hoogland et al., 2010), asymptomatic atherosclerosis (Bolton et al., 2010)) have reported no association between *COMT* genotype and cognitive performance. In particular, there is a general lack of consensus with respect to the impact that *COMT* genotype has on cognitive performance in healthy older adults, with studies finding a positive influence of *COMT*^{Met} (Bellander et al., 2015; Degen et al., 2016; Nagel et al., 2008; Papenberg et al., 2014; Starr et al., 2007) or no significant effect (de Frias et al., 2010; O'Hara et al., 2006; Stuart et al., 2014). This inconsistency in results could, in part, be accounted for the by variability in cognitive decline due to underlying pathogenic changes occurring in the brain as a result of age related diseases.

In cohort studies of Alzheimer's disease (AD), there is a lack of consensus about the role played by *COMT*. A comprehensive meta-analysis of 10 case-control studies revealed no significant associations with AD risk either overall or in the Caucasian population, though associations were observed in the Asian population (Yan et al., 2016). An increased risk for Mild Cognitive Impairment (MCI) and AD has previously been reported for *COMT*^{Val} homozygotes, however, but only in *APOE* ϵ 4 carriers (Lanni et al., 2012). Whilst in a further study *COMT*^{Val} homozygotes were associated with conversion from cognitively normal (unimpaired) status to MCI (Dixon et al., 2014). These latter studies suggest that *COMT*^{Val} homozygosity may be associated with early-stage transition of cognitive phenotypes.

Cognitive changes are observable in the preclinical disease stages of AD, which are characterised by high levels of neocortical A β -amyloid (A β) (Lim et al., 2016). Additionally, this decline has been reported to be modified by genetic factors including the Apolipoprotein E (*APOE*) ϵ 4 allele (Lim et al., 2013a, 2015) and the rs6265 and variants of the Brain Derived Neurotrophic Factor (*BDNF*) (Lim et al., 2013b) and Kidney and Brain expressed protein (*KIBRA*) (Porter et al., 2018a) genes, respectively. As such, genetic variation that has a differential impact upon function may impart either susceptibility or resilience to cognitive decline in the presence of the earliest stages of pathological

change, either independently or in combination. Interactional effects of *COMT* and additional genetic factors have been previously investigated in other disorders. However, there is a paucity of knowledge about the impact of genetic variability in *COMT* on cognitive performance in preclinical AD, particularly with respect to A β and *APOE* ϵ 4 mediated decline in cognitive domains that are impacted in the earliest stages of the disease. Episodic memory is one of the earliest cognitive domains to decline, with reductions in functioning reported to occur 4–8 years prior to executive function and up to 7–10 years prior to other cognitive domains (Derby et al., 2013; Elias et al., 2000; Grober et al., 2008).

The aim of this study was to investigate whether, in cognitively normal (CN) older adults, allelic variation in *COMT* would be independently associated with cognitive decline, or modify A β or *APOE*- ϵ 4 mediated decline. The highly characterised Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Aging provided 7.5 years of cognitive and neuroimaging assessment data for longitudinal investigation. The hypothesis of the study was that in CN older adults, carriage of the *COMT*^{Val} allele (i.e. *COMT*^{Val/Val} or *COMT*^{Val/Met}) would be associated with poorer cognitive performance over time, as compared to *COMT*^{Met} homozygotes (i.e. *COMT*^{Met/Met}).

2. Methods

2.1. Participants

This study focused on imaged CN older adults (n = 598) enrolled in the AIBL Study, a prospective longitudinal study of ageing launched in 2006. Additional information regarding the study design, enrolment process, neuropsychological assessments, and exclusion and diagnostic criteria has been previously described (Ellis et al., 2009). Each of the AIBL Study member institutions (Austin Health, St Vincent's Health, Hollywood Private Hospital, and Edith Cowan University) granted ethics approval for the study and informed written consent was provided by all volunteers.

2.2. Cognitive measures

At each 18-month data collection participants complete the AIBL Study neuropsychological test battery, which includes the Mini-Mental State Examination (MMSE), Clock Drawing Test, California Verbal Learning Test-Second edition (CVLT-II), Logical Memory I and II (LMI; LMII; Story A only), D-KEFS verbal fluency, a 30-item version of the Boston Naming Test (BNT), Wechsler Test of Adult Reading (WTAR) for premorbid IQ, Digit Span and Digit Symbol-Coding subtests of the Wechsler Adult Intelligence Scale-Third edition (WAIS-III), the Stroop task (Victoria version), and the Rey Complex Figure Test (RCFT) (Ellis et al., 2009). Cognitive composite scores were calculated using the neuropsychological test battery data in combination with the Clinical Dementia Rating (CDR) as described previously (Burnham et al., 2015; Donohue et al., 2014). Briefly, the cognitive composites investigated herein included two measures of global cognition: a statistically driven global cognition composite (CDR_{SB}, MMSE, LMII, CVLT_{FP} and Clock) (Burnham et al., 2015), and the Pre-Alzheimer's cognitive composite (PACC (CVLT-II, LMII, MMSE, WAIS-III)) (Donohue et al., 2014), and a measure of verbal episodic memory (CDR sum of boxes (CDR_{SB}), LMII, CVLT-II recognition false positives (CVLT_{FP}) and long delay free recall (CVLT_{LDFR})) (Burnham et al., 2015). The calculations of the statistically driven global cognition and verbal episodic memory composites and calculations included corrections for age, gender, years of education, WTAR-estimated premorbid IQ (WAIS-III Full Scale Intelligence Quotient (FSIQ)) and depressive symptoms (Geriatric Depression Scale (GDS)) (Burnham et al., 2015).

2.3. A β -amyloid imaging

598 CN older adults underwent A β imaging with positron emission

tomography (PET) using 11C-Pittsburgh Compound B (PiB), 18F-florbetapir or 18F-flutemetamol as previously described (Clark et al., 2011; Rowe et al., 2010; Vandenberghe et al., 2010). PET standardized uptake value ratios (SUVR) were determined for all tracers using CapAIBL, a web-based freely available MR-less methodology (Bourgeat et al., 2015). Briefly, SUVs were summed and normalized to either the cerebellar cortex SUV (PiB), whole cerebellum SUV (florbetapir) or pons SUV (flutemetamol) to yield the target-region to reference-region SUVR. These SUVRs were then classified as either low ($A\beta^{low}$) or high ($A\beta^{high}$) $A\beta$ burden, based on a tracer-specific SUVR threshold: ≥ 1.4 , ≥ 1.05 and ≥ 0.55 for PiB, florbetapir and flutemetamol, respectively (Rowe et al., 2013).

2.4. Genotyping

Methods for DNA extraction and genotyping have been previously described (Brown et al., 2014; Porter et al., 2018a, b). Briefly, QIAamp DNA Blood Maxi Kits (Qiagen, Hilden, Germany) were used for DNA extraction from whole blood as per manufacturer's instructions. TaqMan[®] genotyping assays (Life Technologies, Carlsbad, CA) for *APOE* (rs7412, assay ID: C_904973_10; rs429358, assay ID: C_3084793_20) and *COMT* (rs4680, assay ID: C_25746809_50) were performed on a QuantStudio 12K Flex[™] Real-Time-PCR systems (Applied Biosystems, Foster City, CA) using TaqMan[®] GTXpress[™] Master Mix (Life Technologies) following manufacturer's instructions. *APOE* status was defined by the presence (1 or 2 copies; *APOE* $\epsilon 4 + ve$) or absence (0 copies; *APOE* $\epsilon 4 - ve$) of the *APOE* $\epsilon 4$ allele. Further, all analyses were performed based on a dominant model for the *COMT* Val allele ($COMT^{Val} = COMT^{Val/Val}/COMT^{Val/Met}$; $COMT^{Met} = COMT^{Met/Met}$).

2.5. Data analysis

All statistical analyses were performed using Rstudio (Rstudio Team, 2015) Version 0.98.1103 for Macintosh (RStudio Team, 2015). Baseline demographic data analyses provided means, counts, standard deviations and percentages across the selected sample and stratified by *COMT*^{Val} and *COMT*^{Met} status. Significant differences in demographic measures between groups stratified by *COMT*^{Val} and *COMT*^{Met} status, were assessed using Student's t-tests for continuous variables (e.g. age, premorbid IQ, depressive symptoms (GDS)) and chi-squared tests for categorical variables (gender, years of education, *APOE* and $A\beta$ burden status).

Random intercepts linear mixed-effects (LME) models were performed using the "nlme" package in R to assess differences in rates of cognitive change relative to *COMT*. Initially, to investigate the effect of *COMT* on the rate of cognitive decline, a *COMT* \times Time interaction was modelled across the entire sample, covarying for *APOE* $\epsilon 4$ carrier and $A\beta$ burden status, with the cognitive composites as the dependent variables. Additionally, analyses in which the PACC is assessed age and sex are included as covariates. The effect of $A\beta$ status in combination with *COMT* was then investigated by modelling an $A\beta \times COMT \times Time$ interaction, covarying for *APOE* $\epsilon 4$ carrier status. The final analysis focused on low ($A\beta^{low}$) and high $A\beta$ ($A\beta^{high}$) participants separately, and included *APOE* $\epsilon 4$ carrier status within the model by an *APOE* $\times COMT \times Time$ interaction. When nominally significant associations were observed analyses were corrected for the False Discovery Rate (FDR) using Q-Value (bootstrap method) (Storey, 2002).

3. Results

No significant differences were observed between either *COMT*^{Met} or *COMT*^{Val} with respect to demographic variables with the exception of depression (Table 1). As the mean depression values were well below the clinically relevant threshold this result was not investigated further. No associations between either *COMT*^{Met} or *COMT*^{Val} and differential

rates of decline were observed for any composite measures (Table 2). *COMT* did not modify the impact of $A\beta$ on cognition, with significant differences only observed between $A\beta$ groups in terms of rates of decline (i.e. $A\beta^{low}/COMT^{Met}$ and $A\beta^{low}/COMT^{Val}$ significantly differed to $A\beta^{high}/COMT^{Met}$ and $A\beta^{high}/COMT^{Val}$; Table 3).

Further, *COMT* did not modify the effects of *APOE* in the $A\beta^{low}$ or $A\beta^{high}$ samples. In $A\beta^{low}$ ($n = 340$) no significant differences were observed between any group's rates of decline in any composites (Table 4). Further, in $A\beta^{high}$ ($n = 258$) significant differences in rates of decline were only observed between *APOE* groups (i.e. *APOE* $\epsilon 4 - ve / COMT^{Met}$ and *APOE* $\epsilon 4 - ve / COMT^{Val}$ significantly differed to *APOE* $\epsilon 4 + ve / COMT^{Met}$ and *APOE* $\epsilon 4 + ve / COMT^{Val}$; Table 4) in all composites. Similar results to those presented above were also observed when investigating *COMT* using the dominant model for the Met allele ($COMT^{Met} = COMT^{Met/Met}/COMT^{Val/Met}$; $COMT^{Val} = COMT^{Val/Val}$) and are presented in the Supplementary data (Tables A1–A4).

4. Discussion

The findings from this study do not support the initial hypothesis that *COMT*^{Val} carriers have significantly higher rates of cognitive decline compared to *COMT*^{Met} homozygotes. No significant modification of cognitive decline by *COMT* was observed in any model investigated; that is, independent of $A\beta$ and *APOE* $\epsilon 4$ status *COMT* was not independently associated with cognitive decline in measures of global cognition, verbal episodic memory, or the PACC. Further, *COMT* did not modify $A\beta$ -associated cognitive decline, nor was it observed to modify the effect of *APOE* $\epsilon 4$ carrier status in individuals with high $A\beta$ burden.

COMT has previously been associated with measures of cognition in cognitively normal older adults (Bellander et al., 2015; Starr et al., 2007), in particular episodic memory (Papenberg et al., 2014), working memory (Nagel et al., 2008), and attention (Degen et al., 2016). However, there have been a number of studies in cognitively normal older adults that have reported no significant associations with measures of episodic memory (O'Hara et al., 2006; Stuart et al., 2014), working memory (de Frias et al., 2010), verbal ability (O'Hara et al., 2006), attention or speed of processing (O'Hara et al., 2006). As such, the current study presented here is not unique in finding no significant associations between *COMT* and cognitive performance. To the authors knowledge this is the first study to investigate the modifying effects of *COMT* on $A\beta$ and *APOE* $\epsilon 4$ mediated cognitive decline in cognitively normal older adults over a duration of 90 months.

The important role *COMT* has in regulating the availability of dopamine in the prefrontal cortex may contribute to the associations between *COMT* and cognitive tests that reflect changes in prefrontal cortex function. However, similar to the current study several of the aforementioned studies also failed to identify associations between domains affected in preclinical AD and *COMT*. This current study focused primarily on cognitive composite scores that measure verbal episodic memory, the cognitive domain affected earliest in AD (Derby et al., 2013; Elias et al., 2000; Grober et al., 2008), or composites that are statistically derived to reflect change in global cognition at the earliest stages of the disease process. The lack of significant associations observed could be due in part to the current study's focus on preclinical AD and specifically the cognitive domains impaired in these early stages of preclinical AD. Further, episodic memory impairment is known to result from damage to the medial temporal lobe, in particular the hippocampus, rather than the prefrontal cortex, which is affected later in AD and for which previous associations with *COMT* have been reported.

Here we have thoroughly investigated the influence of *COMT* on cognitive decline in cognitively normal older adults from a well characterised longitudinal cohort of preclinical AD. The utilisation of composite scores for cognitive domains that are impacted at the earliest stages of AD is a strength of this study as it avoids the study of domains that are likely to have a much smaller effect size and thus be

Table 1
Demographic Information.

	Overall n = 598	COMT ^{Met} n = 139	COMT ^{Val} n = 459	p
Age [years], mean (SD)	70.87 (6.45)	70.64 (6.39)	70.94 (6.47)	0.633
Female, n (%)	331 (55.35)	73 (52.52)	258 (56.21)	0.503
Years of Education, n (%)				0.435
	0–8	46 (7.72)	13 (9.35)	
	9–12	218 (36.58)	45 (32.37)	
	13–15	124 (20.81)	34 (24.46)	
	15+	208 (34.90)	47 (33.81)	
Premorbid IQ [FSIQ] mean (SD)	108.00 (7.24)	108.42 (6.82)	107.87 (7.36)	0.434
Depressive Symptoms [GDS], mean (SD)	1.05 (1.32)	0.83 (1.06)	1.12 (1.32)	0.043
APOE ε4 carriage, n (%)	167 (27.93)	37 (26.62)	130 (28.32)	0.776
High Aβ burden, n (%)	258 (43.14)	55 (39.57)	203 (44.23)	0.382

Baseline demographic and clinical characteristics of all imaged cognitively normal adults in the AIBL Study, and stratified by COMT status (COMT^{Val} and COMT^{Met}). p-values represent statistical significance when comparing COMT status. GDS, Geriatric Depression Scale; FSIQ, Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) Full Scale Intelligence Quotient; SD, standard deviation.

Table 2
Mean slopes for cognitive composites in cognitively normal adults.

	COMT ^{Met} n = 139 β	COMT ^{Val} n = 459 β	p
Global	0.021	0.029	0.647
Verbal Episodic Memory	0.025	0.033	0.626
PACC	−0.024	−0.017	0.875

Mean slopes for cognitive composites (presented in SD/year; n = 598) in all imaged cognitively normal participants, controlling for APOE ε4 carrier, Aβ status and additionally age and sex in the PACC.

significantly affected by sample size considerations. For example, Flint et al. reported that considering the expected effect size of COMT on working memory, a sample of 1700 participants would be required for a significant association to be observed (Flint and Munafo, 2007). However, it is acknowledged that the study may be limited by the nature of the recruitment of participants into the AIBL Study. AIBL Study participants are not randomly selected and involvement is voluntary. Voluntary involvement may have resulted in participants with higher levels of education than would be expected from random community recruitment, and this could have further hindered efforts to observe an influence of COMT on cognitive decline.

5. Conclusion

Genetic variation has been suggested as a major contributing factor to underpinning vulnerability or resilience to cognitive decline in the presence of the earliest stages of pathological change in AD. This study represents the first assessment of the influence of COMT on Aβ and APOE ε4 mediated cognitive decline in a preclinical AD sample. The results here suggest no independent or interactional influence, with APOE or Aβ, of the COMT variant on measures of global cognition, verbal episodic memory or the PACC. Whilst no independent effects were observed it does not rule out the possibility that COMT may impart some influence on preclinical AD cognitive decline when combined with other genetic factors.

Table 3
Mean slopes for cognitive composites in cognitively normal adults, Aβ-amyloid interaction.

	Aβ ^{low} /COMT ^{Met} n = 84 β	Aβ ^{low} /COMT ^{Val} n = 256 β	Aβ ^{high} /COMT ^{Met} n = 55 β	Aβ ^{high} /COMT ^{Val} n = 203 β
Global	0.049 φ	0.050 φ	−0.022 *^	−0.007 *^
Verbal Episodic Memory	0.054 φ	0.052 φ	−0.019 *^	0.002 *^
PACC	0.043 φ	0.049 φ	−0.128 *^	−0.122 *^

Mean slopes for cognitive composites (presented in SD/year; n = 598) in all imaged cognitively normal participants, controlling for APOE ε4 carrier and additionally age and sex in the PACC. *p < 0.05 when comparing to the Aβ^{low}/COMT^{Met} group, ^p < 0.05 when comparing to the Aβ^{low}/COMT^{Val} group, φ p < 0.05 when comparing to the Aβ^{high}/COMT^{Met} group.

Table 4
Mean slopes for cognitive composites in cognitively normal adults stratified by Aβ status, APOE ε4 interaction.

	APOE ε4-ve COMT ^{Met} β	APOE ε4-ve COMT ^{Val} β	APOE ε4+ve COMT ^{Met} β	APOE ε4+ve COMT ^{Val} β
Aβ^{low}	n = 71	n = 211	n = 13	n = 45
Global	0.053	0.051	0.031	0.050
Verbal Episodic Memory	0.057	0.053	0.037	0.050
PACC	0.039	0.043	0.049	0.070
Aβ^{high}	n = 31	n = 118	n = 24	n = 85
Global	0.028 φ	0.024 φ	−0.105 *^	−0.059 *^
Verbal Episodic Memory	0.028 φ	0.029 φ	−0.094 *^	−0.044 *^
PACC	0.134 φ	0.107 φ	−0.227 *^	−0.142 *^

Mean slopes for cognitive composites (presented in SD/year) in cognitively normal participants with low Aβ-amyloid burden (Aβ^{low}; n = 340) or high Aβ-amyloid burden (Aβ^{high}; n = 258), controlling for age and sex in the PACC analysis. *p < 0.05 when comparing to the APOE ε4-ve COMT^{Met} group, ^p < 0.05 when comparing to the APOE ε4-ve COMT^{Val} group, φ p < 0.05 when comparing to the APOE ε4+ve COMT^{Met} group.

Conflicts of interest

CLM is an advisor to Prana Biotechnology Ltd and a consultant to Eli Lilly. PM is a full-time employee of Cogstate Ltd. DA has served on scientific advisory boards for Novartis, Eli Lilly, Janssen, and Pfizer Inc. HRS has received/is receiving remuneration from activities with Pfizer and Takeda pharmaceuticals. RNM is a consultant to Alzhyne. CCR has served on scientific advisory boards for Bayer Pharma, Elan Corporation, GE Healthcare and AstraZeneca; has received speaker honoraria from Bayer Pharma and GE Healthcare; and has received research support from Bayer Pharma, GE Healthcare, Piramal Lifesciences and Avid Radiopharmaceuticals. VLV served as a consultant for Bayer Pharma; and received research support from a NEDO grant from Japan. All other authors have nothing to disclose.

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