The impact of the COMT genotype and cognitive demands on facets of Intra-Subject Variability

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Abstract

Intra-Subject Variability (ISV), a potential index of catecholaminergic regulation, is elevated in several disorders linked with altered dopamine function. ISV has typically been defined as reaction time standard deviation. However, the ex-Gaussian and spectral measures capture different aspects and may delineate different underlying sources of ISV; thus reflecting different facets of the construct. We examined the impact of factors associated with dopamine metabolism, namely, Catechol-O-Methyltransferase Val158Met (COMT) genotype and Working Memory (WM) and response-switching on ISV facets in young healthy adults. The Met allele was associated with overall increased variability. The rather exclusive sensitivity of ex-Gaussian tau to frequencies below 0.025Hz and the quasi-periodic structure of particularly slow responses support the interpretation of tau as low frequency fluctuations of neuronal networks. Sigma, by contrast, may reflect neural noise. Regarding cognitive demands, a WM load-related increase in variability was present for all genotypes and all ISV facets. Contrastingly, ISV facets reacted differently to variations in response-switching as, across genotypes, sigma was elevated for rare target trials whereas tau was elevated for frequent standard trials, particularly for Met homozygotes. Our findings support the significant role of COMT in regulating behavioural ISV with its facetted structure and presumed underlying neural processes.

1. Introduction

Intra-subject variability (ISV) refers to within-person variations in performance over short periods of time. ISV of reaction times (RTs) is elevated in schizophrenia (Kaiser et al., 2008; Smyrnis et al., 2009; Rentrop et al., 2010), methamphetamine psychosis (Fassbender et al., 2015), bipolar disorder (Brotman, Rooney, Skup, Pine & Leibenluft, 2009), attention-deficit/hyperactivity disorder (ADHD; Klein, Wendling, Huettner, Ruder & Peper, 2006) and Parkinson's disease (Burton, Strauss, Hultsch, Moll, & Hunter, 2006), which have all been associated with altered dopaminergic function. Contrastingly, for depression (Schwartz et al., 1989), obsessive-compulsive disorder (Damilou et al., 2016) or autism (Adamo et al., 2014), ISV was not found to be elevated. In ADHD literature, increased ISV of RTs is amongst the most consistent findings (Kofler et al., 2013) and considered to reflect underlying neural aetiology (Kuntsi & Klein, 2012). As ADHD patients demonstrated greatly elevated reaction time standard deviation (RTSD) after accounting for mean RT, but slower mean RT was no longer detectable after accounting for elevated RTSD (Klein et al., 2006), ISV is unlikely to be a consequence of response slowing and must be studied as an independent construct.

ISV is considered to be modulated by catecholaminergic activity in the prefrontal cortex (PFC) (Winterer et al., 2006a, 2006b). The action of dopamine (DA) released in the synaptic cleft is terminated either by DA transporters (DAT) reuptake, diffusion out of the synapse or by catabolism of the Val^{158}Met polymorphism (rs4680) of the Catechol-O-methyl-transferase (COMT) enzyme (Slifstein et al., 2008). The COMT genotype plays a particularly important role in catabolism of extracellular DA in the PFC (Turnbridge et al., 2004) due to that lower concentration of DAT here than in the striatum (Lewis et al., 2001; Sesack et al., 1998). The substitution of the Met allele by the Val allele leads to a three-to-four-fold increase in enzymatic activity, resulting in lower DA signalling (Lachman et al., 1996). COMT is therefore a promising gene for the study of mechanisms underlying differences in ISV.

Previous work examining the link between the COMT gene and ISV is limited and has produced contradicting results. The Val allele was linked with higher ISV of RTs following target trials in a continuous performance task (Stefanis et al., 2005) and with higher ISV of RT and P3b latencies of unfamiliar faces compared to familiar faces in a face-recognition task (Rostami et al., 2017). Contrastingly, the Met allele was associated with higher ISV of anti-saccade latency (Haraldsson et al., 2010). While each of these studies is highly suggestive of a link between COMT and ISV in various cognitive tasks, they all confined the measurement of variability to RTSD, a sensitive but non-specific global measure of ISV.

Given that variability of biological systems rarely exhibits absolute stochastic or strictly periodic patterns (Billman, 2011) but rather combines elements of both types of processes (Auffray et al., 2003), RTSD likely represents the amalgamation of various types of ISV (e.g. (non-)linear, (non-)periodic). In this regard, the use of distributional (e.g. ex-Gaussian, see below) and time-series (e.g. frequency-spectral measures to capture periodicity of RTs) measures may characterize and unmask potentially unique neural sources of variability; and thus collectively reflect different "facets" of ISV. The ex-Gaussian model describes the shape of individual RT distributions with mu and sigma describing the mean and standard deviation of a Gaussian RT component, respectively, and tau, describing the mean and standard deviation of the ex-Gaussian RT component.

Ex-Gaussian tau is proposed to reflect lapses of attention (Leth-Steensen et al., 2000) which are considered to emerge due to poor suppression of the default mode network (DMN) in ADHD (Fassbender et al., 2009). Using Fast Fourier Transform (FFT) based filtering techniques on distributional measures, we have shown that tau is rather exclusively characterised by ultra-slow quasi-periodic RT fluctuations in ADHD children (Feige et al., 2013); a spectral signature that corresponds directly with that of electrophysiological fluctuations linked with the DMN (Ko et al., 2011). A replication of this finding in a larger

healthy sample would further support the interpretation of elevated tau as recurrent lapses of attention due to DMN interference (Sonuga-Barke & Castellanos, 2007). With regard to the Gaussian potion of RT distributions, the consensus on a psychological interpretation is less clear that for tau. Yet, as the Gaussian mean, mu, has been linked with rather "basic" internal processes such as neural transmission or sensory and motor processes (see review by Matzke & Wagenmakers, 2009); sigma may index neural noise. Based on previous COMT studies in which Val allele carriers appropriately deactivated DMN-related regions (Stokes et al., 2011; Ettinger et al., 2008) and had increased prefrontal "noise" while performing various cognitive tasks (Egan et al., 2001; Winterer et al., 2006a, 2006b), it is plausible that ISV for these carriers is characterized by generally lower tau and elevated sigma. Yet, results may vary largely depending on task requirements.

Based on the tonic-phasic theory, variations in levels of DA via COMT may be beneficial or detrimental for performance depending on the cognitive demands of the task at hand (Bilder et al., 2004). The Met allele, associated with high tonic DA transmission and cortical D1 stimulation, is linked with higher cognitive stability. Conversely, the Val allele, linked with high phasic DA transmission and subcortical D2 stimulation, is related with higher cognitive flexibility. The critical association between DA and cognitive demands may underlie the contradiction in previous COMT studies on ISV (Stefanis et al., 2005; Rostami et al., 2017; Haraldsson et al., 2010). As such, a more detailed examination of the demands of working memory (WM) and response-switching and their interactions with COMT on ISV facets is warranted.

WM refers to the storage of information in the context of processing, and coordination of elements into new structures (Oberauer et al., 2003). Concerning the impact of WM on ISV facets, a strong negative association between WM and ex-Gaussian tau, suggesting that improved WM performance was related to smaller tau, has previously been reported (Schmiedek et al., 2007). If this association is stronger than that of other ISV facets, altering

WM loads would have a greater impact on tau than the others; but a systematic examination of the impact of these task effects on ISV facets is required to clarify whether this is the case. Additionally, it is intriguing whether the modulation of ISV facets by WM differs for the COMT genotypes as WM relies on, both, cognitive stability and cognitive flexibility (Bilder et al., 2004), and as the possibility that WM modulating increased ISV in ADHD (Klein et al., 2006) may be related to the involvement of the COMT gene in the disorder (Bellgrove et al., 2005). In this context, Val allele carriers may have a lower load-related increase in tau given that they better suppressed DMN-related neural activity than in Met allele carriers while performing an *n*-Back task (NBT) of WM (Stokes et al., 2011).

Response-switching involves the ability to shift between responding to frequent and rare stimuli; thus, requiring cognitive flexibility. Based on the tonic-phasic theory, Val allele carriers with high phasic dopaminergic state can be considered to be at an advantage here (Bilder et al., 2004). Indeed, previous work has shown that these carriers were more accurate (Nolan et al., 2004) and had lower switch costs (Colzato et al., 2010) in tasks demanding high cognitive flexibility. Although little is known about the impact of response-switching or its interaction with COMT on ISV facets, it is possible that Val homozygotes have lower tau when responding to less-frequent trials as they better suppressed DMN-related activity during performance of tasks with high demands of cognitive flexibility (Stokes et al., 2011; Ettinger et al., 2008).

Based on the considerations that inter-individual (or group) differences of reaction times should be described in terms of various ISV measures, we examined the impact of (i) COMT, (ii) cognitive demands of WM and response-switching, and their interactions with COMT, on ISV facets in healthy young adults. Alongside, spectral features of distributional ISV measures were studied to verify the plausibility of the assumption that ex-Gaussian tau reflects low frequency fluctuations of the DMN.

2. Methods

All procedures were in line with the Declaration of Helsinki and were approved by the ethics committee at the School of Psychology, Bangor University. Written informed consent was given by all participants before the study.

2.1 Participants

The present study is part of a previous ERP study that has been published elsewhere (Saville et al., 2014). Participants were mainly students or staff members at Bangor University recruited from a panel of Caucasian Western European genotyped volunteers. The exclusion criteria were personal or family history of psychiatric, neurological, genetic disorders or major systemic illnesses. Data for 70 participants consisting of 16 Met/Met carriers (age 20.1±1.8 years, 63% females, 81% right-handed), 36 Val/Met carriers (age 21.4±2.8 years, 61% females, 94% right-handed) and 18 Val/Val carriers (age 21.5±2.9 years, 39% females, 89% right-handed) were available for statistical analysis.

2.2 Apparatus and Materials

The experiment was conducted in a sound-attenuated Faraday cage and stimuli were presented on a 17" LCD monitor with an electrically shielded power source. DNA was obtained using saliva samples. 'Illumina BeadXPress Golden Gate assay' was used to identify 96 SNPs, one of which was the COMT Val^{158}Met genotype. 'Pico Green assay' was used to examine nucleic acid quality and concentration levels. Default settings were used for genotype calling and annotation using 'GenomeStudio assay' (all Illumina, San Diego, USA).

2.3 Stimuli and Procedure

We administered three NBTs: 0-back task (0BT), 1-back task (1BT) and 2-back task (2BT). In all tasks, a series of 280 letters was presented on the computer screen and

participants were instructed to respond to each letter by pressing one key if the letter was a standard trial (75% probability) and another key if the letter was target (25% probability). Targets were defined differently for each task: the letter 'E' for the 0BT, the letter matching the one preceding it for the 1BT, and a letter matching the previous-but-one for the 2BT. Response-switching demands were considered to be higher when responding to rare targets than to frequent standards. Although ours is not a state-of-the-art set-shifting paradigm, the switch required to respond to rare trials may represent this component. Participants were instructed to respond as quickly and accurately as possible. Participants completed one block of each task (0BT, 1 BT, 2BT) in an order that was a counterbalanced across the sample; and then a second block of each task in the same order. Between the blocks two and three, and four and five, resting state EEG was recorded for 5 minutes. The stimuli were white Arial letters presented on a black background at a visual angle of ~3°. Stimulus duration was 1000ms and the stimulus onset synchrony was varied between 1,950ms and 2,050ms in steps of 25ms, with a mean of 2000ms. E-Prime V1.2 software was used for presenting the stimuli.

2.4 Data Analysis

In order to visualize differences between groups for RT distributions, the total number of correct (upwards) vs. incorrect responses (downwards) were plotted in bins of 25ms separately for the three groups for the entire response period of 0-1500ms (**Figure 1a**). Incorrect responses were those in which participants responded with the wrong key – falsely classifying a target as a standard trial or vice versa. RTs 200ms or faster were considered to be anticipations and excluded from further analyses. The significant effects of WM LOAD (0BT/1BT/2BT), TRIALTYPE (targets/standards), RUN (first/second) and time-on-task (by including the onset-time of each trial as a covariate for linear trends e.g. fatigue) were subtracted from the RTs resulting in "residualised" RT. This procedure was done to "extract"

the endogenous Type I (except time-on-task) and Type II types of RT-ISV (Fiske & Rice, 1955).

Subsequently, different ISV estimates including Reaction Time Standard Deviation (RTSD), Consecutive Standard Deviation (CSD), Coefficient of Variation (CoV; RTSD/mean RT) and ex-Gaussian measures, sigma and tau, were computed. CSD or trial-to-trial variability was derived using the following formula: $\text{sqrt}(\sum(RT_i-RT_{i+1})^2/(n-1))$; i=trial number; n=number of trials. Spectral power was examined by resampling residualised RTs to 1 Hz using linear interpolation and then performing FFT in bins of 0.004Hz for the range of 0-0.25Hz on RT data for each participant and each block separately.

To determine whether tau is exclusively sensitive to low frequencies, we examined the contribution of spectral bands to various distributional ISV measures. Extraction filters (filter out all but the specified band) were applied to the time series data for each block of each participant and consequently scores of RTSD, CSD, sigma and tau were recomputed (see Feige et al., 2013). The extraction and suppression filters were applied in bands of width 0.025Hz for the range of 0-0.25Hz.

From a time series perspective, a low spectral characteristic for tau would suggest that particularly slow responses have a quasi-periodic occurrence within a background of generally faster responses. To test whether particularly slow RTs that significantly contribute to tau tend to emerge from slow RT-phases of background fluctuations, we proceeded to employ the following procedures (as introduced by Feige et al., 2013). Particularly slow or fast RTs were defined as the theoretical 1%-threshold of the Gaussian distribution (median±2.33SD; SD=IQR/1.349, IQR=Inter-Quartile Range) of the residualised RT data of each task block. For all the remaining RTs, "background fluctuation" was computed using a running median of 20 seconds (time window corresponding with one half of a cycle for the lowest frequency band of 0-0.025Hz). The "background fluctuation" was consequently

separated into three classes based on whether the given RT was positioned in the lower, middle or upper tertile of the overall RTs. We then statistically compared the total number of occurrences of particularly slow and particularly fast RTs as well as omission errors within the upper, middle and lower tertiles using chi² tests.

Finally, to complete our systematic comparisons, measures of speed (mean RTs, median RTs and mu) and accuracy (percentages of incorrect responses, omission errors (no response key pressed) and anticipation errors) were also examined.

2.5 Statistical analysis

ANOVAs were used to examine measures of ISV (RTSD, CSD, sigma, tau, spectral power of <0.1Hz; CoV), speed (mean RTs, median RTs, mu) and accuracy (percentages for-anticipation errors, incorrect responses, omission errors) with between-subject factor GENOTYPE (Val/Val, Met/Met, Val/Met) and within-subject factors LOAD (0BT, 1BT, 2BT) and TRIALTYPE (targets, standards; for all measures except CSD and spectral power). All ANOVAs were computed using the ezANOVA command of the 'ez' package (Lawrence, 2016) in R (R Core Team, 2017). Follow-up ANOVAs were used for post-hoc analyses. Greenhouse-Geisser corrected p-values were reported for all main effects of WM and interaction effects of WM*GENOTYPE due to violation of the assumption of sphericity.

3. Results

**********Insert **Table 1** about here**********

3.1 What is the impact of COMT on ISV facets?

Probability density plots show that RT distributions were flatter and broader for carriers with a higher number of Met alleles (**Figure 1a**). As can be seen from the descriptive statistics in **Table 1**, there was a clear ordinal relationship between number of Met alleles and ISV, showing that RT performance became more variable with increasing numbers of Met alleles. The corresponding GENOTYPE main effects underline the statistical significance of these group differences found for RTSD, CSD, sigma, spectral power of RTs (<.1Hz; also see **Figure 1b**), marginally for CoV, but not for tau (but see significant GENOTYPE*TRIALTYPE effect in **section 3.2**). Effect sizes highlight that group differences for all ISV measures emerged primarily from the comparison of the homozygous groups.

Examining the spectral composition of tau (**Figure 1c**) reveals that, unlike the fast RT variability measures (**Figures 1d, e, f**), it was the low frequency 0-.025Hz band *in particular* that contributed most to the ex-Gaussian measure. Overlapping confidence intervals indicate that the COMT genotypes did not differ in terms of the impact of this low spectral band on tau. A successive examination of RTs within the time domain revealed that the number of particularly slow responses was significantly higher in the slow RT tertile (Val/Val: $\chi^2_{(2)}$=193.89, p<.001; Met/Met: $\chi^2_{(2)}$=188.39, p<.001; Val/Met: $\chi^2_{(2)}$=472.74, p<.001) whereas the number of particularly fast RTs was significantly higher in the fast RT tertile (Val/Val: $\chi^2_{(2)}$=18.07, p<.001; Met/Met: $\chi^2_{(2)}$=18.85, p<.001; Val/Met: $\chi^2_{(2)}$=46.59, p<.001) for all genotypes; but the Val/Met group in particular. Contrastingly, omission errors were not preferentially associated with any tertile in Val allele carriers (Val/Val: $\chi^2_{(2)}$=0.45, p=.798; Val/Met: $\chi^2_{(2)}$=2.99, p=.225) but preferentially emerged from the slow RT tertile in Met/Met carriers ($\chi^2_{(2)}$=16.58, p<.001).

**********Insert **Figure 1** about here**********

3.2 What impact cognitive demands have on ISV facets? If present, does this impact differ across the COMT genotypes?

Inferential statistics for main effects for WM, TRIALTYPE and their respective interactions with GENOTYPE can be found in **Table 2**. The main effects of WM were significant for all ISV measures since variability increased from 0BT to 1BT ($23 \leq F \leq 84$, $p \leq .001$, $.04 \leq G\eta^2 \leq .13$ with effect sizes in the following descending order: CSD, RTSD, CoV, tau,<.1Hz, sigma) and even more so from 1BT to 2BT ($64 \leq F \leq 344$, $p \leq .001$, $.14 \leq G\eta^2 \leq .42$ with effect sizes in the following descending order: CSD, RTSD, <.1Hz, CoV, tau, sigma); a pattern that was uniform in all genotypes (all WM*GENOTYPE interactions: $p \geq .055$; $G\eta^2 \leq .019$).

Significant main effects for TRIALTYPE reflected higher RTSD, tau and CoV for standards than targets; but higher sigma for targets than standards. These effects were uniform across genotypes for RTSD, CoV and sigma, but not for tau (GENOTYPE*TRIALTYPE) since Met/Met carriers had higher tau than Val/Val carriers for frequent standards (GENOTYPE: $F_{(1,32)}=6.13$, $p=.002$, $G\eta^2=.133$), but not for rare targets (GENOTYPE: $F_{(1,32)}=0.81$, $p=.374$, $G\eta^2=.011$). The WM*TRIALTYPE*GENOTYPE interactions were non-significant ($p \geq .113$; $G\eta^2 \leq .011$) for all ISV facets.

**********Insert **Table 2** about here**********

3.3 Additional results

3.3.1 The impact of COMT on speed or accuracy

RTs became slower with increasing copies of the Met allele, indicating an ordinal pattern between the number of Met alleles and response speed. Relatedly, the GENOTYPE effects were significant for mean and median RTs, but not mu; and the significant effects were tendered by the comparison of the homozygous groups (see **Table 1**). Regarding accuracy, groups did not differ for anticipations or omission errors, but a significant GENOTYPE effect reflected more incorrect responses by Met/Met carriers than Val/Met carriers (**Table 1**).

3.3.2 The impact of cognitive demands and their interactions with COMT on speed and accuracy

Table 2 shows that significant main effects of WM on response time measures indicated response slowing from 0BT to 1BT ($7 \leq F \leq 53$, $p \leq .006$, $.011 \leq G\eta^2 \leq .061$) and 1BT to 2BT ($41 \leq F \leq 178.5$, $p \leq .001$, $.107 \leq G\eta^2 \leq .284$) for mean RTs>median RTs>mu; a pattern that was consistent across genotypes (WM*GENOTYPE). The number of anticipations did not differ with increasing WM loads. By contrast, significant main effects of WM indicated an increase in incorrect responses from 0BT to 1BT ($F_{(1, 67)}=30.04$, $p<.001$, $G\eta^2=.031$) and from 1BT to 2BT ($F_{(1, 67)}=211.23$, $p<.001$, $G\eta^2=.180$); and for omission errors from 1BT to 2BT ($F_{(1, 67)}=4.40$, $p=.040$, $G\eta^2=.028$), but not from 0BT to 1BT ($F_{(1, 67)}=1.06$, $p=.307$, $G\eta^2=.002$). The impact of load was uniform across genotypes for omission errors but not for incorrect responses (WM*GENOTYPE **in Table 2**; see below).

Response speed was significantly longer for targets than standards (TRIALTYPE) in all genotypes (TRIALTYPE*GENOTYPE **in Table 2**). The proportion of anticipation errors was

overall consistent across trials but incorrect responses and omission errors were significantly higher following targets than standards (TRIALTYPE). This pattern was uniform across genotypes for omission errors, but not incorrect responses (TRIALTYPE*GENOTYPE **in Table 2**; see below). Of all the response speed and accuracy measures, the interaction of WM*TRIALTYPE*GENOTYPE was significant for incorrect responses alone. The significance of this interaction, and that of WM*GENOTYPE or TRIALTYPE*GENOTYPE, reflect a disproportionately greater load-related increase in incorrect responses for Met/Met carriers than Val allele carriers (WM*GENOTYPE for Met/Met vs. Val/Met: $F_{(1.8,88.6)}$=11.06, p<.001, Gη²=.023; Met/Met vs. Val/Val: $F_{(1.6,51.4)}$=7.67, p=.002, Gη²=.027; Val/Val vs. Val/Met: $F_{(1.2,64.4)}$=0.61, p=.496, Gη²=.001) following targets (WM*GENOTYPE x: $F_{(3.3,222.6)}$=6.22, p<.001, Gη²=.042) but not standards (WM*GENOTYPE: $F_{(2.5,169.8)}$=0.63, p=.570, Gη²=.009).

4. Discussion

4.1 What is the impact of COMT on ISV facets?

This is the first study to investigate facets of ISV across variants of the COMT gene which revealed that the Met-allele is characterized by elevated scores for RTSD, low spectral power (<0.1Hz), trial-to-trial variability (CSD), sigma and, only for frequent standard trials, tau. Compared to Val homozygotes, Met homozygotes had elevated CoV suggesting that greater variability of these carriers was unrelated to their longer mean responding. The "headline" ISV finding of elevated RTSD in Met homozygotes (Saville et al., 2014) is in line with some (Haraldsson et al., 2010) but not all previous work (Stefanis et al., 2005; Rostami et al., 2017).

A characterization of the distributional ISV measures by their spectral characteristics to provide a more-informed psychological interpretation for them revealed that, unlike other

ISV facets, tau had an ultra-slow quasi-periodic structure (<.025Hz; i.e., 40s cycle) – corresponding with the temporal dynamics of the DMN interferences during task performance (<.1 Hz; Ko et al., 2011). If tau and low frequencies are indeed associated with DMN interferences, then, within the time-domain, particularly slow responses should occur quasi-periodically within slow RT phases. Indeed, we found that across all genotypes, particularly slow responses accumulated preferentially in the slow phases whereas particularly fast responses accumulated preferentially in the fast phases of ultra-slow background RT fluctuations. Omission errors, by contrast, did not generally accumulate in any background tertile suggesting that they may represent different type of attentional lapses than tau, possibly with a unique temporal structure. Taken together, the present study thus provides a replication of our previous work on ADHD in childhood (Feige et al., 2013) in a sample of healthy young adults, producing further evidence to support the interpretation of tau as attentional lapses (Leth-Steensen et al., 2000) due to poor suppression of the DMN interferences (Weissman et al., 2006; Sonuga-Barke & Castellanos, 2007). Also, the stronger association of trial-to-trial variability (CSD) with tau (r=.90) than sigma (r=.56) may be related to particularly slow responses occurring quasi-periodically rather than consequently in a time series. It is likely that the larger number of particularly slow responses (tau) following frequent standard trials contribute largely to a higher mean RT in Met homozygotes, since these carriers are not overall slower (mu).

The finding of elevated tau in Met homozygotes for frequent standard trials is consistent with the hypothesis that low frequency fluctuations in neuronal activity are modulated by catecholaminergic activity (Castellanos et al., 2005) and with previous studies in which these carriers showed reduced deactivations of neural structures associated with the DMN during an anti-saccade task (Ettinger et al., 2008) and in 2BT (compared to rest) or No-Go trials (compared to Go trials) (Stokes et al., 2011); possibly due to unfavorably high

prefrontal DA receptor stimulation. However, as Met homozygotes have shown appropriate deactivation of DMN-related regions during a pro-saccade task, the association of COMT with functional activity may be mediated by task demands (Ettinger et al., 2008, *also see section 4.2*).

Sigma, on the other hand, may be an index of neuromodulation, which according to computational models, relies on the efficiency of catecholaminergic functioning (Li, Lindenberger & Frensch, 2000). The present findings of elevated sigma in Met homozygotes may contradict studies wherein Val homozygotes had greater prefrontal "noise" (Winterer et al., 1006a, 2006b, Egan et al., 2001). However, our results are in line with evidence that underlines the significant role of extra-striatal neural regions and D2 receptors for ISV. An functional MRI (fMRI) study by van Belle et al. (2015) found that in a sample of children and young healthy controls, but not ADHD patients, an age-related decrease in sigma was associated with increased activity in the dorsal anterior cingulate gyrus. In a sample of otherwise healthy adults, reduced DA D2 receptor bindings in extra-striatal regions, particularly in the anterior cingulate cortex, was associated with elevated ISV considered to reflect poor signal-to-noise ratio of neural information (MacDonald et al., 2009). It is possible that elevated sigma in Met homozygotes is an index of poor neuromodulation due to high tonic and, reciprocally, low phasic DA D2 actions in subcortical regions (Bilder et al., 2004).

4.2 What impact do cognitive demands have on ISV facets? If present, does this impact differ across the COMT genotypes?

Greater "taxing" of WM functions led to an increase in ISV, an effect that is in principle in line with correlated individual differences in WM proficiency and ISV (Schmiedek et al., 2007). As in Schmiedek and colleagues' study and when considering effect

the sizes of the ex-Gaussian parameters, this relationship was somewhat greater for tau than for sigma. The magnitude of this load-related increase in ISV was, however, greater for CSD, RTSD, and, at a high WM load, also for low spectral power than for the two ex-Gaussian ISV parameters. Contrary to the assumption that Val allele carriers may have lower load-related increase in tau as they have previously shown better suppression of DMN activity during an NBT (Stokes et al., 2011), the load-related increase in ISV was uniform across genotypes for all measures. However, there was a disproportionate load-related increase in incorrect responses was found for Met/Met carriers which may be related to too much prefrontal DA D1 receptor stimulation associated with poor WM performance (Vijayraghavan et al., 2007). Hence, the critical impact of frontal DA availability on WM performance may be unrelated to ISV. In the context of the potential involvement of COMT in ADHD (Bellgrove et al., 2005), our findings do not support the notion that WM disproportionately increases ISV in the disorder (Klein et al., 2006; Kofler et al., 2014), but are in line with some recent studies (Feige et al., 2013; Salunkhe et al., 2018).

Shifting responding from frequent standard trials to rare targets led to an overall decrease in RTSD, CoV and tau, but an increase in sigma. With regard to the ex-Gaussian measures in particular, previous empirical work discouraged the interpretation of these measures as psychological processes as they did not correspond uniquely with diffusion model parameters (Matzke & Wagenmakers, 2009). In this regard, the differential reactivity of sigma and tau to response-switching demands argues in favor of, at least, a dissociation of these parameters. Variations in response-switching were also sensitive to genotypic differences in tau and incorrect responses, but none of the other examined measures, as Met/Met carriers had disproportionally higher tau for standard trials only and made more incorrect responses with increasing load for target trials only. For rare target trials, the unexpected lack of group differences in tau (a measure of above average slow responses) may

be related to the overall greater response slowing for this condition in all genotypes, and the higher number of incorrect responses by Met/Met carriers potentially due to a dopaminergic state that is non-conducive to cognitive flexibility (Bilder et al., 2004). It is also noteworthy that the interaction of COMT and response-switching, previously shown to modulate accuracy (Nolan et al., 2004), may also modulate specific aspects of ISV like tau. Based on our results, the contradiction in literature regarding the role of COMT on ISV (Stefanis et al., 2005; Haraldsson et al., 2010; Rostami et al., 2017) may be related to different task or cognitive demands that have a significant impact on the faceted structure of this construct.

The present study is not without limitations. Firstly, the modest sample size and its composition (mainly students) limit the generalizability of our findings. Secondly, while the administered NBT is suited to examine the impact of increasing WM loads on ISV measures, the examination of cognitive flexibility may be better studied using more state-of-the-art paradigms such as the Competing Programs Task (Nolan et al., 2004) or the Task-Switching Task (Colzato et al., 2010). Nevertheless, our findings contribute to a better understanding of the nature of increased ISV in Met homozygotes with the use of facets that differ in their spectral characteristics and reactivity to cognitive demands.

Figures (Title and caption for Fig1.pdf)

Figure 1 – RT analyses for COMT genotypes

A) RT density plots for correct (above) and incorrect responses (below). **B**) Spectral power density plots with uncorrected- pointwise significance ($p<.05$) markings for comparisons between pairs of genotypes are plotted below the frequency bands (Orange: Val/Val vs. Met/Met; Purple: Met/Met vs. Val/Met; Red: Val/Met vs. Val/Val). Extraction filters for **C**) tau, **D**) sigma, **E**) RTSD and **F**) CSD; with confidence intervals along the margin of the y-axis.

Tables

Table 1 – Descriptive statistics and Main effect of GENOTYPE

		Descriptive statistics			Omnibus Model df(2,67)			Val/Val vs. Met/Met df(1,32)			Val/Val vs. Val/Met df(1,52)			Val/Met vs. Met/Met df(1,50)		
		Val/Val	**Val/Met**	**Met/Met**	***F***	***p***	**Gη²**	***F***	***p***	**Gη²**	***F***	***p***	**Gη²**	***F***	***p***	**Gη²**
ISV	**RTSD**	100.6±38.3	111.6±39.4	125.4±44.4	**5.01**	**.009**	**.094**	**7.18**	**.012**	**.142**	**4.09**	**.048**	**.046**	3.76	.058	.051
	CSD	128.9±49.5	140.7±50.3	161.6±57.1	**5.54**	**.006**	**.115**	**7.71**	**.009**	**.164**	3.05	.087	.040	**5.23**	**.026**	**.079**
	Tau	79.1±43.1	89.8±44.6	96.5±50.7	2.49	.090	.033	3.69	.064	.053	3.54	.066	.027	0.83	.367	.008
	Sigma	49.4±24.1	56.3±24.4	65.8±32.5	**4.88**	**.010**	**.054**	**7.07**	**.012**	**.090**	3.60	.063	.024	3.91	.054	.029
	FB <.1 Hz	37.3±14.6	41.9±14.5	46.7±17.7	**3.89**	**.025**	**.086**	**5.47**	**.026**	**.127**	**4.19**	**.042**	**.055**	2.35	.132	.038
	CoV	.201±.06	.215±.06	.228±.06	3.05	.054	.049	**4.29**	**.047**	**.079**	2.66	.108	.026	2.14	.150	.023
Speed	**Mu**	411.6±79.1	419.5±67.8	437.0±70.0	1.61	.207	.025	2.72	.109	.041	0.37	.544	.004	2.43	.125	.022
	Mn. RTs	491.0±89.3	510.7±85.0	539.5±78.6	**3.68**	**.030**	**.069**	**6.82**	**.014**	**.125**	1.66	.203	.021	3.64	.062	.046
	Md. RTs	473.8±86.6	493.0±81.3	520.7±78.1	**3.67**	**.031**	**.066**	**6.66**	**.015**	**.118**	1.67	.202	.020	3.70	.060	.045
Accuracy	**%Anticipations**	0.10±0.25	0.29±1.08	0.12±0.28	0.58	.561	.013	0.09	.766	.001	0.68	.413	.010	0.50	.481	.008
	%Incorrect	8.40±10.43	7.62±9.45	11.73±15.0	**4.98**	**.001**	**.057**	3.59	.067	.045	0.50	.482	.004	**9.69**	**.003**	**.075**
	%Omission	0.67±3.31	0.42±0.84	0.57±0.98	0.32	.725	.004	0.04	.852	.004	0.51	.479	.004	0.59	.446	.007

Note: *RTSD*: Reaction time standard deviation; *CSD*: consecutive standard deviation; *FB*: Frequency Bands; CoV: Coefficient of Variation; *Mn. RTs*: mean RTs; *Md. RTs*: median RTs; *%Anticipations:* percentage of responses with latency 200ms or faster; *%Incorrect:* percentage of incorrect responses; %*Omission:* percentage of omission errors.

Table 2 –Inferential statistics for cognitive demands and GENOTYPE-related interactions

		WM df(2, 134)			WM*GENOTYPE df(4,134)			TRIALTYPE df(1,67)			TRIALTYPE*GENOTYPE df(2,67)		
		F	***p***	**Gη²**	***F***	***p***	**Gη²**	***F***	***p***	**Gη²**	***F***	***p***	**Gη²**
ISV	**RTSD**	**368.83**	**<.001**	**.492**	1.81	.138	.009	**42.38**	**<.001**	**.033**	0.54	.584	<.001
	CSD	**345.48**	**<.001**	**.526**	1.76	.148	.010	-	-	-	-	-	-
	Tau	**132.75**	**<.001**	**.336**	2.58	.055	.019	**93.76**	**<.001**	**.124**	**3.40**	**.039**	**.010**
	Sigma	**78.00**	**<.001**	**.223**	1.31	.275	.010	**16.31**	**<.001**	**.032**	1.78	.176	.007
	FB <.1 Hz	**308.21**	**<.001**	**.466**	1.29	.278	.007	-	-	-	-	-	-
	CoV	**187.66**	**<.001**	**.363**	1.52	.201	.009	**110.04**	**<.001**	**.174**	0.69	.505	.003
Speed	**Mu**	**43.79**	**<.001**	**.141**	0.13	.930	.001	**152.77**	**<.001**	**.234**	0.50	.610	.002
	Mn. RTs	**199.98**	**<.001**	**.372**	0.76	.515	.004	**87.10**	**<.001**	**.101**	0.17	.842	<.001
	Md. RTs	**153.42**	**<.001**	**.325**	0.47	.693	.003	**110.38**	**<.001**	**.134**	0.41	.665	.001
Accuracy	**%Anticipations**	0.89	.399	.001	0.55	.668	.002	0.01	.941	<.001	0.54	.583	<.001
	%Incorrect	**183.10**	**<.001**	**.247**	**6.24**	**<.001**	**.022**	**220.45**	**<.001**	**.536**	**4.88**	**.011**	**.049**
	%Omission	**4.65**	**.033**	**.037**	1.04	.360	.017	**18.60**	**<.001**	**.006**	0.59	.556	<.001

Note: *RTSD*: Reaction time standard deviation; *CSD*: consecutive standard deviation; *FB*: Frequency Bands; CoV: Coefficient of Variation; *Mn. RTs*: mean RTs; *Md. RTs*: median RTs; *%Anticipations:* percentage of responses with latency 200ms or faster; *%Incorrect:* percentage of incorrect responses; %*Omission:* percentage of omission errors, WM: Working Memory. TRIALTYPE was not included as a factor for CSD or for the FBs. For the main effect of WM and interaction effect of WM*GENOTYPE, Greenhouse Geisser corrected p-values are shown due violation of sphericity; degrees of freedom in the table are uncorrected.

References

Adamo, N., Huo, L., Adelsberg, S., Petkova, E., Castellanos, F. X., & Di Martino, A. (2014). Response time intra-subject variability: commonalities between children with autism spectrum disorders and children with ADHD. *European Child & Adolescent Psychiatry*, *23*(2), 69–79. doi:10.1007/s00787-013-0428-4

Auffray, B. Y. C., Imbeaud, S., Roux-rouquie, M., & Hood, L. (2003). Self-organized living systems : conjunction of a stable organization with chaotic fluctuations in biological space-time. *Hilosophical Transactions: Mathematical, Physical and Engineering Sciences*, *361*(1807), 1125–1139.

Bellgrove, M. a, Domschke, K., Hawi, Z., Kirley, A., Mullins, C., Robertson, I. H., & Gill, M. (2005). The methionine allele of the COMT polymorphism impairs prefrontal cognition in children and adolescents with ADHD. *Experimental Brain Research*, *163*(3), 352–60. doi:10.1007/s00221-004-2180-y

Billman, G. E. (2011). Heart rate variability - A historical perspective. *Frontiers in Physiology*, *2*(86), 1–13. doi:10.3389/fphys.2011.00086

Brotman, M., Rooney, M., Skup, M., Pine, D., & Leibenluft, E. (2009). Increased Intra Subject Variability in Response Time in Youths with Bipolar Disorder and At-Risk family members. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*(6), 628–635. doi:10.1097/CHI.0b013e3181a27527.

Burton, C. L., Strauss, E., Hultsch, D. F., Moll, A., & Hunter, M. A. (2006). Intraindividual variability as a marker of neurological dysfunction: A comparison of Alzheimer's disease and Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*, 28(1), 67–83.

Castellanos, F. X., Sonuga-Barke, E. J. S., Scheres, A., Di Martino, A., Hyde, C., & Walters, J. R. (2005). Varieties of Attention-Deficit/Hyperactivity Disorder-Related Intra- Individual Variability. *Biological Psychiatry*, 57(11), 1416–1423. doi:10.1016/j.biopsych.2004.12.005

Colzato, L. S., Waszak, F., Nieuwenhuis, S., Posthuma, D., & Hommel, B. (2010). The flexible mind is associated with the catechol-O-methyltransferase (COMT) Val158Met polymorphism: evidence for a role of dopamine in the control of task-switching. *Neuropsychologia*, *48*(9), 2764–8. doi:10.1016/j.neuropsychologia.2010.04.023

Damilou, A., Apostolakis, S., Thrapsanioti, E., Theleritis, C., & Smyrnis, N. (2016). Shared and distinct oculomotor function deficits in schizophrenia and obsessive compulsive disorder. *Psychophysiology*, *53*(6), 796–805. doi:10.1111/psyp.12630

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., … Weinberger, D. R. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(12), 6917–22. doi:10.1073/pnas.111134598

Ettinger, U., Kumari, V., Collier, D. a, Powell, J., Luzi, S., Michel, T. M., … Williams, S. C. R. (2008). Catechol-O-methyltransferase (COMT) val158met genotype is associated with BOLD response as a function of task characteristic. *Neuropsychopharmacology : Official*

Publication of the American College of Neuropsychopharmacology, *33*(13), 3046–3057. doi:10.1038/sj.npp.1301658

Fassbender, C., Lesh, T. A., Ursu, S., & Salo, R. (2015). Reaction Time Variability and Related Brain Activity in Methamphetamine Psychosis. *Biol Psychiatry*, *77*(5), 465–474. doi:10.1016/j.biopsych.2014.07.028.

Feige, B., Biscaldi, M., Saville, C. W. N., Kluckert, C., Bender, S., Ebner-Priemer, U., … Klein, C. (2013). On the Temporal Characteristics of Performance Variability in Attention Deficit Hyperactivity Disorder (ADHD). *PLoS ONE*, 8(10), e69674. doi:10.1371/journal.pone.0069674

Fiske D., & Rice L. (1955). Intra-Individual Response Variability. *Psychological Bulletin*, 52(3), 217–250.

Floresco, S. B., & Magyar, O. (2006). Mesocortical dopamine modulation of executive functions: Beyond working memory. *Psychopharmacology*, *188*(4), 567–585. doi:10.1007/s00213-006-0404-5

Haraldsson, H. M., Ettinger, U., Magnusdottir, B. B., Sigmundsson, T., Sigurdsson, E., Ingason, A., & Petursson, H. (2010). Catechol-O-methyltransferase Val 158 Met polymorphism and antisaccade eye movements in schizophrenia. *Schizophrenia Bulletin*, 36(1), 157–64. doi:10.1093/schbul/sbn064

Kaiser, S., Roth, A., Rentrop, M., Friederich, H.-C., Bender, S., & Weisbrod, M. (2008). Intra-individual reaction time variability in schizophrenia, depression and borderline personality disorder. *Brain and Cognition*, *66*(1), 73–82. doi:10.1016/j.bandc.2007.05.007

Klein, C., Wendling, K., Huettner, P., Ruder, H., & Peper, M. (2006). Intra-subject variability in attention-deficit hyperactivity disorder. *Biological Psychiatry*, *60*(10), 1088–97. doi:10.1016/j.biopsych.2006.04.003

Ko, A. L., Poliakov, A., Sorensen, L. B., Ojemann, J., & Darvas, F. (2011). Quasi-periodic Fluctuations in Default Mode Network Electrophysiology. *Journal of Neuroscience*, *31*(32), 11728–11732. doi:10.1523/jneurosci.5730-10.2011

Kofler, M. J., Alderson, R. M., Raiker, J. S., Bolden, J., Sarver, D. E., & Rapport, M. D. (2014). Working memory and intraindividual variability as neurocognitive indicators in ADHD: Examining competing model predictions. *Neuropsychology*, *28*(3), 459–471. doi:10.1037/neu0000050

Kofler, M. J., Rapport, M. D., Sarver, D. E., Raiker, J. S., Orban, S. A., Friedman, L. M., & Kolomeyer, E. G. (2013). Reaction time variability in ADHD: a meta-analytic review of 319 studies. *Clinical Psychology Review*, *33*(6), 795–811. https://doi.org/10.1016/j.cpr.2013.06.001

Kuntsi, J., & Klein, C. (2012). Intraindividual variability in ADHD and its implications for research of causal links. In *Behavioral neuroscience of attention deficit hyperactivity disorder and its treatment* (pp. 67-91). doi:10.1007/7854_2011_145

Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM (1996) Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics*, 6, 243–250.

Lawrence, M. A. (2016). ez: Easy Analysis and Visualization of Factorial Experiments. R package version 4.4-0. https://CRAN.R-project.org/package=ez

Leth-Steensen, C., King Elbaz, Z., Douglas, V. I., Elbaz, Z. K., & Douglas, V. I. (2000). Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. *Acta Psychologica*, 104(2), 167–90. doi:10.1016/S0001-6918(00)00019-6

Lewis, D. A., Melchitzky, D. S., Sesack, S. R., Whitehead, R. E., Auh, S., & Sampson, A. (2001). Dopamine Transporter Immunoreactivity in Monkey Cerebral Cortex : Regional, Laminar and Ultrastructural Localization. *Journal of Comparative Neurology*, *136*(2001), 119–136.

Li, S., Lindenberger, U., & Frensch, P. (1999). Unifying cognitive aging: From neurotransmission to representation to cognition. *32nd Annual Meeting of the Society for Mathematical Psychology*, *33*, 879–890.

MacDonald, S. W. S., Cervenka, S., Farde, L., Nyberg, L., & Bäckman, L. (2009). Extrastriatal dopamine D2 receptor binding modulates intraindividual variability in episodic recognition and executive functioning. *Neuropsychologia*, *47*(11), 2299–304. doi:10.1016/j.neuropsychologia.2009.01.016

Matzke, D., & Wagenmakers, E. J. (2009). Psychological interpretation of the ex-gaussian and shifted wald parameters: A diffusion model analysis. *Psychonomic Bulletin and Review*, *16*(5), 798–817. doi:10.3758/PBR.16.5.798

Nolan, K. A., Ph, D., Bilder, R. M., Lachman, H. M., & Volavka, J. (2004). COMT and schizophrenia: Differential effects of alleles on Cognitive Stability and Flexibility. *American Journal of Psychiatry*, *3*(161), 359–361.

Oberauer, K., Süß, H.-M., Wilhelm, O., & Wittman, W. W. (2003). The multiple faces of working memory. *Intelligence*, *31*(2), 167–193. doi:10.1016/S0160-2896(02)00115-0

R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Rentrop, M., Rodewald, K., Roth, A., Simon, J., Walther, S., Fiedler, P., … Kaiser, S. (2010). Intra-individual variability in high-functioning patients with schizophrenia. *Psychiatry Research*, *178*(1), 27–32. doi:10.1016/j.psychres.2010.04.009

Rostami, H. N., Saville, C. W. N., Klein, C., Ouyang, G., Sommer, W., Zhou, C., & Hildebrandt, A. (2017). COMT genotype is di ff erentially associated with single trial variability of ERPs as a function of memory type. *Biological Psychology*, 127, 209–219. doi:10.1016/j.biopsycho.2017.06.002

Salunkhe, G., Weissbrodt, K., Feige, B., Saville, C. W. N., Berger, A., Dundon, N. M., … Klein, C. (2018). Examining the Overlap Between ADHD and Autism Spectrum Disorder (ASD) Using Candidate Endophenotypes of ADHD. *Journal of Attention Disorders*. doi:10.1177/1087054718778114

Saville, C. W. N., Lancaster, T. M., Stefanou, M. E., Salunkhe, G., Lourmpa, I., Nadkarni, a., … Klein, C. (2014). COMT Val158Met genotype is associated with fluctuations in working memory performance: Converging evidence from behavioural and single-trial P3b measures. *NeuroImage*, *100*, 489–497. doi:10.1016/j.neuroimage.2014.06.006

Schmiedek, F., Oberauer, K., Wilhelm, O., Süss, H.-M., & Wittmann, W. W. (2007). Individual differences in components of reaction time distributions and their relations to working memory and intelligence. *Journal of Experimental Psychology*. General, 136(3), 414–29. doi:10.1037/0096-3445.136.3.414

Sesack, S. R., Hawrylak, V. A., Matus, C., Guido, M. A., Levey, A. I., Das, S., … Weinberger, D. R. (1998). Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex exhibit sparse immunoreactivity for the dopamine transporter. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *18*(7), 2697–708. doi:10.1523/jneurosci.0476-05.2005

Schwartz, F., Carr, A. C., Munich, R. L., Glauber, S., Lesser, B., & Murray, J. (1989). Reaction time impairment in schizophrenia and affective illness: The role of attention. *Biological Psychiatry*, *25*(5), 540–548. doi:10.1016/0006-3223(89)90214-X

Slifstein, M., Kolachana, B., Simpson, E. H., Tabares, P., Cheng, B., Duvall, M., … Abi-Dargham, A. (2008). COMT genotype predicts cortical-limbic D1 receptor availability measured with [11C]NNC112 and PET. *Molecular Psychiatry*, *13*(8), 821–827. doi:10.1038/mp.2008.19

Smyrnis, N., Karantinos, T., Malogiannis, I., Theleritis, C., Mantas, A., Stefanis, N. C., … Evdokimidis, I. (2009). Larger variability of saccadic reaction times in schizophrenia patients. *Psychiatry Research*, *168*(2), 129–36. doi:10.1016/j.psychres.2008.04.015

Sonuga-Barke, E. J. S., & Castellanos, F. X. (2007). Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. *Neuroscience and Biobehavioral Reviews*, 31, 977–986. doi:10.1016/j.neubiorev.2007.02.005

Stefanis, N. C., van Os, J., Avramopoulos, D., Smyrnis, N., Evdokimidis, I., & Stefanis, C. N. (2005). Effect of COMT Val158Met polymorphism on the Continuous Performance Test, Identical Pairs Version: tuning rather than improving performance. *The American Journal of Psychiatry*, 162(9), 1752–4. doi:10.1176/appi.ajp.162.9.1752

Stokes, P. R. a, Rhodes, R. a, Grasby, P. M., & Mehta, M. a. (2011). The effects of the COMT Val108/158Met polymorphism on BOLD activation during working memory, planning, and response inhibition: a role for the posterior cingulate cortex? *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *36*(4), 763–71. doi:10.1038/npp.2010.210

Turnbridge, E.M., Bannerman, D.M., Sharp, T., Harrison, P.J. (2004).Catechol-o-methyltransferase inhibition improves set-shifting performance and elevates stimulated dopamine release in the rat prefrontal cortex. *J. Neurosci.* 24, 5331–5335.

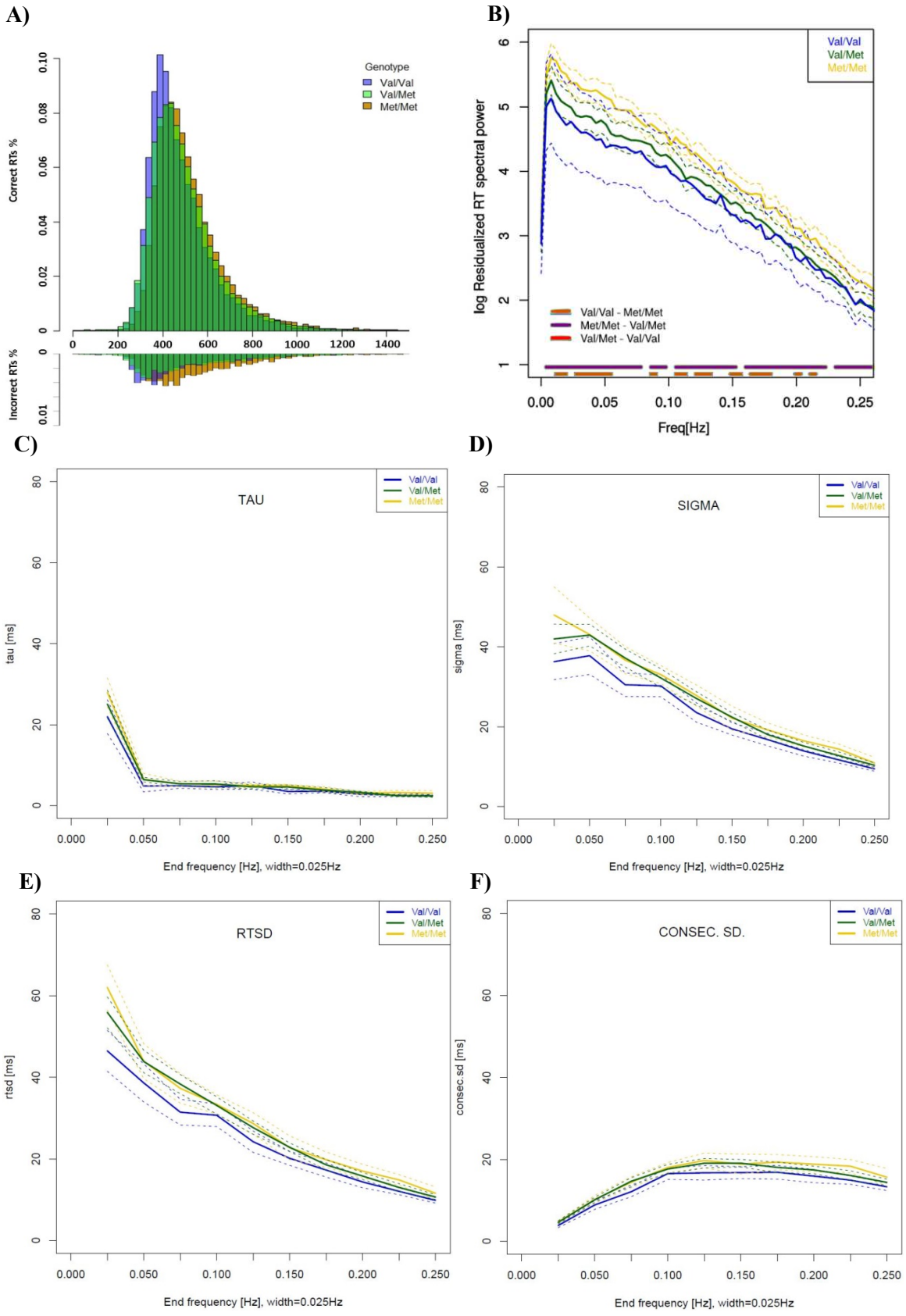
Van Belle, J., Van Raalten, T., Bos, D. J., Zandbelt, B. B., Oranje, B., & Durston, S. (2015). Capturing the dynamics of response variability in the brain in ADHD. *NeuroImage: Clinical*, *7*, 132–141. doi:10.1016/j.nicl.2014.11.014

Vijayraghavan, S., Wang, M., Birnbaum, S. G., Williams, G. V, & Arnsten, A. F. T. (2007). Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nature Neuroscience*, *10*(3), 376–84. doi:10.1038/nn1846

Weissman, D. H., Roberts, K. C., Visscher, K. M., & Woldorff, M. G. (2006). The neural bases of momentary lapses in attention. *Nature Neuroscience*, *9*(7), 971–8. doi:10.1038/nn1727

Winterer, G., Egan, M. F., Kolachana, B. S., Goldberg, T. E., Coppola, R., & Weinberger, D. R. (2006a). Prefrontal electrophysiologic "noise" and catechol-O-methyltransferase genotype in schizophrenia. *Biological Psychiatry*, 60(6), 578–84. doi:10.1016/j.biopsych.2006.03.023

Winterer, G., Musso, F., Vucurevic, G., Stoeter, P., Konrad, A., Seker, B., … Weinberger, D. R. (2006b). COMT genotype predicts BOLD signal and noise characteristics in prefrontal circuits. *NeuroImage*, 32(4), 1722–32. doi:10.1016/j.neuroimage.2006.05.058


A)
Genotype
Val/Val
Val/Met
Met/Met
Correct RTs %
Incorrect RTs %
B)
log Residualized RT spectral power
Freq[Hz]
Val/Val - Met/Met
Met/Met - Val/Met
Val/Met - Val/Val
C)
TAU
tau [ms]
End frequency [Hz], width=0.025Hz
D)
SIGMA
sigma [ms]
End frequency [Hz], width=0.025Hz
E)
RTSD
rtsd [ms]
End frequency [Hz], width=0.025Hz
F)
CONSEC. SD.
consec.sd [ms]
End frequency [Hz], width=0.025Hz