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COMT genotype is differentially associated with single trial variability of ERPs as a function of memory type

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ABSTRACT

Previous research on the association between intra-subject variability (ISV) in reaction times (RTs) and the Val[158]Met polymorphism of the catechol-o-methyltransferase gene (COMT; rs4680) has yielded mixed results. The present study compared the associations between COMT genotype and ISV in P3b latency measured during working and secondary memory tasks using residue iteration decomposition (RIDE) of single trial latencies. We compared the outcome of the present analyses with a previous analysis of the same data (N = 70, n-back tasks) using an alternative single-trial method. Additionally, we used RIDE to analyse the association between COMT genotype and ISV in an independent sample performing a different task (N = 91, face-recognition task). Analyses reconfirmed previous results from the n-back tasks, showing that Val alleles are associated with lower ISV. In the face recognition tasks, genotype interacted with task conditions, so Val homozygotes had higher ISV to unfamiliar faces than familiar ones but Met carriers showed no effect of familiarity. Moreover, in both datasets trial-by-trial RTs were predicted by P3b latencies. Therefore, the present data suggests that associations between COMT genotype and ISV depend on the type of cognitive processes, which may explain heterogeneity in previous results.

1. Introduction

Intra-subject variability (ISV) in reaction times (RTs), that is, the degree of inconsistency in response speed during cognitive tasks, has long been neglected in favour of measures of average RTs. However, ISV appears not only to be a stable trait (Saville et al., 2011), rather than an error term, but is also elevated in a number of clinically relevant conditions, including ADHD (Klein, Wendling, Huettner, Ruder, & Peper, 2006;Kofler et al., 2013; Saville et al., 2015a, 2015b), schizophrenia (Rentrop et al., 2010), and terminal decline (Macdonald, Hultsch, & Dixon, 2008).

Converging evidence further suggests that ISV may be sensitive to the status of the catecholaminergic neuromodulatory system. Psychopharmacological studies in both healthy adults (Nandam et al., 2011; Rammsayer & Stahl, 2006) and psychiatric groups (Spencer et al., 2009) have shown reductions of ISV after administration of catecholaminergic agonists. Increased ISV, relative to healthy controls, has also been found for patients with Parkinson's disease, a disorder associated with loss of catecholaminergic neurons (de Frias, Dixon, Fisher, & Camicioli, 2007).

Alongside psychopharmacological and patient studies, molecular genetics also suggests a link between ISV and catecholamine function. The Val[158]Met polymorphism of the catechol-*o*-methyltransferase (COMT) gene (rs4680) is a widely studied polymorphism, coding for an enzyme that breaks down catecholamines (dopamine, epinephrine, and norepinephrine) by methylation. This polymorphism is especially important for the deactivation of dopamine in the prefrontal cortex. Val homozygotes show three times greater COMT activity as compared with Met homozygotes, with intermediate levels for heterozygotes (Weinshilboum et al., 1999). Thus, dopamine availability in prefrontal cortex is lowest for Val/Val homozygotes, intermediate for Val/Met heterozygotes and greatest for Met/Met homozygotes.

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The COMT polymorphism has been associated with ISV in several studies (e.g., Haraldsson et al., 2010; Stefanis et al., 2005). However, the results are contradictory. For example, relative to the low-activity Met allele, the high-activity Val allele has been associated with increased ISV in a one-back memory task (Stefanis et al., 2005), but with decreased ISV in an antisaccade paradigm (Haraldsson et al., 2010). Therefore, the relationship between catecholamines and ISV may be complex and different task demands may favour different catecholaminergic states (Cools & Esposito, 2011).

ISV in RTs can stem from increased latency variability in different stages of cognitive processing – including stimulus-related (perceptual), central (decision related), and response-related (preparation and motor) stages. One approach to identify at what stage of processing ISV arises is to use event-related potentials (ERP). By analysing covert subprocesses that correspond to different stages of processing, we can obtain a more fine-tuned view than using RTs alone.

The study of ERPs, however, has been dominated by the averaging technique. ERPs have low amplitude compared to the background electroencephalographic (EEG) signal and hence are difficult to measure accurately on a single trial level. Using averaging to obtain ERPs makes the simplifying assumption that fluctuations in voltage that occur with consistent timing across trials represent evoked activity, *i.e.* signal, while variation between trials likely represents unrelated background processes, *i.e.* noise. By averaging voltages across trials time-locked to a reference event, evoked activity is revealed because the background EEG is attenuated. This assumption has proven reasonable in a wide range of experimental settings, and the approach has been very productive. The assumption of invariance of the signal across trials, however, is only an approximation and clearly inappropriate when ISV is the issue.

Instead of average ERPs, electrophysiological research into ISV has made use of single trial approaches. To this end, many researchers use time-frequency methods, and measure variability in phase at particular frequency bands, or other similar quantities (McLoughlin, Palmer, Rijsdijk, & Makeig, 2014). Other researchers use what might be called a neoclassical approach to ERPs, aiming to identify waveforms similar to classical ERP components in single trials, and directly measure variability in latency or amplitude (Saville et al., 2011; Ouyang, Herzmann, Zhou, & Sommer, 2011; Bender et al., 2015). For studying ISV at the electrophysiological level, and investigating its relationship with behaviour, along with its genetic basis and relations with psychiatric conditions, it is necessary to obtain a better understanding of how results obtained by different single trial approaches to ERPs correspond to one another. Widespread use of the average ERP means that researchers have a common frame of reference; this is not the case for single trial analysis. Furthermore, their relationships with behaviour need to be established in order to validate them and to investigate the commonalities and differences of the hitherto proposed single trial ERP methods.

Using the single trial approach of Saville et al. (2011), a method of identifying single trial ERP peaks using data aggregation across electrodes and peak picking, Saville et al. (2014) found Val genotypes to be associated with lower behavioural and electroencephalographic ISV, similar to the findings of Haraldsson et al. (2010), but different from those of Stefanis et al. (2005). The present study explored the replicability and generalizability of the findings of Saville et al. (2014) in two ways. Firstly, we reanalysed Saville et al.'s (2014) data using an alternative method of single trial analysis that has been evaluated multiple times in recent work. By applying the Residue Iteration Decomposition (RIDE; Ouyang et al., 2011; Ouyang, Sommer, & Zhou, 2015) method, we will assess the generalizability of these findings across these two analysis approaches. The RIDE method was developed to decompose ERPs into component clusters that can be distinguished by their latencies being timelocked to stimulus onset (S component cluster) or response time (R component cluster) or by not being timelocked to either of those (C component cluster). In a RIDE framework, the most obvious measure of ISV is the latency variability of the C component cluster. Depending on the task, the C components cluster may capture different components but in many tasks the dominant component is the P3b or late positive complex.

Moreover, as discussed above, previous findings regarding the association between COMT Val^{158}Met genotype and ISV at the level of behaviour have been inconsistent, possibly due to differences in experimental paradigms or tasks. We therefore reanalysed a second dataset from a face recognition task, reported previously in Kaltwasser et al. (2014), but for an independent research question as compared with the present one. For the present analysis we applied RIDE method to the electrophysiological data and related the obtained ISV measures to the COMT genotypes, asking whether the associations found in Saville et al. (2014) would generalize to a different task requiring familiarity decisions about faces within a repetition priming paradigm.

Hence, Objective 1 of this study is to assess the relationship between ISV at the electrophysiological and behavioural level and to determine whether this relationship is moderated by tasks and COMT genotypes.

Secondly, Objective 2 of the present work is to assess the association between COMT genotypes and ISV, measured as trial-to-trial variability in the latency of the C component in two data sets: The original Bangor data (Saville et al., 2014) and a second dataset collected in Berlin (Kaltwasser, Hildebrandt, Recio, Wilhelm, & Sommer, 2014). Replication of Saville et al's (2014) results in the same data with a new method will assess to what extent RIDE and Saville et al's neoclassical approach give converging results. Extension in the Berlin data, which were obtained in a long-term memory retrieval task rather than in a short-term memory task, will assess the robustness and generalizability of the results with regard to the COMT polymorphism and ISV.

2. Materials and methods

In this study we reanalysed two different datasets. One dataset was collected in Bangor to study the specific processes underlying the association between ISV and the COMT Val^{158}Met polymorphism and was reported in Saville et al. (2014) An analysis of the association between ISV and the ZNF804A gene was also conducted with this dataset (Saville et al., 2015a, 2015b).

The other dataset was collected in Berlin to study the neural mechanisms underlying individual differences in face cognition and was previously reported by Kaltwasser et al. (2014).

2.1. Participants

2.1.1. Bangor study

The Bangor sample consisted of 70 healthy young Caucasian adults, predominantly students from Bangor University. All participants had normal or corrected-to-normal visual acuity. The sample includes 18 (25.7% of participants) Val/Val carriers (age 21.5 ± 2.9, 41% female, 88% right-handed), 36 (51.4% of participants) Val/Met carriers (age 21.3 ± 2.8, 61% female, 94% right-handed), and 16 (22.8% of participants) Met/Met carriers (age 20.1 ± 1.8, 63% female, 81% right-handed). Hardy-Weinberg equilibrium was assessed using a chi-squared test, and did not appear to be violated ($\chi^2 = 0.06$, $p = 0.82$). An additional three participants' data were excluded, one because genotyping failed and two because they reported ≤ 4 h sleep the previous night.

2.1.2. Berlin study

The Berlin sample consisted of 91 healthy young Caucasian adults with heterogeneous occupational and educational backgrounds (38.2% with high school degree, 26.4% with university degree, 46.4% student, 34.5% employed, 13.6% unemployed). All participants had normal or corrected-to-normal visual acuity. The sample includes 20 (21.9% of participants) Val/Val carriers (age 26.50 ± 4.98, 45.0% female, 90.0% right-handed), 44 (48.3% of participants) Val/Met carriers (age 27.04 ± 5.08, 45.4% female, 81.8% right-handed), and 27 (29.6% of