HELLENIC REPUBLIC

National and Kapodistrian University of Athens

EST. 1837

MSc: Clinical Neuropsychology- Cognitive Neurosciences

Medical School

Title: Relation of reaction time intra-individual variability to fMRI activation during a reward related choice-RT task in patients with schizophrenia and healthy controls.

Polymnia Proestaki

Supervisors: Nikolaos Smyrnis, Foteini Christidi

Committee: Constantin Potagas, Sokratis Papageorgiou

Contents

Abstract

Patients suffering from schizophrenia (SCZ) respond slower in a variety of tasks. The distribution of reaction time (RT) shows a variance in RT response within subjects, knowing as intra-subject or intra-individual RT variability. Yet there have been few investigations of the neural correlates of trial-to-trial RT variability in schizophrenia. We sought to determine the neural correlates of intra-individual RT variability using functional magnetic resonance imaging (fMRI) in SCZ during a reward related choice-RT task. In this study the median RT and its variability were measured in 22 healthy controls (CON) and 16 SCZ. Trial-to-trial deviation from the mean was calculated by subtracting the RT of each trial from the meanRT of that block [ABS (RT-meanRT)]. SCZ showed greater intra-individual RT variability compared to CON ($p<0.001$). Higher intra-individual RT variability was related to increased BOLD activation mainly in prefrontal, parietal and insular cortices and decreased activation in middle and superior temporal gyrus and precuneus when SCZ and CON were examined together, with a similar pattern of neural correlates within each group. By comparing the two groups on the pattern of neural correlates of intra-individual RT variability, we found a significant difference (CON > SCZ) only on left supramarginal gyrus for the contrast "higher RT variability associated with increased BOLD activation". In conclusion, we identified that the neural correlates of intra-individual RT variability include prefrontal, parietal and insular regions. Higher BOLD activation is mostly associated with increased RT variability in both SCZ and CON but this association is significantly higher in supramarginal gyrus in CON compared to SCZ which highlights the possible significant role of inferior parietal lobule in RT and attention in general and specifically in SCZ.

1. Introduction

Psychomotor retardation (or psychomotor slowing or psychomotor poverty), as a deficit in information processing, has been observed in schizophrenia in a large variety of simple sensorimotor decision tasks (Nuechterlein, 1977). Increased meanRT has been observed in SCZ compared to CON (Rodnick and Shakow, 1940; Nuechterlein, 1977; Shakow, 1962). However, psychomotor slowing has also been observed in other mental disorders (such as autism (Verte et al, 2005), bipolar disorder with psychotic symptoms (Bora et al, 2006), post-traumatic stress disorder (Tinius et al, 2003), early stages of Alzheimer's disease (Duchek et al, 2009), Parkinson's disease (Camicioli et al, 2008), Attention Deficit Hyperactivity Disorder/ADHD (Castellanos and Tannock, 2002; Kuntsi and Klein, 2011), suggesting that this phenomenon might not be specific to schizophrenia (Schwartz, 1989).

The distribution of RT in such studies carries more information than can be captured by meanRT. Such a consistent information is the larger inter-subject and intra-subject RT variability in SCZ compared with CON. Intra-individual RT variability, i.e. the trial-to-trial variability in behavioural response, has been proposed as a specific measure of sensorimotor and cognitive processing stability that is independent of the meanRT (Kuntsi and Klein, 2011; Rentrop et al., 2010; Kim et al., 2009). Although, the distribution of RT variability has attracted little literature, it contains valuable information on cognitive function and is associated with the phenomenon of psychomotor retardation.

Several studies have examined intra-individual RT variability as a biomarker for schizophrenia. Huston et al. (1937) studied the increase of RT variability in scizophrenia and highlighted that SCZ show a deficit in preparation level during audiovisual stimulus processing. In another study, the intra-individual RT variability was founded larger in schizophrenia (Schwartz et al., 1989). In addition, increase of RT variability has been observed in a lexical decision choice reaction time (CRT) task in SCZ and predicted the severity of psychotic and disorganization symptoms (Vinogradov et al., 1998). Other studies using visually-guided saccade tasks report larger intra individual RT variability but not meanRT in SCZ compared with CON (Smyrnis et al., 2003; Smyrnis et al., 2009). Kaiser et al. (2008), compared three groups of patients and found that increased intra- individual RT variability separated the group of SCZ from patients with severe depression and patients with borderline personality disorder, even though this phenomenon was observed in all three disorders. Another confirmation of specificity of RT deviance in a simple oculomotor decision process in schizophenia came from another recent study in which were used young healthy men, healthy children, older adults, SCZ, and patients with obsessive compulsive disorder (Theleritis et al., 2014). Finally, in a recent study, using a simple working memory task, both meanRT and intra-individual RT variability were similarly increased for SCZ and their unaffected siblings compared to CON. This finding provides preliminary evidence for the usefulness of modelling the RT distribution to reveal candidate endophenotypes in schizophrenia (Fish et al., 2018).

The association between intra-individual RT variability and neural activity has attracted very little attention in the relevant literature. One reanalysis of five previous fMRI datasets in CON identified that in a widely distributed set of white and gray matter regions, activation was delayed on trials with long RTs relative to short RTs, suggesting delayed initiation of underlying physiological processes. Additionaly, in lateral and medial frontal regions, activation showed a ‘‘time-on-task’’ effect, increasing linearly as a function of RT. Finally, RT variance reliably

modulated the BOLD signal not only in gray matter but also in diffuse regions of white matter. These results raised the possibility that measues of RT variance may provide a probe for investigating a previously elusive white matter BOLD signal (Yarkoni et al., 2009). In another fMRI study, using a go/no-go response inhibition task in CON, RT variability was significantly associated (indipendently from the task) with greater activation in the left pregenual anterior cingulate, supporting the important role of this region in the dynamic control of attention and efficient response selection and recognising the RT variance as an indicator of the efficiency of attentional control (Johnson et al., 2015). Fassbender et al. (2014) investigated the neural correlates of intra-individual RT variability in schizophenia using a Stroop task. In this study different regions were found to be more activated in healthy individuals compared to SCZ but they didn't directly relate to measures of RT variance. In a recent study, increased temporal variability of the functional connectivity was associated with reduced functional connectivity of early visual and related temporal cortex areas in both first episode and long-term schizophrenia, consistent with decreased stability of attractor networks related to sensory processing (Rolls et al., 2021).

Some investigators report that intra-individual RT variability phenomenon is related to a deficit in the control of attention leading to attentional lapses that are reflected in the large variation of RT from trial to trial in children with ADHD, and further more, make the hypothesis that the increase of RT variance in schizophenia is related to a deficit in the executive control of attention (Tamm et al., 2012). Johnson et al. (2015) found that greater activation of the left pregenual anterior cingulate is associated with greater response stability, but in healty participants. Although, a recent fMRI study using the spatial version of the Eriksen flanker spatial attention task in SCZ and CON, pointed that SCZ produced more errors in their performance compared to CON, while both groups produced significantly more errors in the incongruent trial type, with the error rate significant larger in SCZ. Attention modulation resulted in activation of bilateral frontal and parietal areas that was not different between SCZ and CON. Right middle frontal, right superior temporal and bilateral cingulate areas were more active in CON compared to SCZ independent of congruency. .This result confirmed a deficit in attention control for SCZ. But hypo-activity of the right prefrontal cortex predicted increased intra-individual RT variability only in SCZ. (Panagiotaropoulou et al., 2019).

In the present study, we used a two-choice RT task combined with the monetary incentive delay (MID) task to study behavioural and neural responses in SCZ and CON. Specifically, we sought to explore the neural correlates of intra-individual RT variability using a whole-brain analysis of fMRI data. We also sought to investigate whether this neural network differs between SCZ and CON.

2. Material and Methods

2.1 Participants

We used previous fMRI datasets from a recent study by Simon Fish et al. (2021). Our sample consisted of 16 SCZ [age (mean ± SD): 30.19 ± 8.34 years, gender (M/F): 12/4] and 22 CON [age (mean ± SD): 27.91 ± 4.69 years, gender (M/F): 12/10]. All participants provided written, informed consent and the study protocol was approved by the Ethics committee of Eginition University Hospital. Patients were diagnosed by trained psychiatrists using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) criteria (World Health Organization, 1992). Most of the patients received atypical antipsychotics (risperidone, paliperidone, olanzapine, amisulpride, quetiapine, aripiprazole, clozapine). Exclusion criteria for all patients were diagnosis of neurological, neurodevelopmental or other psychiatric disorders. Exclusion criteria for CON also included current use of prescription medication and personal or familial history of psychiatric or neurological disorder. Participants were also excluded if they were intoxicated with alcohol or had contraindications for MRI exam (i.e. metal implants, claustrophobia). At the time of testing, all SCZ were stabilized (they were not currently experiencing a psychotic episode and positive symptoms were in remission) and treated with antipsychotic medication; no participant received benzodiazepines or beta-blockers on the day of testing.

2.2 Behavioral task design

A two-choice RT task was used with elements of the MID and Eriksen flanker tasks. All participants completed in one session the procedure to reduce the likelihood of learning effects, while being scanned using fMRI. Each participant was instructed to respond to a series of five arrow heads appearing for a fixed period and put a button with their left or right index finger, in accordance with the pointing direction of the central arrowhead. Only the incongruent stimulus was used (<< > << or >> < >>). Before the stimulus, a valence cue (+ (win), − (lose) or * (neutral)) was first presented for a variable period (0.8, 2.8 or 4.8 seconds), followed by a magnitude cue representing the amount of the upcoming reward (high: 20, low: 5, or none: 0) that was presented for 1 second. After the 1 second response period, feedback was presented for 1.2 seconds. The participant had to gain a maximal amount of points responding accurately and quickly. As RT was considered the total time elapsed (in milliseconds) between the onset of a stimulus and registration of the participant's manual response (figure 1).

The task was devided into 6 blocks of 60 trials each. The first block was used only as a

baseline meanRT from correct answers of each participant. Each block from the other five contained twelve trials of each condition (high punishment, low punishment, neutral, low reward, high reward). A trial was successful if the participant responded with the correct button-press and faster or equal to his meanRT from the first block. RTs < 120 ms where excluded, considered as anticipatory responses.

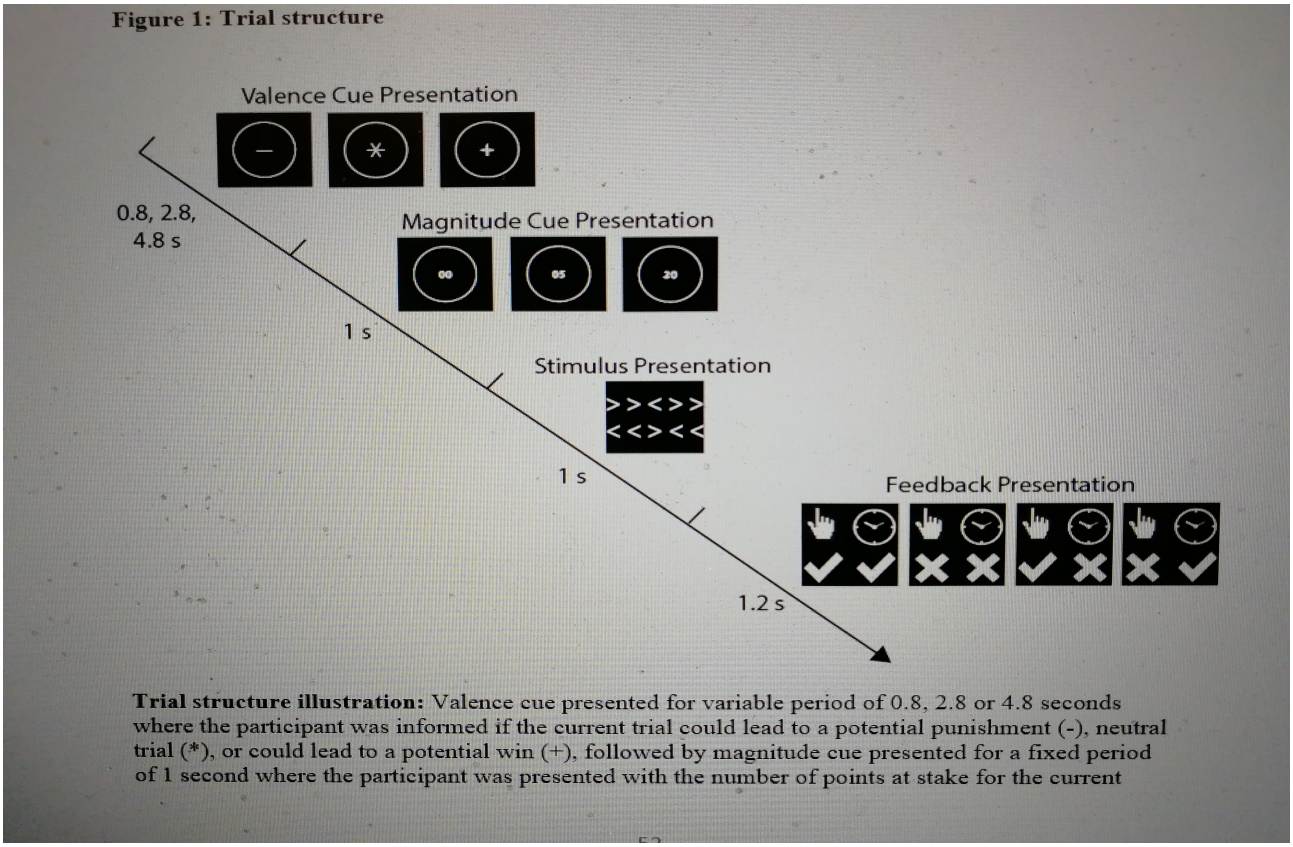


Figure 1. Presentation of the design of each trial (borrowed by Fish et al, 2021).

2.3 Behavioural data acquisition and analysis

RT data were analyzed for the five blocks of each participant. RT were recorded for each participant and each condition. In order to assess trial-to-trial RT variability, we applied a similar approach to Johnson et al., (2015), Weissman et al. (2006) and Esterman et al. (2013, 2014). For each participant, the meanRT for all trials was calculated for each condition per each block. Then, trial-to-trial deviation from the mean was calculated by subtracting the RT of each trial from the meanRT of that condition for that block (absolute [RT-mean RT], i.e. ABS_RTmRT). In contrast to previous studies, we included RTs from both correctly and incorrectly performed trials in the calculation of meanRT and absolute RT deviation. By subtracting the RT from the meanRT

(RT - meanRT) of each condition per each block, we eliminated the effects of the task and the individual differences and calculated the intra-individual RT variability (ABS_RTmRT), as in previous studies (e.g. Johnson et al., 2015). Both meanRT and ABS_RTmRT were examined for normality and parametric tests were then applied. Comparisons between CON and SCZ on meanRT and ABS_RTmRT were carried out using independent sample t-tests. The statistical threshold was set at $p < 0.05$. All analyses on behavioural data were conducted on SPSS v. 26.

2.4 fMRI data acquisition and analysis

We included previous fMRI data acquired on a Philips Achieva ^{TX} 3.0T MRI scanner equipped with echo-planar imaging (TR = 2 s, 36 slices covering almost all of the cerebral cortex, voxel size 3 × 3 × 3). A high-resolution T1 anatomical image with 1 × 1 × 1 mm voxel size was also acquired for each participant. Quality control was performed using ArtRepair software (Center for Interdisciplinary Brain Sciences, Stanford University, USA). For all imaging data analysis we used SPM12 toolbox for MATLAB (Wellcome Trust Centre for Neuroimaging, London, UK). Raw images were spatially realigned (motion correction) and temporally interpolated to compensate for acquisition delay. Data with registered motion >3 mm or 1 degree was excluded. The high-resolution anatomical image was used to perform tissue segmentation into gray and white matter and cerebrospinal fluid (CSF). Images were normalized to standard Montreal Neurological Institute (MNI) space and smoothed with an 8 mm FWHM (full width at half maximum) Gaussian kernel. A high-pass filter of 128 s cut off was applied, to eliminate physiological components such as respiration or heartbeat (Fish et al., 2021).

We then applied a parametric model. At first-level within-subject analysis, we used all scans in one condition regardless of the block (task) they belonged to. We further included the ABS_RT - meanRT as a parametric modulator. The parametric modulator is expected to predict variance across trials that is not simply explained by the fact that the subjects are sometimes doing a task and sometimes not. Additional regressors included motion correction parameters estimated from the realignment step of the pre-processing. For each participant both positive and negative contrasts were examined. For the positive contrast, the higher the ABS_RTmRT value (i.e. increased RT variability), the higher the neural activation. For the negative contrast, the higher the ABS_RTmRT value, the lower the neural activation. At second level group analysis, one sample t-test was carried out for each contrast including all CON and SCZ in order to identify the neural network associated with trial-to-trail RT variability (i.e. ABS_RTmRT). The identified regions were then included as a binary mask and differences between CON and SCZ only in these regions were examined using an independent sample t-test. For both one-sample t-test and independent samples t-test, we first

applied a statistical threshold of $p < 0.05$, family-wise error corrected for multiple comparisons, and we then applied a more liberal threshold ($p < 0.001$ uncorrected, with cluster-extent threshold).

3. Results

3.1 Behavioural data: RT variability

We found a significant difference between CON and SCZ on the mean RT. SCZ showed significantly larger mean RT compared to CON [SCZ (mean ± SD) = 577.06 ± 44.25, CON (mean ± SD) = 458.55 ± 43.52, $p < 0.001$]. Additionally, we found significant difference between the two groups on the RT variability (ABS_RTmRT). SCZ showed significantly larger RT variability compared to CON [SCZ (mean ± SD) = 71.44 ± 13.76, CON (mean ± SD) = 37.67 ± 11.67, $p < 0.001$].

3.2. fMRI data: neural correlates of intra-individual RT variability

One-sample t-tests across all subjects showed a positive correlation between larger RT variability and higher BOLD activation in left inferior parietal lobule/supramarginal gyrus,left anterior inferior insula/inferior frontal gyrus-pars triangularis, right inferior frontal gyrus-pars opercularis-anterior insula, right supramarginal gyrus/ inferior parietal lobule, left precentra gyrus, left superior frontal gyrus-medial/supplementary motor area, left medial frontal gyrus/inferior frontal gyrus-pars triangularis, right precuneus (Table 1, Figure 2).

A negative correlation between larger RT variability and lower BOLD activation were found in left medial temporal gyrus/ superior temporal gyrus, left/right precuneus, right superior temporal gyrus (Table 1, Figure 3).

Table 1. Regions positively or negatively associated (BOLD activation) with higher RT variability across all subjects

Cluster	Anatomical label	Hemisphere	MNI coordinates (x, y, z)	T	Voxels
Positive contrast: higher RT variability associated with increased BOLD activation					
1	IPL/SMG	L	-60, -37, 40	6.43	341
2	aINS/IFG-Tri	L	-27, 26, -5	5.62	266
3	IFG-Oper/aIns	R	30, 23, 4	5.56	496
4	SMG/IPL	R	33, -52, 43	5.47	408
5	PrCG	L	-39, 2, 31	5.13	57
6	SFG-Med/SMA	L	0, 20, 52	5.12	279
7	MFG/IFG-Tri	L	-45, 29, 28	4.33	24
8	Precuneus	R	12, -70, 43	4.01	25
Negative contrast: higher RT variability associated with decreased BOLD activation					
1	MTG/STG	L	-63, -19, 1	4.63	62
2	Precuneus	L/R	0, -55, 25	4.54	70
3	STG	R	66, -19, 4	3.94	18

Note. IPL = inferior parietal lobule, SM = supramarginal gyrus, aINS = anterior inferior insula ,IFG-Tri = inferior frontal gyrus-pars triangularis, IFG-Oper = inferior frontal gyrus -pars opercularis,PrCG = precentral gyrus, SFG-Med = superior frontal gyrus-medial, SMA=supplementary motor area, MFG = medial frontal gyrus, STG = superior temporal gyrus, MTG = medial temporal gyrus. We present only the anatomical regions survived at $p < 0.001$ uncorrected with cluster-extent threshold of 15 voxels.

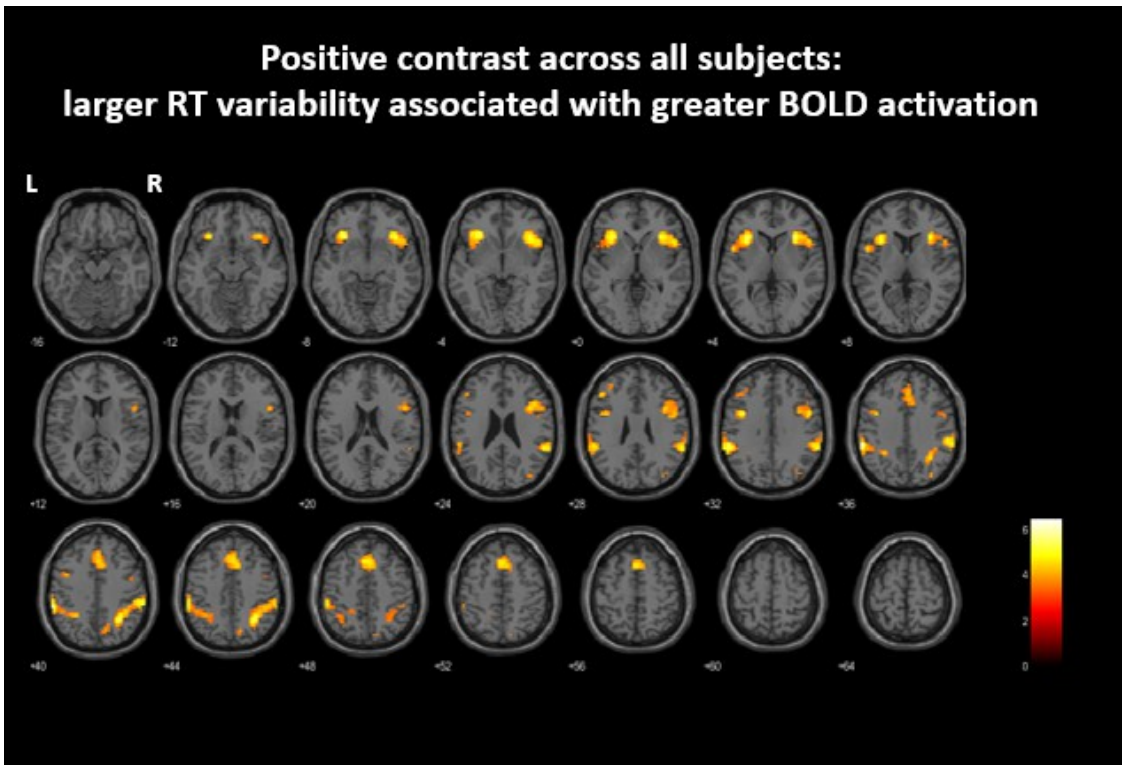


Figure 2. Anatomical regions showing increased BOLD activation when intra-individual RT variability is larger (one-sample t-test across all subject, p < 0.001 uncorrected, cluster extent threshold 15 voxels).

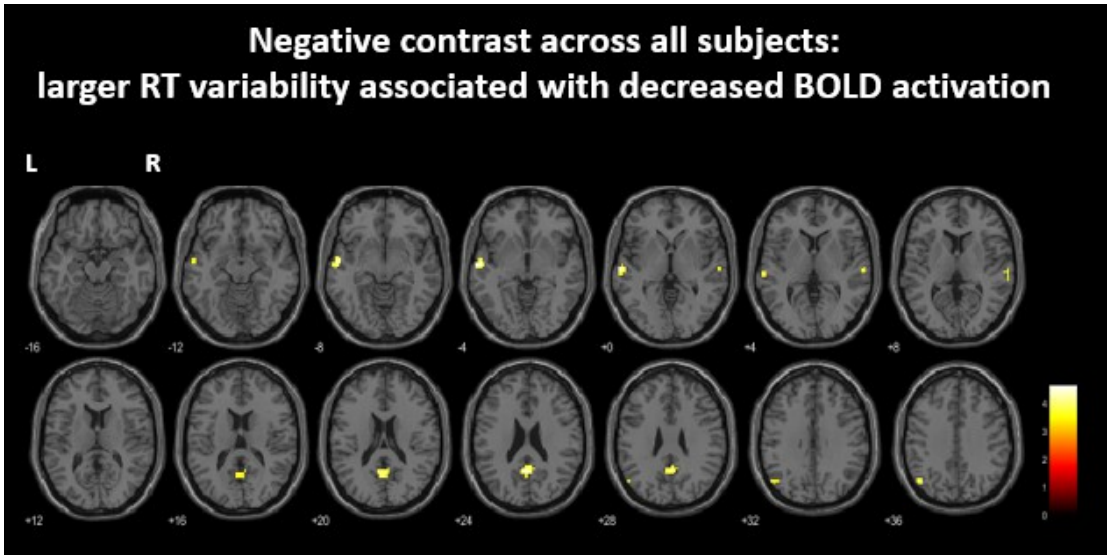
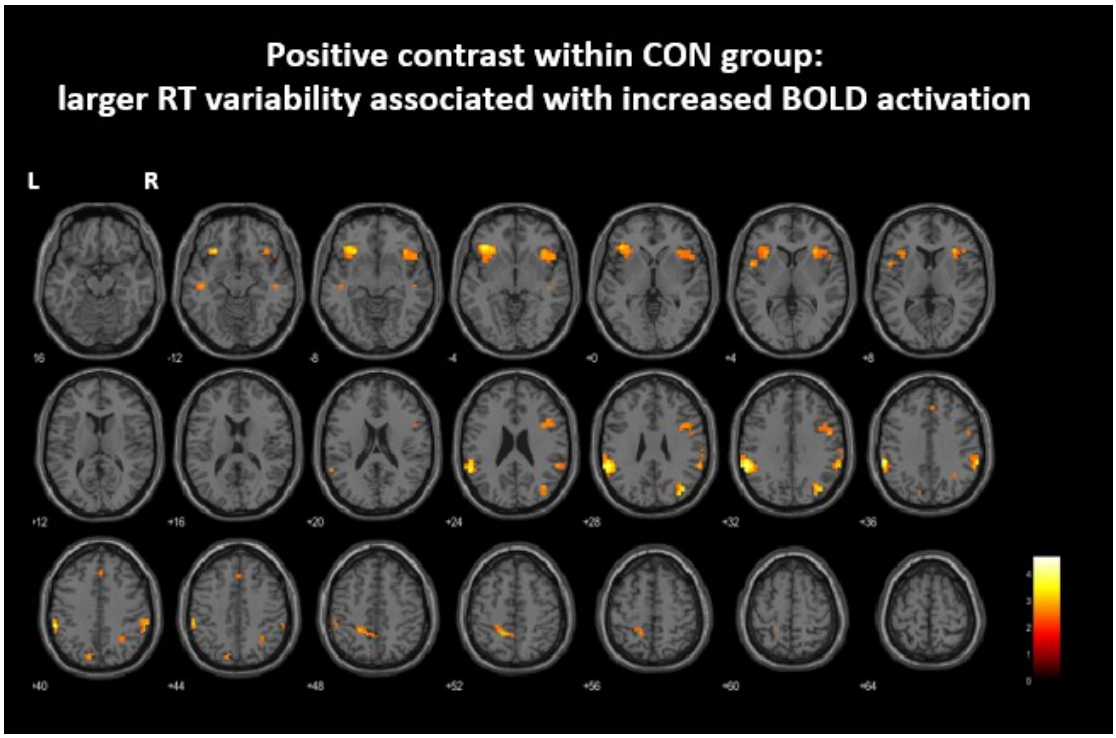
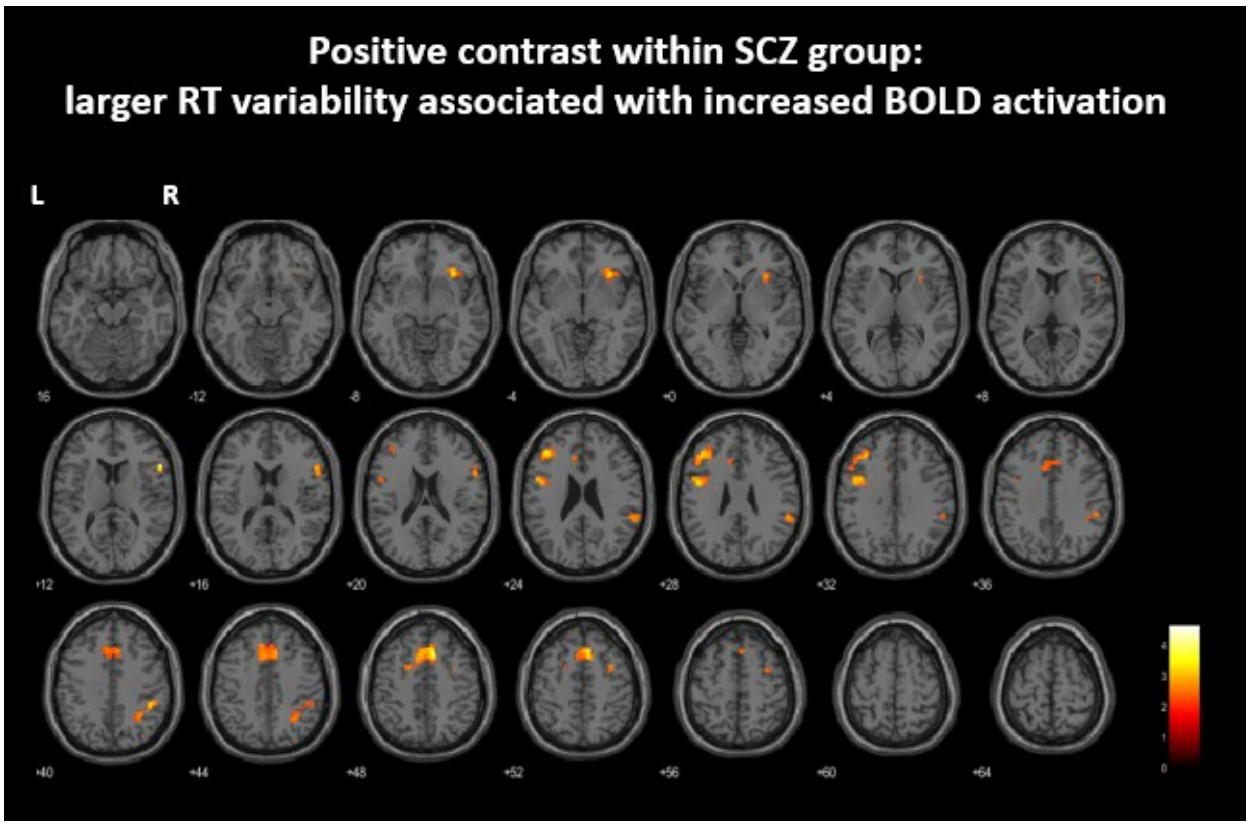


Figure 3. Anatomical regions showing decreased BOLD activation when intra-individual RT variability is larger (one-sample t-test across all subject, p < 0.001 uncorrected, cluster extent threshold 15 voxels).

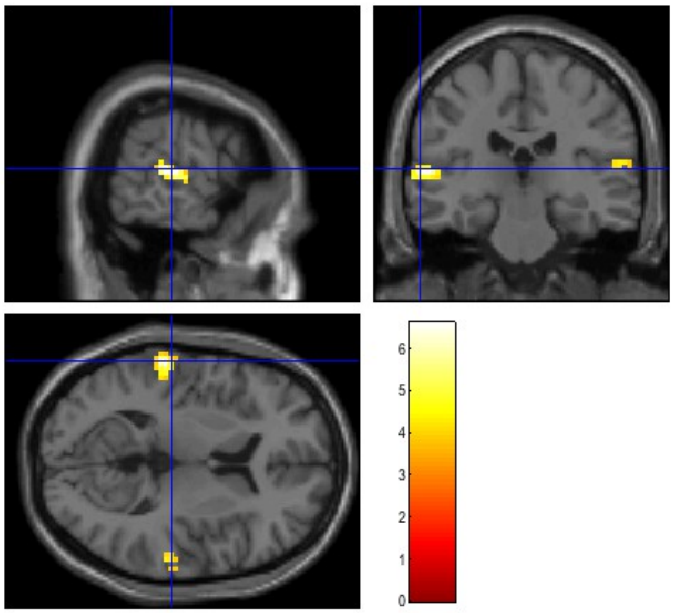
In a supplementary analysis, we also examined the neural correlates of intra-individual RT variability separately in CON and SCZ, using $p < 0.001$ uncorrected, with cluster extent threshold of 11 voxels. Anatomical regions surpassed the statistical threshold both in CON (Supplementary Figure 1) and SCZ (Supplementary Figure 2) groups for the positive contrast and only in SCZ group for the negative contrast (Supplementary Figure 3).



Supplementary Figure 1. Anatomical regions showing increased BOLD activation when intra-individual RT variability is larger (one-sample t-test within CON group, $p < 0.001$ uncorrected, cluster extent threshold 11 voxels).



Supplementary Figure 2. Anatomical regions showing increased BOLD activation when intra-individual RT variability is larger (one-sample t-test within SCZ group, p < 0.001 uncorrected, cluster extent threshold 11 voxels).



Supplementary Figure 3. Anatomical regions showing decreased BOLD activation when intra-individual RT variability is larger (one-sample t-test within SCZ group, p < 0.001 uncorrected, cluster extent threshold 11 voxels).

Based on the results across all subjects, further analysis was carried out to identify between-group differences on the neural correlates of intra-individual RT variability. We found significant between-group differences (CON > SCZ) for the previous positive contrast (i.e. higher RT variability associated with greater BOLD activation) in left supramarginal gyrus [MNI coordinates (x, y, z) = -63, -46, 28, T score = 4.20, cluster size = 21 voxels, Figure 4]. No other clusters reached corrected significance at this threshold neither for the CON > SCZ nor for the CON < SCZ contrast.

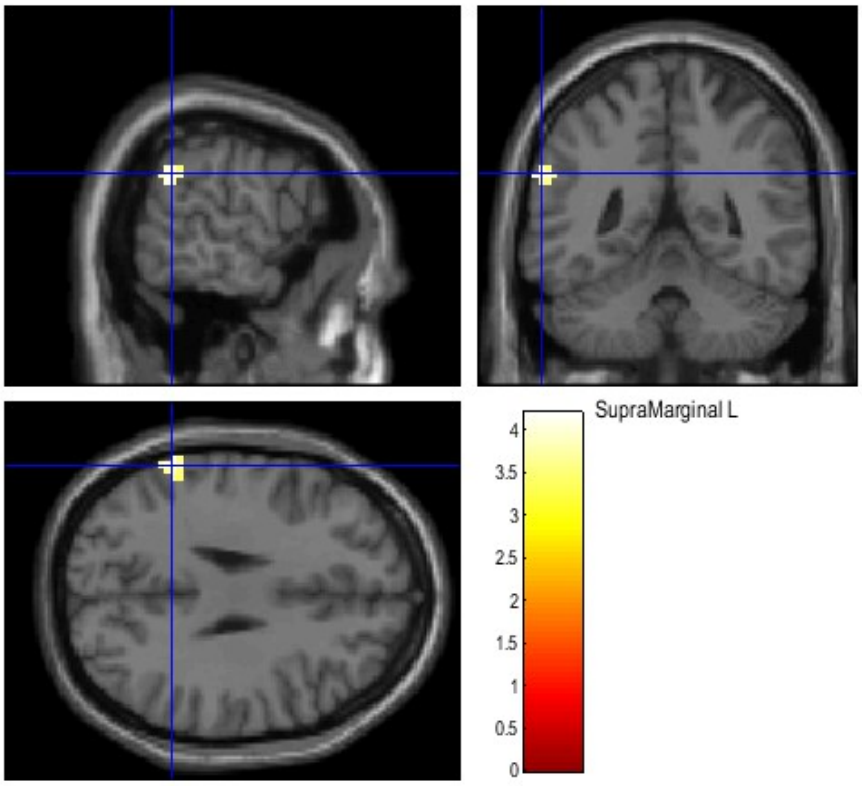


Figure 4. Location of the left supramarginal gyrus showing significant difference between healthy individuals and patients with schizophrenia (CON > SCZ) for the positive contrast of one-sample t-test analysis (i.e. decreased BOLD activation associated with larger intra-individual RT variability) ($p < 0.001$ uncorrected, cluster extent threshold 15 voxels).

4. Discussion

In this study, we investigated the neural correlates of intra-individual variability on RT on healthy individuals and SCZ and examined between-group differences on behavioral and fMRI data, using a two-choice RT task with elements of the MID and Eriksen flanker tasks.

SCZ produced more errors in their performance compared to CON confirming results of previous studies measuring intra-individual RT variability in schizophrenia (Fassbender et al., 2014; Fish et al., 2018; Kaiser et al., 2008; Karantinos et al., 2014; Rentrop et al., 2010).

According to the whole-brain analysis across all participants, we found that higher intra-individual RT variability is associated with greater BOLD activation in prefrontal and parietal cortical areas in both hemispheres, as well as bilateral insula and left supplementary motor area. A link between increased activation of the bilateral dorsolateral prefrontal cortex was found to be specifically correlated with intra-individual RT variability in a go-no/go task in healthy adults (Bellgrove et al., 2004). The authors concluded that higher activation of these areas in individuals with higher intra-individual RT variability reflects a greater requirement of top-down inhibitory control. A more recent study in large sample of healthy individuals identified a wide array of anatomical regions associated with intra-individual RT variability irrespective of the fMRI task, including left insula, left anterior prefrontal cortex, precuneus, left inferior parietal lobule (Yarkoni et al., 2009), which were found in our study. Studying SCZ, Panagiotaropoulou et al. (2019) found that intra- individual RTvariability doesn't correlate with a deficit in attention and is connected with an hypo-activity in the dorsolateral prefrontal cortex. This hypo-activity has been related to deficits in inhibitory control of behavior (Lesh et al., 2013; Minzenberg et al., 2009; Yoon et al., 2008). Stuss et al. (2003) showed that patients with lesions specifically in the left and right dorsolateral prefrontal cortex had increased intra- individual RT variability in a series of fast decision tasks including a simple RT task, as well as simple and complex two-choice RT tasks. It is therefore suggested that this hypo-activity could also result in larger intra-individual RT variability and loss of cognitive stability in schizophrenia.

The positive correlation between RT variability and BOLD activation means that as RT variance increases so does the BOLD activation of that network. Additionally, we found a negative correlation (the higher the RT variance, the lower the activation) located in left middle temporal gyrus, bilateral superior temporal gyri, bilateral precuneus. According to a supplementary one-sample t-test analysis within each group of CON and SCZ (Supplementary Figures 1,2 and 3), we can support that there is a common network for CON and SCZ and the difference between them might be in relation to the degree of BOLD activation of these brain areas. The finding that SCZ

show increased intra-individual RT variability could be interpreted based on the hypothesis that psychomotor slowing is associated with an hyperactivity in some regions in order to compensate for that delay. This finding should be investigated more thoroughly.

Our finding for the left SMG (CON < SCZ) when we compared the neural network of intra-individual RT variability between SCZ and CON reflects the important role of inferior parietal lobule which is generally believed to be implicated in schizophenia (Torrey, 2007). Of note, most studies in schizophrenia have generally focused on frontal and temporal dysfunction and there has been little systematic literature for inferior parietal lobule especially in the left hemisphere. An fMRI study, reported decreased activation of the left SMG of SCZ(Lathi et al., 2001) while Das et al. (2018) report that parietal disconnectivity influence the processing speed and has a role in global functioning deficits in schizophenia. Lower BOLD activation in left frontoparietal network during verbal working memory task has been associated with the severity of negative and disorganised symptoms (Sanz et al., 2009). Other investigators also found an association between impaired parietoccipital functionnal connectivity and the positive symptoms of schizophenia (Henseler et al., 2010). In another fMRI study, the BOLD activation of left SMG of SCZ was associated with a deficit in working memory (Kinderman et al., 2004).

Further functional and structural neuroimaging research will be important to clarify the brain networks and structural and functional connectivity between them in defining multiple components in SCZ. Additional studies on the functional role of inferior parietal cortex in SCZ are necessary based on its involvement on body image, executive function, and aspects of sensory integration (Torrey, 2007). Furthermore, considering the critical role of left SMG in CON in the suppression of the incorrect responces' release and action control (Hartwingsen et al., 2012), in phonological processing and in integration of body representation (Petridis, 2013, 2016), it is important to further investigate the role of inferior parietal lobule including SMG as a multimodal region which might be associated with different aspects of symptoms in schizophenia.

One limitation of the current study is that the sample of participants was small (n=38) and the results have to confirmed in studies with larger sample sizes. On the other hand, the vast majority of patients were medicated with atypical antipsychotics. The interaction of medication remains an issue that needs to be addressed in future studies investigating the intra-individual RT variability phenomenon in medicated or drug-naïve patients. Future examination of intra-individual RT variability and how it relates to distinct sub-regions of that network, along with structural connectivity across frontal networks and neuromodulation by different neurotransmitters, will be an important next step in understanding the neurobiological basis of schizophrenia.

5. Conclusion

In conclusion, we identified the neural correlates of intra-individual RT variability in SCZ and CON using a two-choice RT task with elements of the MID and Eriksen flanker tasks. Higher intra-individual RT variability is related to increased BOLD activation mainly in prefrontal, parietal and insular cortices and decreased BOLD activation in temporal gyrus and precuneus. A pattern of similar neural correlates in CON and SCZ highlights the existence of a common neural network which may account for trial-to-trial RT variability when performing cognitive tasks. The finding of significant between-group differences (CON > SCZ) for the previous positive contrast (i.e. higher RT variability associated with greater BOLD activation) in left supramarginal gyrus may reflects the important role of inferior parietal lobule in attentional control in general and specifically in schizophrenia.

References

Bellgrove, M., Hester, R. and Garavan, H., 2004. The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. *Neuropsychologia*, 42(14), pp.1910-1916. doi:10.1016/j.neuropsychologia.2004.05.007

Bora, E., Vahip, S. and Akdeniz, F., 2006. Sustained attention deficits in manic and euthymic patients with bipolar disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 30(6), pp.1097-1102. doi:10.1016/j.pnpbp.2006.04.016

Camicioli, R., Wieler, M., de Frias, C. and Martin, W., 2008. Early, untreated Parkinson's disease patients show reaction time variability. *Neuroscience Letters*, 441(1), pp.77-80. doi:10.1016/j.neulet.2008.06.004

Castellanos, F., Sonuga-Barke, E., Milham, M. and Tannock, R., 2006. Characterizing cognition in ADHD: beyond executive dysfunction. *Trends in Cognitive Sciences*, 10(3), pp.117-123. doi:10.1016/j.tics.2006.01.011

Das, T., Liddle, P. and Palaniyappan, L., 2018. T142. PARIETAL CONNECTIVITY IN SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDER: A COMBINED STRUCTURAL AND DYNAMIC FUNCTIONAL CONNECTIVITY STUDY. *Schizophrenia Bulletin*, 44(suppl_1), pp.S170-S171. doi.org/10.1093/schbul/sby016.418

Duchek, J., Balota, D., Tse, C., Holtzman, D., Fagan, A. and Goate, A., 2009. The utility of intraindividual variability in selective attention tasks as an early marker for Alzheimer's disease. *Neuropsychology*, 23(6), pp.746-758. DOI: 10.1037/a0016583

Esterman, M., Rosenberg, M.D., Noonan, S., 2014. Intrinsic fluctuations in sustained attention and distractor processing. J. Neurosci. 34 (5), 1724–1730.

Esterman, M., Noonan, S.K., Rosenberg, M., Degutis, J., 2013. In the zone or zoning out? Tracking behavioral and neural fluctuations during sustained attention. Cereb. Cortex 23, 2712–2723. doi.org/10.1093/cercor/bhs261.

Fassbender, C., Scangos, K., Lesh, T. and Carter, C., 2014. RT distributional analysis of cognitive-control-related brain activity in first-episode schizophrenia. *Cognitive, Affective, & Behavioral Neuroscience*, 14(1), pp.175-188. doi:10.3758/s13415-014-0252-4

Fish, S., Christidi, F., Karavasilis, E., Velonakis, G., Kelekis, N., Klein, C., Stefanis, N. and Smyrnis, N., 2021. Interaction of schizophrenia and chronic cannabis use on reward anticipation sensitivity.*npj Schizophrenia*, 7(1). doi.org/10.1038/s41537-021-00163-2

Fish, S., Toumaian, M., Pappa, E., Davies, T., Tanti, R., Saville, C., Theleritis, C., Economou, M., Klein, C. and Smyrnis, N., 2018. Modelling reaction time distribution of fast decision tasks in schizophrenia: Evidence for novel candidate endophenotypes. Psychiatry Research, 269, pp.212-220. doi.org/10.1016/j.psychres.2018.08.067

Henseler, I., Falkai, P. and Gruber, O., 2010. Disturbed functional connectivity within brain networks subserving domain-specific subcomponents of working memory in schizophrenia: Relation to performance and clinical symptoms. *Journal of Psychiatric Research*, 44(6), pp.364-372. DOI: 10.1016/j.jpsychires.2009.09.003

Huston, P., Shakow, D. and Riggs, L., 1937. Studies of Motor Function in Schizophrenia: II. Reaction Time. *The Journal of General Psychology*, 16(1), pp.39-82. DOI: 10.1080/00221309.1937.9917940

Johnson, B., Pinar, A., Fornito, A., Nandam, L., Hester, R. and Bellgrove, M., 2015. Left anterior cingulate activity predicts intra-individual reaction time variability in healthy adults. *Neuropsychologia*, 72, pp.22-26. doi.org/10.1016/j.neuropsychologia.2015.03.015

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

Karantinos, T., Tsoukas, E., Mantas, A., Kattoulas, E., Stefanis, N., Evdokimidis, I. and Smyrnis, N., 2014. Increased intra-subject reaction time variability in the volitional control of movement in schizophrenia. *Psychiatry Research*, 215(1), pp.26-32. doi.org/10.1016/j.psychres.2013.10.031

Kim, C., Lee, G., Choi, H.and Goh, J., 2009. Repeated Measures of Reaction Times among Patients with Schizophrenia. Korean College of Neuropsychopharmacology, 7 (1), pp.20-22.

Kindermann, S.S., Brown, G.G., Zorrilla, L.E., Olsen, R.K., Jeste, D.V., 2004. Spatial working memory among middle-aged and older patients with schizophrenia and volunteers using fMRI. Schizophr. Res. 68 (2-3), 203–216.

Kuntsi, J. and Klein, C., 2011. Intraindividual Variability in ADHD and Its Implications for Research of Causal Links. *Behavioral Neuroscience of Attention Deficit Hyperactivity Disorder and Its Treatment*, pp.67-91.

Lahti, A.C., Holcomb, H.H., Medoff, D.R., Weiler, M.A., Tamminga, C.A., Carpenter, W.T., 2001. Abnormal patterns of regional cerebral blood flow in schizophrenia with primary negative symptoms during an effortful auditory recognition task. Am. J. Psychiatry 158 (11), 1797–1808.

Lesh, T., Westphal, A., Niendam, T., Yoon, J., Minzenberg, M., Ragland, J., Solomon, M. and Carter, C., 2013. Proactive and reactive cognitive control and dorsolateral prefrontal cortex dysfunction in first episode schizophrenia. *NeuroImage: Clinical*, 2, pp.590-599. doi.org/10.1016/j.nicl.2013.04.010

Minzenberg, M., Laird, A., Thelen, S., Carter, C. and Glahn, D., 2009. Meta-analysis of 41 Functional Neuroimaging Studies of Executive Function in Schizophrenia. *Archives of General Psychiatry*, 66(8), p.811.

Nuechterlein, K., 1977. Reaction Time and Attention in Schizophrenia: A Critical Evaluation of the Data and Theories*.*Schizophrenia Bulletin*, 3(3), pp.373-428.

Panagiotaropoulou, G., Thrapsanioti, E., Pappa, E., Grigoras, C., Mylonas, D., Karavasilis, E., Velonakis, G., Kelekis, N. and Smyrnis, N., 2019. Hypo-activity of the dorsolateral prefrontal cortex relates to increased reaction time variability in patients with schizophrenia. NeuroImage: Clinical, 23. doi.org/10.1016/j.nicl.2019.101853

Petrides, M., 2016. The Ventrolateral Frontal Region. *Neurobiology of Language*, pp.25-33. doi.org/10.1016/B978-0-12-407794-2.00003-1

Petrides, M., 2013. The Mid-Dorsolateral Prefronto-Parietal Network and the Epoptic Process. *Principles of Frontal Lobe Function*, pp.79-90. DOI:10.1093/med/9780199837755.003.0008

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

RODNICK, E. and SHAKOW, D., 1940. SET IN THE SCHIZOPHRENIC AS MEASURED BY A COMPOSITE REACTION TIME INDEX. *American Journal of Psychiatry*, 97(1), pp.214-225.

Rolls, E., Cheng, W. and Feng, J., 2021. Brain dynamics: Synchronous peaks, functional connectivity, and its temporal variability. *Human Brain Mapping*, 42(9), pp.2790-2801.

Sanz, J., Karlsgodt, K., Bearden, C., van Erp, T., Nandy, R., Ventura, J., Nuechterlein, K. and Cannon, T., 2009. Symptomatic and functional correlates of regional brain physiology during working memory processing in patients with recent onset schizophrenia. *Psychiatry Research: Neuroimaging*, 173(3), pp.177-182. Doi: 10.1016/j.pscychresns.2009.02.008

Schwartz, F., Carr, A., Munich, R., Glauber, S., Lesser, B. and Murray, J., 1989. Reaction time impairment in schizophrenia and affective illness: The role of attention. *Biological Psychiatry*, 25(5), pp.540-548.

SHAKOW, D., 1962. Segmental Set. *Archives of General Psychiatry*, 6(1), p.1.

Smyrnis, N., Karantinos, T., Malogiannis, I., Theleritis, C., Mantas, A., Stefanis, N., Hatzimanolis, J. and Evdokimidis, I., 2009. Larger variability of saccadic reaction times in schizophrenia patients. Psychiatry Research, 168(2), pp.129-136. doi:10.1016/j.psychres.2008.04.015

Smyrnis, N., Evdokimidis, I., Stefanis, N., Avramopoulos, D., Constantinidis, T., Stavropoulos, A. and Stefanis, C., 2003. Antisaccade performance of 1,273 men: Effects of schizotypy, anxiety, and depression. *Journal of Abnormal Psychology*, 112(3), pp.403-414. DOI: 10.1037/0021-843X.112.3.403

Stuss, D., 2003. Staying on the job: the frontal lobes control individual performance variability. *Brain*, 126(11), pp.2363-2380. DOI: 10.1093/brain/awg237

Tamm, L., Narad, M., Antonini, T., O'Brien, K., Hawk, L. and Epstein, J., 2012. Reaction Time Variability in ADHD: A Review. *Neurotherapeutics*, 9(3), pp.500-508. DOI 10.1007/s13311-012-0138-5

Theleritis, C., Evdokimidis, I. and Smyrnis, N., 2014. Variability in the decision process leading to saccades: A specific marker for schizophrenia?. Psychophysiology, 51(4), pp.327-336. DOI: 10.1111/psyp.12178

Tinius TP. The intermediate visual and auditory continuous performance test as a neuropsychological measure. Arch Clin Neuropsychol. 2003 Mar;18(2):199-214. PMID: 14591471.

Torrey, E., 2007. Schizophrenia and the inferior parietal lobule. *Schizophrenia Research*, 97(1-3), pp.215-225 DOI:10.1016/j.schres.2007.08.023

VERTÉ, S., GEURTS, H., ROEYERS, H., OOSTERLAAN, J. and SERGEANT, J., 2005. Executive functioning in children with autism and Tourette syndrome. *Development and Psychopathology*, 17(02).
DOI: 10.10170S0954579405050200

Vinogradov, S., Poole, J., Willis-Shore, J., Ober, B. and Shenaut, G., 1998. Slower and more variable reaction times in schizophrenia: what do they signify?. *Schizophrenia Research*, 32(3), pp.183-190.

Weissman, D.H., Roberts, K.C., Visscher, K.M., Woldorff, M.G., 2006. The neural bases of momentary lapses in attention. Nat. Neurosci. 9 (7), 971–978. doi.org/10.1038/nn1727.

World Health Organization, 1992. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines.

Yarkoni, T., Barch, D., Gray, J., Conturo, T. and Braver, T., 2009. BOLD Correlates of Trial-by-Trial Reaction Time Variability in Gray and White Matter: A Multi-Study fMRI Analysis. *PLoS ONE*, 4(1), p.e4257. doi:10.1371/journal.pone.0004257

Yoon, J., Minzenberg, M., Ursu, S., Walters, R., Wendelken, C., Ragland, J. and Carter, C., 2008. Association of Dorsolateral Prefrontal Cortex Dysfunction With Disrupted Coordinated Brain Activity in Schizophrenia: Relationship With Impaired Cognition, Behavioral Disorganization, and Global Function. *American Journal of Psychiatry*, 165(8), pp.1006-1014.