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Original article

Associations between COMTVal^{158}Met polymorphism and cognition: direct or indirect effects?

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Abstract

Background: Previous work suggests that reaction time variability (RTV) in attentional tasks, as a measure of cognitive stability, is associated with degree of *Val* loading in COMT *Val*^{158}*Met* genotype, and that this association may be relevant for the aetiology of schizophrenia. This study examined (i) to what degree RTV pertaining to tasks of varying cognitive complexity would be associated with increased risk for schizophrenia and (ii) to what degree this would be mediated by *Val* loading.

Methods: COMT genotyping was investigated in a sample of 23 patients with schizophrenia, 33 first-degree relatives, and 21 controls. All participants performed the Flanker continuous performance test.

Results: Schizophrenia liability was associated with number of correct trials of the Flanker test, but not with RTV, and this association was not mediated by COMT *Val*^{158}*Met* genotype. Similarly, *Met* loading was associated with number of correct trials and with RTV, but this was not mediated by schizophrenia liability.

Conclusions: Associations between COMT *Val*^{158}*Met* genotype and RTV do not appear to reflect transmission of schizophrenia liability in families. Differential associations with *Val* and *Met* alleles across studies suggest indirect effects through gene–gene interactions or the influence of a functional polymorphism near COMT *Val*^{158}*Met*.

Keywords: Schizophrenia; Relatives; COMT; Cognition; Reaction time variability

1. Introduction

Selective inhibitors of the enzyme catechol-*O*-methyltransferase (COMT), involved in dopamine degradation, improve cognitive function in animals [12] and in patients with Parkinson's disease [6]. A G-to-A transition at codon 158 of the COMT gene, resulting in a valine (*Val*)-to-methionine (*Met*) substitution yielding different *Val*^{158}*Met* genotypes, has been associated with differential COMT activity. The *Val* allele results in a thermostabile protein with a three to fourfold increase in enzymatic activity [15,19] compared to the *Met* allele. Given the effects of COMT-inhibitors on cognition, variation in COMT activity associated with genotype may also result in poorer performance of frontally mediated cognitive tasks. In particular the *Val* allele has been suggested to affect frontal cognitive function and risk for schizophrenia.

However, findings relating COMT-genotype with measures of cognition have been inconsistent, both in terms of finding associations and, in the case of positive associations, the type of cognitive task and the type of allele, i.e. *Val* or *Met* [1–3,7,14,16,18,21,23,24]. In addition, the most recent meta-analytic work for a contribution of the *Val* allele to schizophrenia risk suggest only minimal evidence for an association [5] and one

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study in patients found an association between severity of symptomatology and the *Met* allele rather than *Val* [2].

It has been suggested that inconsistencies in the findings relating COMT-genotype to cognition may be caused by the failure to distinguish between cognitive tasks that differentially depend on tonic and phasic dopamine signalling in the prefrontal cortex, as the low activity *Met* allele may be expected to be of benefit in tasks of cognitive stability (stability of working memory traces) requiring tonic dopamine activation but have negative effects on tasks of cognitive flexibility (resetting or updating working memory traces) requiring phasic activation [9,16]. For example, in the largest study to date involving a representative sample of 543 young men, no effect of COMT-genotype was found on either working memory or attention [21], but when associations with a parameter more specific for cognitive stability, namely reaction time variability (RTV) was examined, the degree of *Val* loading predicted poorer performance [22]. Similarly, one study reported that if a cognitive task includes separable aspects of cognitive stability and cognitive flexibility, differential associations with *Met* and *Val* loading can be demonstrated [16].

Previous findings on cognitive stability were based on a measure of RTV in a continuous performance test (CPT) involving a considerable amount of workload [22]. In order to investigate whether the association between RTV and COMT-genotype *Val* loading would be robust across different levels of cognitive effort, the present study used a CPT paradigm with varying task demands. Thus, the aim of the current study was to examine the hypothesis that associations between schizophrenia liability and different RTV measures representing cognitive stability would be mediated by COMT-genotype *Val* loading. We predicted that the association between schizophrenia and cognitive stability would be independent of the association between *Val* loading and cognitive stability.

2. Subjects and methods

2.1. Sample

Patients who had a DSM-IV diagnosis of schizophrenia according to the participating clinician, and who were attending the catchment area Community Mental Health Centre in the city of Llodio, Spain (population: 39,000), were asked to participate in the study. First-degree relatives of patients were asked to participate as well. Controls were a community sample collected among local businesses in the area, and first-degree relatives of controls were similarly asked to participate. Guided by published literature [2], 80% power at conventional alpha required 16 individuals in each group given an effect size of 1 standard deviation for the difference between *Val*/*Val* and *Met*/*Met* genotypes and 28 individuals in each group if the effect size was 0.75 S.D. The study was approved by the local ethics committee and patients provided written informed consent.

2.2. Cognitive measures

The Flanker CPT (Cognitive Therapeutics Ltd.) [4,17] is a measure of executive control of attention. The task is to respond by pressing the right or left mouse button depending on whether the middle element in a display of five lines has an arrowhead pointing to the right or left. There are three trial types. In neutral trials, the flankers are just horizontal lines without arrowheads. In congruent trials, all flankers have arrowheads pointing in the same direction as the target. In incongruent trials the flankers have arrowheads pointing in the direction opposite that of the target. The incongruent condition involves more cognitive effort, because the flankers are associated with a response that needs to be suppressed. One half of the trials of each trial type is presented with the stimuli above the fixation cross on the screen, the other half are presented below fixation, in order to prevent subjects from keeping their gaze fixed in one position. The test consists of 144 trials of neutral, congruent and incongruent flankers, which are presented randomly. Outcome measures were the mean reaction time for correct responses (RT), the standard deviation of the mean reaction time for correct responses (RTV), and the sum of correct trials.

2.3. COMT genotyping

Genomic DNA was extracted by standard procedures. The COMT *Val*^{158}*Met* polymorphism was genotyped using a 5′-nuclease assay on an ABI-PRISM 7700 Sequence Detection System (Applied Biosystems, Foster City, CA, USA). Flanking amplification primers (5′-TCGTGGACGCCGTGATTCAGG-3′ and 5′-AGGTCTGACAACGGGTCAGGC-3′) and two fluorescent probes [5′-6FAM-CGCTGGCGTGAAG-3′ (*Val*) and 5′-TET-TTTCGCTGGCATGAA-3′ (*Met*)] were designed using *PrimerExpress* v.2.0 software (Applied Biosystems) and reactions were performed using the *Taqman® Universal PCR master mix* (Applied Biosystems) following the manufacturer's instructions. All assays were run in duplicate and alleles were called by the *SDS* v.1.9.1 software (Applied Biosystems) using pre-sequenced DNA samples homozygous for either the *Val* or *Met* alleles as standards.

2.4. Analyses

All analyses were carried out using the STATA statistical programme, version 8 [20]. A variable indicating schizophrenia liability was constructed with value 3 for patients, value 2 for relatives and value 1 for controls [13]. The association between schizophrenia liability and cognitive performance was assessed using regression analyses with cognitive test values as the dependent variable and schizophrenia liability as the independent variable. The association with COMT-genotype was similarly assessed in a regression analysis with cognitive test values as the dependent variable and COMT-genotype as the independent variable. As the data were hierarchically structured, with individuals clustered in families, standard errors were corrected