

COMT Val¹⁵⁸Met genotype is associated with fluctuations in working memory performance: converging evidence from behavioural and single-trial P3b measures



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ABSTRACT

Intra-subject variability in reaction times (ISV) is a promising endophenotype for several psychiatric conditions, but its neural underpinnings are not yet established. Converging evidence from neuroimaging, molecular genetics, and psychopharmacology suggests that ISV could index catecholaminergically-mediated neural noise. The fine-grained temporal resolution of electroencephalography is ideal for investigating ISV, but only if potential neural correlates of ISV can be assessed in single trials. Based on evidence that ISV is associated with dopaminergic functioning, we apply a recently developed method of single-trial P3b analysis to investigate the association of COMT Val¹⁵⁸Met genotype with measures of ISV on the behavioural and neural levels at different working memory loads. Greater number of Met alleles was associated with poorer and more intra-individually variable performance on the tasks, and greater latency jitter in single-trial P3bs. These converging results at the behavioural and neurophysiological levels confirm previous observations that prefrontal dopamine availability is associated with stability and accuracy of cognitive performance. Together with previous studies, these data imply pleiotropic cognitive effects of COMT genotype.

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Introduction

Elevated intra-subject variability of reaction times (ISV) is a promising behavioural endophenotype for several psychiatric conditions, including schizophrenia (Kaiser et al., 2008; Smyrnis et al., 2009), bipolar disorder (Brotman et al., 2009), and attention-deficit/hyperactivity disorder (Klein et al., 2006; Kuntsi and Klein, 2012; McLoughlin et al., 2014). High ISV is a stable trait (Saville et al., 2011b), is also associated with frontal lobe injury (Stuss et al., 2003), and, intriguingly, predicts impending death in longitudinal studies (Macdonald et al., 2008). ISV in cognitive tasks has been identified as a possible measure of neural noise (Gilden et al., 1995; Slifkin and Newell, 1998), random fluctuations

of neural behaviour which do not reflect a meaningful signal (Faisal et al., 2008). Specifically ISV has been suggested to be an index of catecholaminergically-mediated prefrontal noise (Winterer et al., 2006a, 2006b).

Studies employing a variety of methodologies suggest a link between ISV and the catecholaminergic system. Two positron emission tomography studies (Aalto et al., 2005; MacDonald et al., 2009) found negative correlations between frontal D₂ dopamine receptor binding and ISV, the latter measured during n-back tasks, and pattern recognition and set-shifting tasks respectively. Psychopharmacological studies also suggest that increased post-synaptic dopamine availability due to methylphenidate, reduces ISV in healthy controls (Costa et al., 2012; Nandam et al., 2011) and ADHD patients (Spencer et al., 2009).

Molecular genetics offer another approach for linking individual differences in ISV and catecholamine functioning. One polymorphism studied profitably is the Val¹⁵⁸Met polymorphism (rs4680) of COMT, located in 22q11.1–q11.2. This polymorphism codes for the catechol-O-methyltransferase enzyme, which metabolises catecholamines. The

^{*} Abbreviations: ISV, intra-subject variability of reaction times; RT, reaction times; COMT, catechol-O-methyltransferase.

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Saliva-derived genomic DNA samples were genotyped using Illumina BeadXPress Golden Gate assay to verify 96 SNPs, including COMT Val¹⁵⁸Met. Nucleic acid quality and concentration were evaluated using PicoGreen assay. Genotyping was conducted according to manufacturer's protocols. Genotype calling and annotation were performed using GenomeStudio assay with default settings (all Illumina, San Diego, USA).

Stimuli and procedure

Participants performed three *n-back* tasks with different working memory loads: a zero-back task (0BT), a one-back task (1BT), and a two-back task (2BT). In all tasks participants watched a series of letters and responded to each letter differentially based on whether it was a target or not. What constituted a target differed across tasks. In the 0BT, the letter "E" was the target, in the 1BT, letters that matched the previous letter were targets, and in the 2BT, letters that matched the previous-but-one letter were targets. Target probability was 25% in all tasks. In all other cases, called *standards*, participants responded with the other hand (75% of trials). Participants were asked to respond as quickly and accurately as possible.

Participants performed one block of each task, then a second block of each task in the same order. Five minutes of resting EEG data were collected between the second and third blocks and between the fourth and fifth blocks. Task order was counterbalanced across participants. Participants were tested in 2.5 hour blocks, approximately an hour and ten minutes of which was spent testing (6×10 -minute blocks, 2×5 -minute resting blocks), and the remainder was spent on participant briefing and consent, hair-washing, and electrode attachment.

Stimuli were white Arial letters, with visual angle of $\sim 3^\circ$, on a black background. Stimulus duration was 1000 ms and stimulus-onset asynchrony was jittered uniformly between 1950 and 2050 ms in 25 ms steps, averaging 2000 ms. Each block contained 280 trials. Stimuli were delivered using E-Prime V1.2 (Psychology Software Tools, PA, USA).

Data analysis

Data were processed blind to participant genotype up to the point of inferential statistics. Analysis of behavioural data was performed in R (R Core Development Team, 2012) and EEG data were analysed using Brain Vision Analyzer 2 (Brain Products, Munich, Germany), The ERP-PCA toolkit (Dien, 2010) for Matlab (MathWorks Inc., Natick, MA, USA), and R (R Core Development Team, 2012).

Behavioural data

Accuracy was defined as the number of correct trials divided by the total number of trials. Once RTs faster than 120 ms (anticipatory RTs) and errors were excluded, MnRT was defined as median RT, and SDRT was defined as standard deviation of RT.

EEG data

Direct-current corrections, channel saturation, and large movements were excluded by rejecting data where amplitude varied by $>1500 \mu\text{V}$ or $<0.5 \mu\text{V}$ in any 200 ms window. Infomax independent components analysis (ICA) was then run on 180 s of data starting 120 s into each task, and factor loadings were applied to the rest of the file. Components representing oculomotor, cardiac, or electromyographic artefacts were visually identified by their topographies and time courses and removed before remaining components were back-projected.

Data were then average-referenced and 0.05–50.00 Hz zero-phase Butterworth filtered (24 dB/octave roll-offs), before a more stringent automatic artefact rejection procedure was run; rejecting data ranging $>150 \mu\text{V}$ in any 200 ms window, as well as data 200 ms before and after this section.

An additional 4 Hz low-pass filter was then applied to the data. This is a rather stringent filter, but, considering the low signal-to-noise ratio of single-trial analysis and the low-frequency support for the P3b, such filters are optimal for single-trial analysis (Smulders et al., 1994).

Stimulus-locked segments, ranging from 600 ms pre-stimulus until 1400 ms post-stimulus, were obtained from target trials with no rejected data and a correct response between 120 and 1400 ms post-stimulus. Average ERPs were computed for each participant.

The procedure used in Saville et al. (2011a, 2012) was employed for single-trial analysis. While peak picking can be facilitated in standard ERP approaches by aggregating data across trials, this is clearly not compatible with a single-trial approach. However, while aggregation across trials is not possible in a single-trial analysis, aggregation across electrodes is a viable means to improve signal-to-noise ratio, and principal components analysis (PCA) is a proven way to derive appropriate weightings for such summation across electrodes. All average ERPs were concatenated along the time-axis, before Dien's (Dien, 2010) ERP-PCA toolkit was used to run spatial principal components analysis. Based on parallel Scree test seven factors were extracted and Infomax-rotated (Bell and Sejnowski, 1995). Factor 1 had a clear P3b topography so it was used henceforth. See Fig. 1 for all factor topographies.

The factor pattern-matrix from factor 1 was applied to unaveraged single-trial data, so each time-point represented the sum of all electrodes, weighted by each electrode's loading on factor 1. Single-trial peaks were identified on each trial as the time-point between 250 and 1000 ms post-stimulus with maximal amplitude.¹ Single-trial P3b latencies and amplitudes were aggregated into stimulus-locked standard deviations of latency (SDLat) and median amplitude (MnAmp).

Inferential statistics

In order to verify that our measure of P3b latency was predictive of RT on a single-trial basis, a linear mixed effects model (Bates et al., 2012), predicting RT, with fixed effects of P3b latency and task, and random intercepts and slopes for P3b latency and load for each participant, was fitted to the concatenated single-trial data for all participants. To test the model, we fitted identical models dropping the fixed effect of P3b latency and task in turn, and compared these models to the full model using Aikake information criteria and R's *anova()* command. The random effects structure was identical in each model (Barr et al., 2013).

Data were analysed using ANOVA, as implemented by the ezANOVA command in the 'ez' package (Lawrence, 2013) for R (R Core Development Team, 2012). This was done separately for Accuracy, MnRT, SDRT, SDLat, and MnAmp. For behavioural parameters, TRIALTYPE (target, standard) was also included as an ANOVA factor. Effect size estimates are reported as generalised eta squared statistics. Post-hoc testing was accomplished by running follow-up ANOVAs with levels dropped from the analysis. While it would have been possible to use *t*-tests instead, ANOVAs were chosen so that effect sizes could be more easily compared across analyses. Greenhouse-Geisser corrections were applied to *p*-values where appropriate.

Results

Quantile-quantile normality plots for each dependent variable were examined to assess the appropriateness of each variable for parametric statistics. With the exception of accuracy, all variables appeared approximately normally distributed. Accuracy, however, was substantially skewed, and the distribution was truncated by a ceiling effect. Consequently, we replaced our planned ANOVA with a bootstrapped analysis, implemented using the ezBoot function in the 'ez' package for R

¹ The sign of factors from Infomax rotation is arbitrary. Here electrodes near Pz were weighted negatively so amplitude was given as a negative figure. This should not be confused with electrical polarity and, to avoid confusion, we refer to amplitude of the P3b factor as positive.

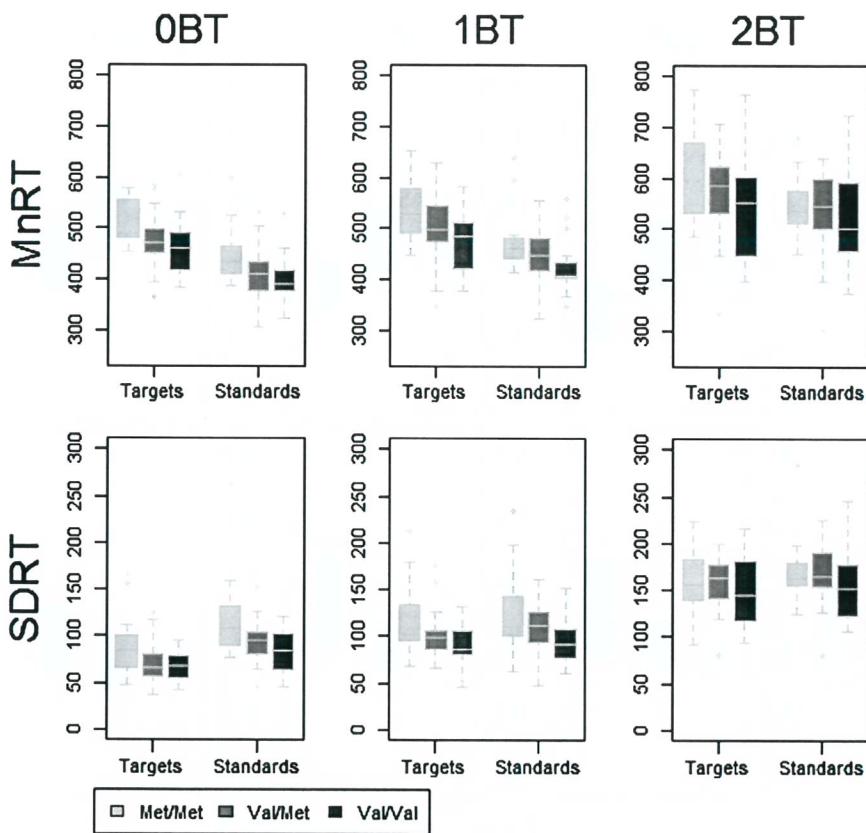


Fig. 3. MnRT (ms) and SDRT (ms) for the three genotype groups on each task, subdivided by trial type.

Single-trial P3b data

Single-trial P3b parameters are presented in Fig. 4. To illustrate the differing distributions of P3b latency in the homozygous groups, Fig. 5. presents 'latency maps' for the three groups, showing what proportion of each participants' trials fell into each of twenty 25 ms latency bins spanning the stimulus-locked peak picking window. For the sake of cross-group comparability, we present a subset of every second Val/Met carrier, sorted by P3b latency variability, so that similar number of participants appear in each panel. The latency map shows increasing dispersal of P3b latencies with increasing working memory load, and greater variability of P3b latencies in Met/Met than Val/Val carriers.

Linear mixed effects analysis

The model fit revealed that both P3b latency ($\beta = .1266$, $\sigma_{\beta} = .0154$, $t = 8.20$) and task ($\beta = 45.2498$, $\sigma_{\beta} = 4.6049$, $t = 9.83$) predicted RT in single-trials, with longer latencies and higher loads being associated with longer RTs. The full model ($AIC = 290257$) outperformed both the model without P3b latency ($AIC = 290318$, $p < .0001$) and the

model without task ($AIC = 290317$, $p < .0001$). This suggested that our measure of P3b latency was functionally relevant, even when accounting for task.

SDLat

There was a main effect of GENOTYPE ($F_{2,67} = 5.57$, $p = .0056$, $G\eta^2 = .115$), reflecting greater SDLat in Met/Met ($F_{1,32} = 6.67$, $p = .0156$, $G\eta^2 = .137$) and Val/Met ($F_{2,67} = 10.85$, $p = .0018$, $G\eta^2 = .136$), compared to Val/Val carriers. The Met-carrier groups had equivalent SDLat ($F_{2,67} = .27$, $p = .8702$, $G\eta^2 < .001$).

There was also a main effect of TASK ($F_{2,134} = 46.63$, $p < .0001$, $G\eta^2 = .134$), representing greater SDLat in the 1BT ($F_{1,67} = 8.91$, $p = .0039$, $G\eta^2 = .018$) and 2BT ($F_{1,67} = 81.08$, $p < .0001$, $G\eta^2 = .184$), compared to the OBT, and greater SDLat in the 2BT than the 1BT ($F_{1,67} = 43.20$, $p < .0001$, $G\eta^2 = .105$). The GENOTYPE*TASK interaction was not significant ($F_{4,134} = .70$, $p = .5922$, $G\eta^2 = .005$).

MnAmp

The GENOTYPE*TASK interaction did not survive Greenhouse-Geisser correction ($F_{4,134} = 2.47$, $p = .0605$, $G\eta^2 = .008$), but there

Table 1

Bootstrapped 95% confidence intervals, and medians, for accuracy, nested by group, task, and trial type.

	Met/Met			Val/Met			Val/Val		
	5%	Median	95%	5%	Median	95%	5%	Median	95%
OBT Targets	0.867	0.893	0.922	0.893	0.908	0.929	0.862	0.896	0.932
1BT Targets	0.749	0.801	0.857	0.875	0.893	0.915	0.845	0.871	0.901
2BT Targets	0.581	0.637	0.695	0.742	0.767	0.793	0.711	0.754	0.799
OBT Standards	0.9790	0.983	0.989	0.989	0.991	0.994	0.987	0.991	0.995
1BT Standards	0.980	0.984	0.988	0.985	0.987	0.990	0.986	0.990	0.994
2BT Standards	0.950	0.959	0.969	0.962	0.966	0.970	0.964	0.969	0.975

was a main effect of GENOTYPE ($F_{2,67} = 3.28, p = .0438, G\eta^2 = .080$), representing higher MnAmp in Val/Val carriers than Val/Met carriers ($F_{1,52} = 6.16, p = .0163, G\eta^2 = .095$). The homozygous groups had equivalent amplitudes ($F_{1,32} = 2.76, p = .1062, G\eta^2 = .071$) and there was no evidence of a difference in MnAmp between the Met-carrier groups ($F_{1,50} = .18, p = .6712, G\eta^2 = .003$). In the interest of possible future meta-analyses we report follow-up ANOVA results for the marginal GENOTYPE*TASK interaction: The effect of GENOTYPE is present for the OBT ($F_{2,67} = 4.01, p = .0226, G\eta^2 = .107$) and 1BT ($F_{2,67} = 3.21, p = .0465, G\eta^2 = .107$), but not the 2BT ($F_{2,67} = 1.92, p = .1548, G\eta^2 = .054$).

The main effect of TASK was significant ($F_{2,134} = 46.71, p < .0001, G\eta^2 = .073$), representing a lower amplitude in the 2BT, compared to the OBT ($F_{1,67} = 43.38, p < .0001, G\eta^2 = .073$), and 1BT ($F_{1,67} = 72.87, p < .0001, G\eta^2 = .098$). The OBT and 1BT did not differ ($F_{1,67} = 2.82, p = .0974, G\eta^2 = .002$).

Discussion

The present study is the first to describe an association between COMT genotype and single-trial P3b parameters. We identified increased behavioural ISV in the two Met-carrier groups, relative to the Val/Val group, results which are in line with those of Haraldsson et al. (2010), but contrast with those of Stefanis et al. (2005). This behavioural effect was paralleled by greater P3b latency variability in Met-carriers, compared to the Val/Val homozygotes. P3b latency predicted RT on a single-trial basis, suggesting that it was a physiologically relevant measure.

Our analyses focused on P3b latency, a measure of the duration of the cognitive aspects of target detection, which is relatively insensitive to factors affecting the response-planning and execution stages of the RT. This revealed that Met-carriers had more intra-individual variability in the duration of this decision process. While increased working memory load also increased P3b latency variability, this effect did not interact with COMT genotype. Such a result implies that the additional variability associated with Met-carriers is relatively difficulty-independent, but the effect on the P3b suggests that it is unlikely to be solely due to increased motor noise.

Failures in sustained attention seem a plausible candidate for such a difficulty-independent system. Previous work has found poorer sustained attention in adolescents carrying at least one Met-allele (Bellgrove et al., 2005a). Met/Met carriers have also demonstrated lower levels of posterior cingulate deactivation during go-no go and n-back tasks (Stokes et al., 2011), a pattern of brain activity associated with attention lapses (Weissman et al., 2006). The literature is mixed however, with evidence for poorer sustained attention in Val-carriers in the placebo condition of a psychopharmacological study (Hamidovic et al., 2010) and poorer on-task behaviour in ADHD patients with the Val/Val genotype (Sengupta et al., 2008).

There was, however, also evidence for poorer working memory performance in Met-carriers. Met/Met carriers showed poorer accuracy, particularly at higher working memory loads. Likewise we found a trend towards interaction on P3b amplitude, which did not survive Greenhouse-Geisser correction, possibly due to the modest power of our study. This manifested as higher amplitude P3bs for Val/Val carriers at the 0-back and 1-back loads, but no group differences on the 2BT. There is a well substantiated reduction of P3b amplitude with increasing working memory load (Morgan et al., 2008), and, taken alone, this finding could be interpreted as a smaller amplitude reduction, indicating superior working memory performance in Met-carriers. However, the abolition of group differences in the 2BT is likely to be due to a Val/Val advantage, as Morgan et al. showed that P3b amplitude reductions were proportionate to participants' working memory capacities. The accuracy data, where the Val/Val advantage became larger with increasing load, are more consistent with this second explanation.

Again the literature on the association between working memory performance and COMT genotype is mixed. While early studies found a Met/Met advantage on working memory tasks (Egan et al., 2001; Goldberg et al., 2003), meta-analysis of the literature revealed no consistent association (Barnett et al., 2008; Wacker, 2011). Recent work has drawn a distinction between different aspects of working memory, contending a Val/Val advantage in updating and manipulating and a Met/Met advantage in maintaining working memory (de Frias et al., 2010; Durstewitz and Seamans, 2008; Ettinger et al., 2008).

Such ambiguities in the literature could be due to a number of factors. As mentioned above, working memory performance relies upon several sub-processes, which may be differentially affected by prefrontal dopamine availability. Work suggests that dopaminergic genotypes may have a pleiotropic effect on these distinct sub-components (Markett et al., 2011; Stelzel et al., 2010). More prosaically, there is substantial heterogeneity in the details of tasks used in this field, even those with the same name. N-back tasks are particularly varied; some require identifying matching targets, some require reporting a sequence with a lag; pacing of stimulus onset varies, as do stimuli themselves; some tasks require responses to all trials, some require responses only to a minority of trials. COMT, with its proposed pleiotropic effects, may be sensitive to these differences and this could make it harder to draw general conclusions across studies.

COMT also appears to have an epistatic relationship with a number of other neurocognitively relevant polymorphisms (El-Hage et al., 2013; Garcia-Garcia et al., 2011; Heinzel et al., 2013), which when combined with the often low sample size of imaging genetics studies could masquerade as a main effect of COMT. Likewise, the dopaminergic system is influenced polygenically and other dopamine genes have been shown to be related to ISV (Bellgrove et al., 2005b), and small studies could fail to isolate the effects of COMT specifically, where other genetic effects contribute to dopamine functioning. As the most important and robust genes and epistatic effects affecting ISV and working memory emerge in the literature, however, such problems will hopefully become easier to identify.

COMT genotype is thought to affect not just how much dopamine is present in the synaptic cleft at any given time, but also the dynamics of its release over time. The tonic-phasic dopamine hypothesis (Bilder et al., 2004) contends that Val/Val carriers have increased phasic, but reduced tonic, dopaminergic activity, while Met/Met carriers have increased tonic, but reduced phasic activity. Evidence from another catecholaminergic system, the noradrenergic projections of the locus coeruleus, suggests that a low tonic-high phasic response of catecholaminergic projections is associated with low ISV and good sustained attention performance in invasive electrophysiological recordings from monkeys (Aston-Jones et al., 1999), consistent with the present data. The noradrenergic signal recorded in this study had marked similarities to the P3b (Nieuwenhuis et al., 2005), suggesting further parallels with our data. Such systems are thought to dynamically balance flexibility and stability of behaviour and mental representations, and work is underway to explore whether this balancing act underpins COMT's apparently pleiotropic effects.

The present study had limitations. Chief amongst these was the modest sample size. This is a common problem with the imaging genetics approach, as phenotyping is typically time-consuming and costly. Suboptimal statistical power has been shown to lead not just to a greater incidence of Type II errors, but also more Type I errors (Button et al., 2013). This is somewhat mitigated by the fact that the present study was following up the results of larger behavioural studies (Haraldsson et al., 2010; Stefanis et al., 2005). However as our study used different tasks to these studies, and a different sample composition to the study, Haraldsson et al., which our results most closely resemble (healthy young adults as opposed to a combined sample of patients with schizophrenia and healthy controls), our study is unable to entirely resolve the ambiguity in the literature. That said, we believe that the additional insights which a single-trial ERP approach yielded justified the reduced power relative to a larger behavioural study.

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