COMT val158met is not associated with A\(\beta\)-amyloid and APOE \(\varepsilon4\) related cognitive decline in cognitively normal older adults

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Research Paper

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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 Aβ-amyloid (Aβ) accumulation and carriage of the apolipoprotein E (APOE) ε4 allele on cognition in preclinical Alzheimer’s disease (AD). In 598 cognitively normal older adults with known neocortical Aβ 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 Aβ-amyloid or APOE ε4 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<sup>Met</sup>) confers a 3 to 4-fold reduction in enzymatic activity resulting in higher levels of CNS dopamine, compared to carriage of Val (COMT<sup>Val</sup>) (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<sup>Val</sup> 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; Hara et al., 2006; Hara et al., 2006; Nolan et al., 2004; 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 (Opepe 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<sup>Met</sup> (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; 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<sup>Val</sup> homozygotes, however, but only in APOE ε4 carriers (Lanni et al., 2012). Whilst in a further study COMT<sup>Val</sup> homozygotes were associated with conversion from cognitively normal (unimpaired) status to MCI (Dixon et al., 2014). These latter studies suggest that COMT<sup>Val</sup> 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 Aβ-amyloid (Aβ) (Lim et al., 2016). Additionally, this decline has been reported to be modified by genetic factors including the Apolipoprotein E (APOE) ε4 allele (Lim et al., 2013a, 2015) and the rs6265 variants of the Brain Derived Neurotropic 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 Aβ and APOE ε4 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 Aβ or APOE ε4 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<sup>Val</sup> allele (i.e. COMT<sup>Val/Val</sup> or COMT<sup>Val/Met</sup>) would be associated with poorer cognitive performance over time, as compared to COMT<sup>Met</sup> homozygotes (i.e. COMT<sup>Met/Met</sup>).

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 (LM; 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好久, MMSE, LMII, CVLT<sub>F</sub> 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<sub>box</sub>), LMII, CVLT-II recognition false positives (CVLT<sub>F</sub>) and long delay free recall (CVLT<sub>LDR</sub>) (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. Aβ-amyloid imaging

598 CN older adults underwent Aβ imaging with positron emission
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) were used for APOE rs7412, assay ID: C_904973_10; rs492358, 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® Genotyping Master Mix (Life Technologies) following manufacturer’s instructions. APOE status was defined as low (APOEε4/ε4) or high (APOEε4/ε4+ve) based on a tracer-specific SUVR threshold: ≥1.4, ≥1.05 and ≥0.55 for PiB, flortaberipir and flutemetamol, respectively (Rove et al., 2013).

2.4. Genotyping

The important role COMT has in regulating the availability of dopamine in the prefrontal cortex may contribute to the associations between COMT and cognitive 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 likely to have a much smaller effect size and thus be

rates of decline were observed for any composite measures (Table 2). COMT did not modify the impact of Aβ on cognition, with significant differences only observed between Aβ groups in terms of rates of decline (i.e. Aβlow/COMTMet and Aβlow/COMTVal significantly differed to Aβhigh/COMTMet and Aβhigh/COMTVal: Table 3).

Further, COMT did not modify the effects of APOE in the Aβlow or Aβhigh samples. In Aβlow (n = 340) no significant differences were observed between any group’s rates of decline in any composites (Table 4). Further, in Aβhigh (n = 258) significant differences in rates of decline were only observed between APOE groups (i.e. APOE ε4/ε4+ve/COMTMet and APOE ε4/ε4/COMTVal significantly differed to APOE ε4+ve/COMTMet and APOE ε4+ve /COMTVal, 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 (COMTMet = COMTVal/Met/COMTVal/Met; COMTVal = COMTMet/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 COMTVal carriers have significantly higher rates of cognitive decline compared to COMTmet homozygotes. No significant modification of cognitive decline by COMT was observed in any model investigated; that is, independent of Aβ and APOE ε4 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 Aβ-associated cognitive decline, nor was it observed to modify the effect of APOE ε4 carrier status in individuals with high Aβ 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 (Pappenberg 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), 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 Aβ and APOE ε4 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>
<thead>
<tr>
<th>APOE status</th>
<th>Aβ4+ve/COMTMet</th>
<th>Aβ4+ve/COMTVal</th>
<th>Aβ4-ve/COMTMet</th>
<th>Aβ4-ve/COMTVal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβlow</td>
<td>0.05</td>
<td>0.04</td>
<td>0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>Aβhigh</td>
<td>0.07</td>
<td>0.06</td>
<td>0.08</td>
<td>0.09</td>
</tr>
</tbody>
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<td>0.08</td>
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<th>Aβ4-ve/COMTMet</th>
<th>Aβ4-ve/COMTVal</th>
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<th>Aβ4-ve/COMTMet</th>
<th>Aβ4-ve/COMTVal</th>
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</thead>
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<td>0.07</td>
</tr>
<tr>
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<td>0.07</td>
<td>0.06</td>
<td>0.08</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Table 1
Demographic Information.

<table>
<thead>
<tr>
<th>Age (years), mean (SD)</th>
<th>Overall n = 598</th>
<th>COMTε4+ve n = 139</th>
<th>COMTε4−ve n = 459</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>70.87 (6.45)</td>
<td>70.64 (6.39)</td>
<td>70.94 (6.47)</td>
<td>0.633</td>
</tr>
<tr>
<td>Years of Education, n (%)</td>
<td>331 (55.35)</td>
<td>73 (52.52)</td>
<td>258 (56.21)</td>
<td>0.503</td>
</tr>
<tr>
<td>0-8</td>
<td>46 (7.72)</td>
<td>13 (9.35)</td>
<td>33 (7.22)</td>
<td>0.435</td>
</tr>
<tr>
<td>9-12</td>
<td>218 (36.58)</td>
<td>45 (32.37)</td>
<td>173 (37.86)</td>
<td></td>
</tr>
<tr>
<td>13-15</td>
<td>124 (20.81)</td>
<td>34 (24.66)</td>
<td>90 (19.69)</td>
<td></td>
</tr>
<tr>
<td>15+</td>
<td>208 (34.90)</td>
<td>47 (33.81)</td>
<td>161 (35.23)</td>
<td></td>
</tr>
<tr>
<td>Preforbid IQ (FSIQ) mean (SD)</td>
<td>108.00 (7.24)</td>
<td>108.42 (6.82)</td>
<td>107.87 (7.36)</td>
<td>0.434</td>
</tr>
<tr>
<td>Depressive Symptoms (GDS), mean (SD)</td>
<td>1.05 (1.32)</td>
<td>0.83 (1.06)</td>
<td>1.12 (1.32)</td>
<td>0.043</td>
</tr>
<tr>
<td>APOE ε4 carriage, n (%)</td>
<td>167 (27.93)</td>
<td>37 (24.66)</td>
<td>130 (28.32)</td>
<td>0.776</td>
</tr>
<tr>
<td>High Aβ burden, n (%)</td>
<td>258 (43.14)</td>
<td>59 (36.62)</td>
<td>203 (44.23)</td>
<td>0.382</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>COMTε4+ve n = 139</th>
<th>COMTε4−ve n = 459</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>β</td>
<td>0.021</td>
<td>0.029</td>
<td>0.647</td>
<td></td>
</tr>
<tr>
<td>Verbal Episodic Memory</td>
<td>0.025</td>
<td>0.033</td>
<td>0.626</td>
<td></td>
</tr>
<tr>
<td>PACC</td>
<td>−0.024</td>
<td>−0.017</td>
<td>0.875</td>
<td></td>
</tr>
</tbody>
</table>

Mean slopes for cognitive composites (presented in SD/year; n = 598) in all imaged cognitively normal participants, controlling for Aβε4 carrier status and additionally age and sex in the PACC.

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 interaction 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.

<table>
<thead>
<tr>
<th></th>
<th>Aβε4+/COMTε4+ve n = 84</th>
<th>Aβε4−/COMTε4+ve n = 256</th>
<th>Aβε4+/COMTε4−ve n = 55</th>
<th>Aβε4−/COMTε4−ve n = 203</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>0.049 β</td>
<td>0.050 β</td>
<td>−0.022 *</td>
<td>−0.007 *</td>
<td></td>
</tr>
<tr>
<td>Verbal Episodic Memory</td>
<td>0.054 β</td>
<td>0.052 β</td>
<td>−0.019 *</td>
<td>0.002 *</td>
<td></td>
</tr>
<tr>
<td>PACC</td>
<td>0.043 β</td>
<td>0.049 β</td>
<td>−0.128 *</td>
<td>−0.122 *</td>
<td></td>
</tr>
</tbody>
</table>

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 Aβε4+/COMTε4−ve group, *p < 0.05 when comparing to the Aβε4−/COMTε4−ve group, *p < 0.05 when comparing to the Aβε4+/COMTε4−ve group.

Baseline demographic and clinical characteristics of all imaged cognitively normal adults in the AIBL Study, and stratified by COMT status (COMTε4+ve and COMTε4−ve). 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.


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