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Selective role for the COMT polymorphism in a trans-diagnostic compulsivity phenotype

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Abstract

Background. Impulsivity and compulsivity are central to understanding a range of psychiatric disorders but also to understanding the spectrum of normative human behavior. It was recently shown that separable latent phenotypes of impulsivity and compulsivity could be fractionated. The possible genetic contributions to these latent phenotypes have yet to be elicited. The catechol-o-methyl transferase (COMT) Val158Met polymorphism (rs4680) regulates cortical dopamine degradation and is a key area of interest in this context.

Methods. COMT Val158Met polymorphism status was obtained from a random subset ($n = 258$) of young adults from an established cohort, for whom latent phenotype scores were previously reported. Differences in latent phenotype scores were explored between COMT groups using analysis of variance (ANOVA) and post-hoc t tests.

Results. The Val-Val subgroup exhibited significantly elevated compulsivity scores compared to both other groups. Impulsivity scores did not differ significantly as a function of COMT Val158Met polymorphism status.

Conclusions. These results suggest that the COMT polymorphism, and by implication cortical dopamine degradation, influences the expression of a trans-diagnostic compulsivity phenotype, even accounting for possible confounding effects of impulsivity.

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Impulsivity refers to behavior that is inappropriate, premature, or unduly hasty (Evdenden, 1999); whereas compulsivity describes a tendency toward habitual, repetitive behavior, for which the link with the original goal has been lost (Gillan *et al.*, 2016). Originally conceptualized as being diametrically opposed, there is cross-talk between these two constructs: comorbidities are commonplace, hence there is a need for latent phenotyping approaches designed to capture differential contributions to both (Fontenelle *et al.*, 2011; Hollander, 2014). Of genes likely to be relevant to understanding these concepts, the catechol-o-methyl transferase (COMT) Val158Met polymorphism (rs4680) is one likely contender. This genetic polymorphism regulates cortical dopamine degradation, with the Val-Val variant being associated with higher enzyme activity and thus with presumptive lower cortical dopamine levels (Tunbridge *et al.*, 2012).

The Val-Val variant of COMT has been linked to worse response inhibition (implicated in impulsivity) and worse set-shifting (implicated in compulsivity) (Mione *et al.*, 2015; van Goozen *et al.*, 2016). In a recent meta-analysis of the literature, the Val-Val form was significantly associated with attention-deficit hyperactivity disorder (ADHD) ($p = 0.005$; 99% confidence interval for odds ratio 0.858–0.994, with <1 indicating Val was over-represented) whereas the association with OCD was equivocal ($p = 0.035$, but 99% confidence for odds ratio 0.972–1.329) (Taylor, 2018). Part of the reason for inconsistent findings in the genetics literature may be a failure to control for the impact of impulsivity on compulsivity and vice versa.

In a recent paper published in *Psychological Medicine* (Chamberlain *et al.*, 2017), we identified separable latent phenotypes of impulsivity and compulsivity in a sample of 576 adults recruited from the general population. These dimensional phenotypes were constructed through latent factor analysis incorporating measures of symptoms, personality traits, and cognitive functioning. Across the study participants, latent scores were significantly associated with worse quality of life, highlighting their clinical relevance. Since publishing this paper we have obtained COMT polymorphism status from a random subset of the sample. The COMT polymorphism was in Hardy–Weinberg equilibrium ($\chi^2 = 0.94$, $p > 0.05$). As shown in Fig. 1, the Val-Val COMT variant was associated with significantly elevated latent phenotype compulsivity scores. No such differences were found for impulsivity scores ($p > 0.10$).

These data suggest that COMT regulation, and by implication the cortical dopamine system, may play a particular role in compulsive traits at the level of the background population,

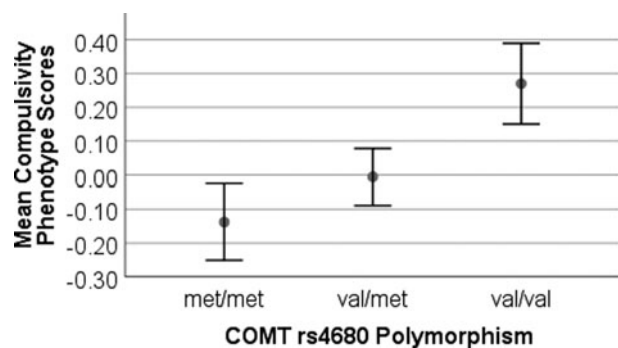


Fig. 1. Mean (SEM) compulsivity scores as a function of the genetic polymorphisms of interest. The main effect of group on compulsivity scores was significant (ANOVA $F = 3.439$, $P = 0.034$); the val/val group ($N = 82$) had significantly higher compulsivity compared to the met/met ($N = 56$) and val/met ($N = 120$) groups ($p = 0.015$ and $p = 0.046$, respectively).

even when confounding effects of impulsivity are accounted for at the latent phenotypic level. We suggest that genetic and biological underpinnings of impulsivity and compulsivity may be further clarified by examining latent phenotypes rather than isolated discrete symptom domains (i.e. single mental disorders). In turn, this may fuel new targeted treatment approaches, given that pharmacological interventions exist that may be capable of selectively modulating cortical dopamine.

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