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Title: Relation of reaction time intra-subject variability to fMRI activation during an attentional choice Reaction Time – task in patients with schizophrenia and healthy controls

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Abstract

Increased reaction time (RT) intra – subject variability (RT-ISV) has been found in patients with schizophrenia (SCZ), regardless of the task they perform. However, there have been only a few investigations of the neural correlates of RT-ISV in healthy individuals and to our knowledge there is only one study that explored neural activation and its possible association with RT-ISV in patients with SCZ. In the present study we used an attentional task and functional brain imaging to probe the neural correlates of increased RT-ISV in schizophrenia.

We included 24 patients with SCZ and 26 healthy controls (HC) who performed an attentional choice RT task inside the MRI scanner, while being recorded for their overall response of the brain using functional magnetic resonance imaging (fMRI). RT of the participants were recorded and analyzed to extract a new variable (ABS_RT-mRT) that conveys the stability of RT within each subject and any trial-by-trial differences. The imaging data were analyzed to explore any possible association between RT-ISV and BOLD activation.

Patients with SCZ had increased RT-ISV compared to HC. When Larger RT-ISV was associated with increased BOLD activation in right inferior frontal gyrus (pars triangularis), right supramarginal gyrus, bilateral insula, left middle frontal gyrus and left caudate nucleus, right middle temporal gyrus, bilateral calcarine sulci and left middle cingulate gyrus when SCZ and HC 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 RT-ISV, we found a significant difference (HC > PAT) in right middle frontal gyrus, left calcarine gyrus, left inferior parietal lobule/supramarginal gyrus and right precuneus.

In conclusion, it appears there is a uniform neural network, whose activation is positively associated with increased RT-ISV for all individuals regardless of any diagnosis and what possibly changes in patients with SCZ is how the intensity of this association differs in specific fronto-temporal regions.

Key – words: reaction time intra-subject variability, schizophrenia, neural correlates, fMRI.

Contents

Introduction

Patients with schizophrenia commonly present a psychomotor slowing, a deficit in information processing speed, which is reflected in various rapid decision-making tasks as increased response reaction time (RT) (Cadenhead et al., 1997). Apart from this, however, they also show characteristic differences in the distribution of RT, which are obvious even in the simplest tasks, where psychomotor slowing cannot be distinguished (Smyrnis et al., 2009). The RT distribution provides much more detailed information compared to simple averages.

One measure of particular interest is the variance of an individuals' RT in many trials during a task. This is considered as RT intra-subject variability (RT-ISV). It is a separate index, irrespective of the average RT, which does not appear to be affected by the different types of tasks and their level of difficulty. Increased (RT – ISV) has been found to be present in patients with schizophrenia (SCZ) (Nuechterlein, 1977), separating them from both healthy individuals and people with other disorders (Kaiser et al., 2008; Theleritis, Evdokimidis & Smyrnis, 2014). The RT of patients with SCZ is not stable from trial to trial, does not have a specific pattern and can change abruptly, regardless of whether the average RT is longer, equal or smaller than that of healthy individuals.

RT-ISV has been widely examined as a feature of children with ADHD (Johnson et al., 2007; Klein et al., 2006) leading to the conclusion that it may be related to an attentional deficit. Recent research has focused on SCZ, questioning to what extent the increased RT-ISV characterizes individuals with this disorder, whether there is a genetic basis and whether it also occurs in their first-relatives (Fish et al., 2018) or it is linked to other cognitive deficits. However, there has not yet been an adequate explanation of what may be causing this phenomenon or further whether there is a neurobiological substrate that supports it and what this might be.

Recently, it has been argued that the problem lies in the control of inhibition rather than that of attention, as a possible explanation for the phenomenon (Panagiotaropoulou et al., 2019), suggesting hypofunction of the dorsolateral prefrontal cortex as responsible for the great variance of reaction times in patients with schizophrenia. Therefore, further research is needed to understand the phenomenon, to investigate how it arises and whether there is a specific neurobiological background behind it.

Regarding the neural correlates of RT-ISV, Yarkoni et al. (2009) in a multi-study fMRI analysis, concluded that there must be task – independent relationships between trial-by-trial differences in RT and gray and white matter BOLD activation. Besides grey matter activation in large bilateral frontal regions (middle frontal gyrus, anterior insula, ventrolateral and dorsolateral prefrontal cortex (PFC), in the precuneus, the right middle temporal gyrus, the left inferior parietal lobule (IPL) and the posterior cingulate, they implied that variability in white matter structure and activation may as well have functional implications for RT variability. Precisely, they found activation within regions in the white matter, covering the right lateral genu of the corpus callosum and parts of the posterior corona radiata bilaterally. Esterman et al. (2012) reported an association between low RT variability and increased BOLD activation of the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC) in healthy individuals. Later, Johnson et al. (2015) also used healthy volunteers and found a negative association between RT variability and activation of the left pregenual anterior cingulate, i.e. increased variability was associated with reduced BOLD activation in this region.

The purpose of our study was to clarify the neural correlates of RT-ISV in patients with SCZ and healthy individuals using an attention choice-RT fMRI task and whether and how the neural network might differ between patients with SCZ and healthy individuals.

Research objectives and hypotheses

Increased RT-ISV in attentional choice and rapid decision – making tasks is frequently observed in patients with schizophrenia. However, this hasn't been studied sufficiently. The main purpose of our study was to investigate whether RT-ISV is related to fMRI activation changes in specific cerebral areas. Empirically and in accordance with previous studies, we expected activation in prefrontal areas to be related to this phenomenon. By conducting a whole brain analysis with no regions of interest (ROIs), we sought to explore any possible relationship between RT-ISV and fMRI activation changes. Secondarily, we hypothesized that there might exist a different pattern of activation in patients with SCZ (compared to healthy individuals) that might explain the increased RT-ISV.

Material and Methods

Participants

Our sample was collected for another study (Panagiotaropoulou et al., 2019) and the data collected were reused and reanalyzed for the purposes of our study. Our sample consisted of 24 patients with SCZ diagnosed and 26 healthy controls (HC). The groups were matched for age and sex. Patients were hospitalized in the psychosis inpatient unit of Eginition University Hospital and their diagnosis was confirmed by an experienced psychiatrist using the DIP-DM diagnostic module (McGuffin et al., 1991). Patients received antipsychotic medication during testing and were in a remission phase a few days prior to, or after discharge from the inpatient unit. Exclusion criteria included organic cerebral illness, mental retardation, and other major psychiatric disorder comorbidity. Systematic cannabis and other illicit drug abuse just prior to admission to the inpatient unit was also a criterion for exclusion. The HC group was also screened for a history of mental disorders.

Behavioral task design and data acquisition

The RT and its distribution were estimated by an attentional choice – reaction time task, performed inside the MRI scanner using two MRI compatible response pads (one in each hand) to answer. The test was programmed using E - Prime software (version 2.0) and was a version of Flanker task of Eriksen.

Specifically, for each trial, participants were asked to look at a screen and focus on a central fixation point indicated by a cross for a period of 2, 4 or 6 seconds. The cross was then replaced by a cue that remained visible for half a second, followed by the stimulus, to which the participant had to respond, also for half a second. The stimulus consisted of 5 arrows in a row, which in the first condition (congruent) all had the same direction (either right or left) while in the second condition (incongruent) the central arrow had the opposite direction from the rest (Picture A, Appendix).

Participants were instructed to respond according to the direction of the central arrow by pressing a button on one of the two pads given to them using their left or right index finger respectively. Each participant performed 75 trials of each condition: 1. congruent left / 2. congruent right / 3. incongruent left / 4. incongruent right, and 300 trials in total. The trials followed a random sequence and were performed in three

blocks of 100 trials. The total response time should not have exceeded 1.5 seconds (0.5 second for stimulus presentation and 1 second until the end of the response). Reaction times and the correct answers were measured. Between each block, participants were given a few minutes to rest while remaining inside the scanner. Before scanning, participants were administered a few trials to familiarize with the procedure.

Behavioral data analysis

In the given analysis we were not concerned about the correct answers of the participants, and we only processed the RT. The RT of each participant in the various trials was used to compute the variable that was then used as the parameter for the analysis of the imaging data. This was the absolute variance of each RT from the mean RT of each participant, separately for each trial and each condition |RT – mean RT| (ABS_RTmRT). Based on previous studies (Johnson et al., 2015), we used this variable to eliminate the effect of individual differences and any effects of the difficulty of the task. It captures the exact variability of the RT within each subject. We performed comparisons (independent samples t-test) between SCZ and HC to examine differences in the mean RT and ABS_RTmRT. For the behavioral data analysis, we used IBM SPSS Statistics 26.0 software with the level of statistical significance set at $p<0.05$.

Functional imaging 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 the 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. Subjects with registered motion >1 mm or 1 degree were discarded. Thirteen participants (4 controls and 9 patients) were excluded due to low image

quality, resulting in a sample of 37 participants. For some participants we excluded only one of the three blocks due to low image quality. 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.

We then applied a parametric modulation model. At first level within-subject analysis, we used all scans in one single condition regardless of the trial/ block they belonged to. We further included the |RT – mean RT| (ABS_RTmRT) 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, a one sample t-test was carried out for each contrast including all HC and patients with SCZ in order to identify the neural network associated with trial-to-trial RT variability (i.e., ABS_RTmRT). The identified regions were then included as a binary mask and differences between HC 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 uncorrected, with cluster-extent threshold). The clusters that emerged as statistically significant were anatomically identified through the Automated Anatomical Labeling atlas 3 (AAL3).

Ethical considerations

This study is in accordance with the Helsinki Declaration of World Medical Association and has been approved by the Research Ethics Committee of the Eginition University Hospital. Participants provided written informed consent regarding the voluntary nature of their participation and their right to withdraw at any time. It was clarified that their personal data would remain confidential and would only be used for research purposes.

Results

Behavioral data

We found significant difference in the means of the two groups [$t(48)=5.53$, $p < 0.001$]. Specifically, patients with SCZ had larger RT-ISV compared to HC, i.e. higher mean ABS_RTmRT. Regarding the effect size, this difference is very large ($d= 1.56$). The results of the analysis are presented in Table 1.

Table 1.

Differences in the mean ABS_RTmRT between healthy controls and patients with schizophrenia

Variable	Healthy controls	Patients with schizophrenia
ABS_RTmRT	38.37 (13.45)	62.32 (17.08)

Note. Standard deviations of each group are presented in the brackets.

fMRI data: neural correlates of intra-subject RT variability

One-sample t-tests across all subjects showed a positive correlation between larger RT variability and higher BOLD activation in 9 clusters covering parts of: the right inferior frontal gyrus (pars triangularis), the right supramarginal gyrus, the left and right insula, the middle frontal gyrus and the caudate nucleus in the left hemisphere, the right middle temporal gyrus, the right and left calcarine sulcus and the left middle cingulate gyrus. Results are presented in Table 2 and Figure 1.

Table 2.

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	Inferior Frontal Gyrus – Tri	R	39, 23, 4	9.17	3292
2	Supramarginal gyrus	R	51, -40, 55	8.21	3087
3	Insula	L	-33, 20, 1	8.15	798
4	Middle Frontal Gyrus	L	-30, 32, 28	6.60	268
5	Caudate	L	-12, 5, 4	6.27	163
6	Middle Temporal Gyrus	R	54, -52, 7	5.76	148
7	Calcarine	R/L	-18, -70, 1	4.48	122
8	Insula	R	36, -22, -5	4.21	11
9	Middle Cingulate Gyrus	L	0, -19, 28	4.05	15
Negative contrast: higher RT variability associated with decreased BOLD activation					
-	-	-	-	-	-

Note. Tri= Inferior frontal gyrus – Pars triangularis, R=right hemisphere, L= left hemisphere. We present only the anatomical regions survived at $p < 0.001$ uncorrected with cluster-extent threshold of 10 voxels.

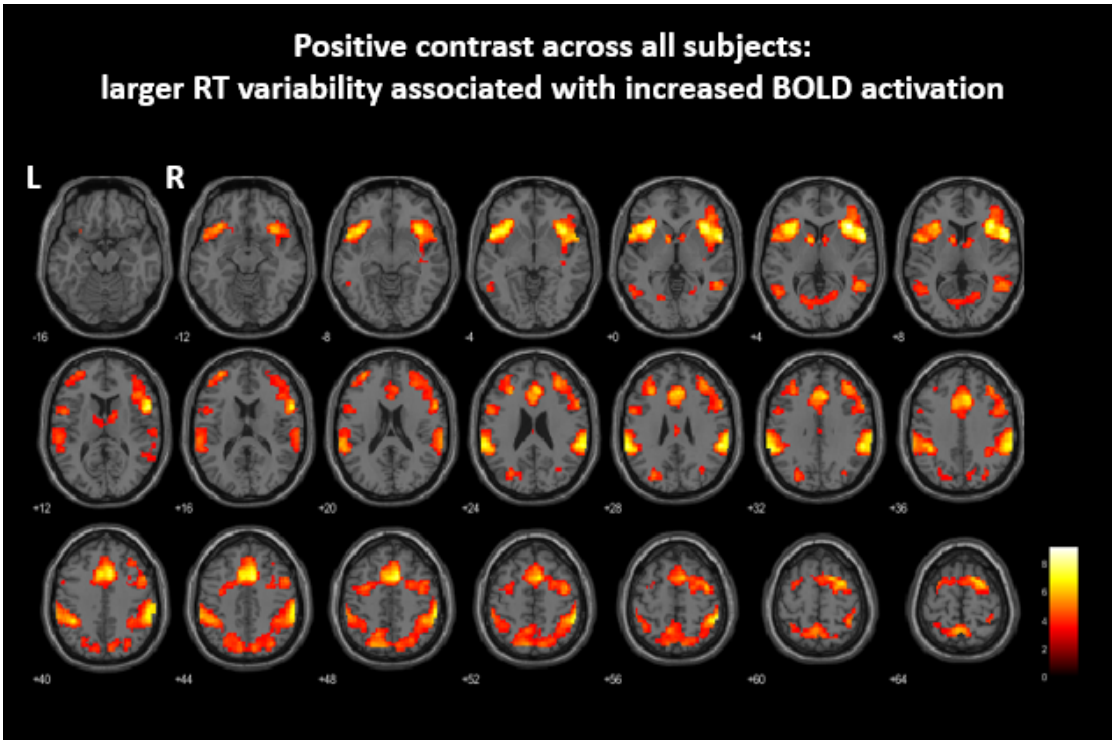
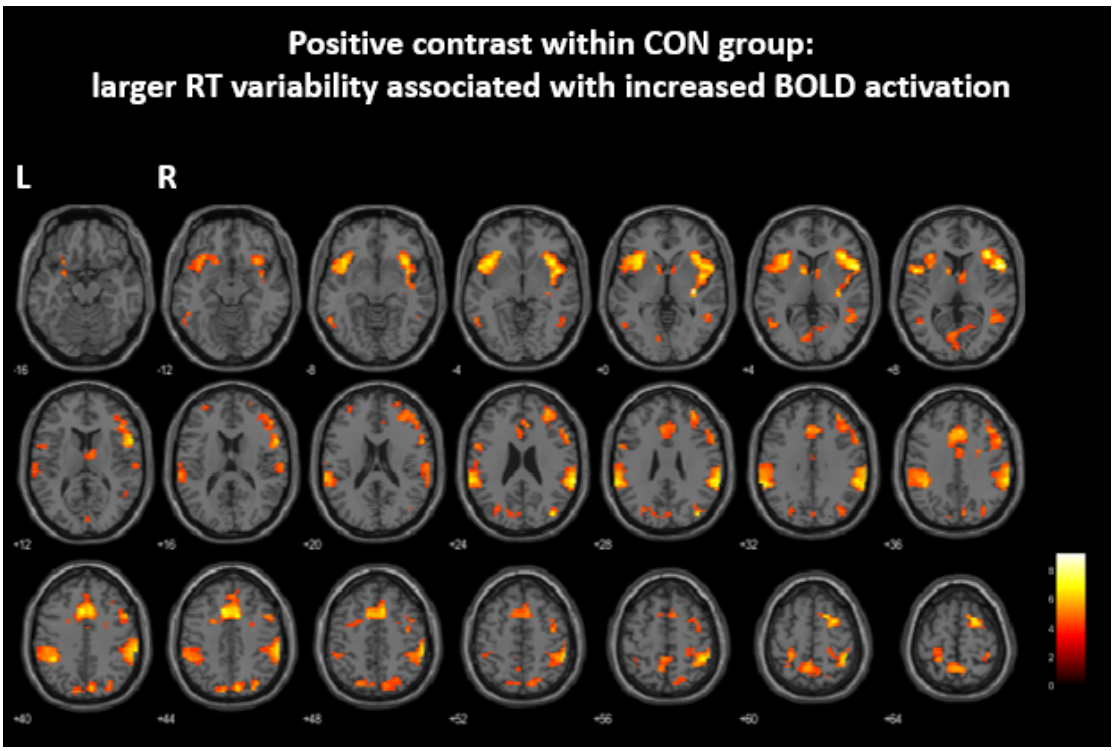
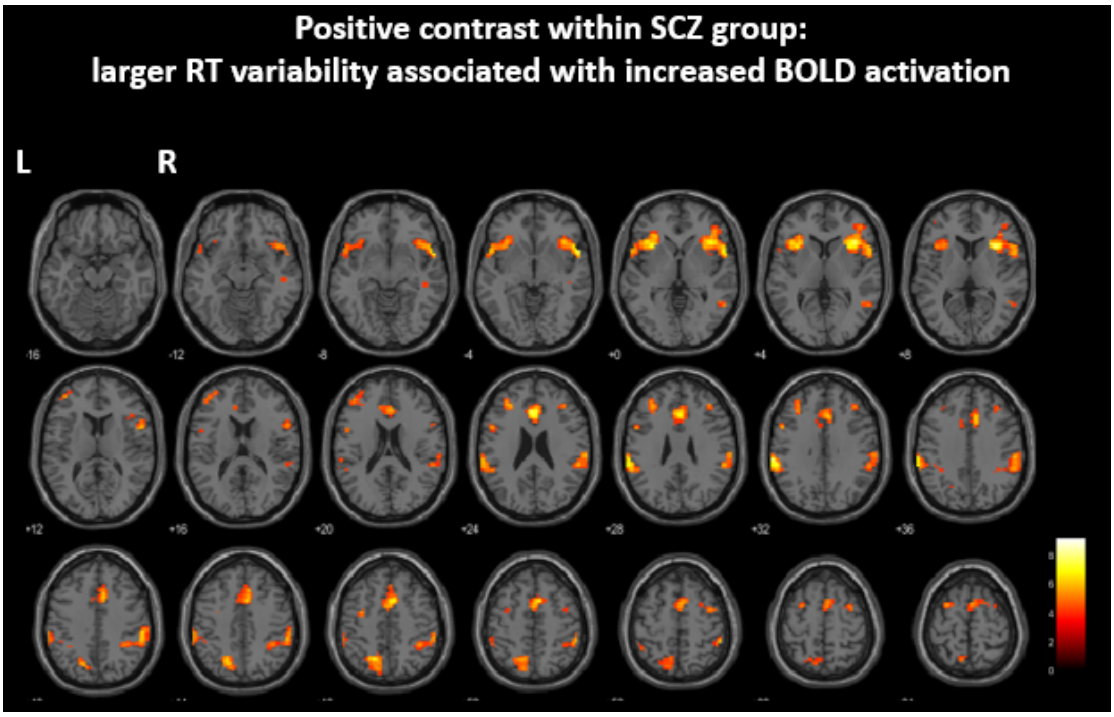


Figure 1. Anatomical regions showing increased BOLD activation when intra-subject RT variability is larger (one-sample t-test across all subjects, $p < 0.001$ uncorrected, cluster extent threshold 10 voxels).

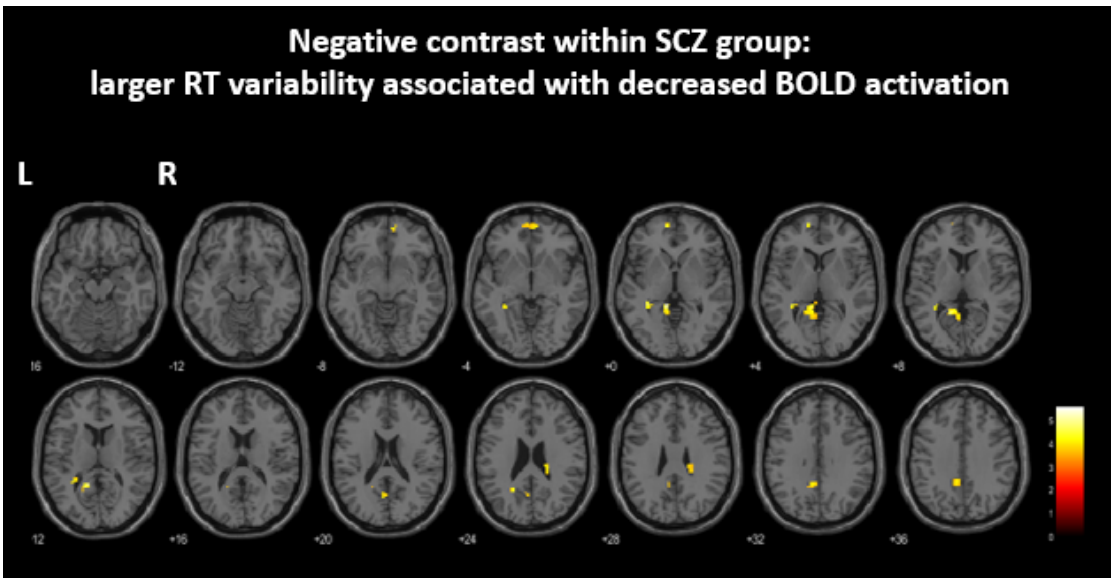
In a supplementary analysis, we also examined the neural correlates of intra-subject RT variability separately in CON and SCZ, using $p < 0.001$ uncorrected, with cluster extent threshold of 9 (CON) and 7 (SCZ) voxels. Anatomical regions surpassed the statistical threshold both in CON (Supplementary 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-subject RT variability is larger (one-sample t-test within CON group, $p < 0.001$ uncorrected, cluster extent threshold 9 voxels).



Supplementary Figure 2. Anatomical regions showing increased BOLD activation when intra-subject RT variability is larger (one-sample t-test within SCZ group, $p < 0.001$ uncorrected, cluster extent threshold 7 voxels).



Supplementary Figure 3. Anatomical regions showing decreased BOLD activation when intra-subject RT variability is larger (one-sample t-test within SCZ group, $p < 0.001$ uncorrected, cluster extent threshold 7 voxels).

Based on the results across all subjects, further analysis was carried out to identify between-group differences on the neural correlates of intra-subject 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 right middle frontal gyrus [MNI coordinates (x, y, z) = 36, 44, 25, T score = 3.50, cluster size = 33 voxels], left calcarine gyrus [MNI coordinates (x, y, z) = -3, -73, 10, T score = 3.49, cluster size = 28 voxels], left inferior parietal lobule/supramarginal gyrus [MNI coordinates (x, y, z) = -48, -31, 40, T score = 3.41, cluster size = 45 voxels], and right precuneus [MNI coordinates (x, y, z) = 9, -76, 43, T score = 3.23, cluster size = 23 voxels]. No other clusters reached corrected significance at this threshold neither for the CON > SCZ nor for the CON < SCZ contrast.

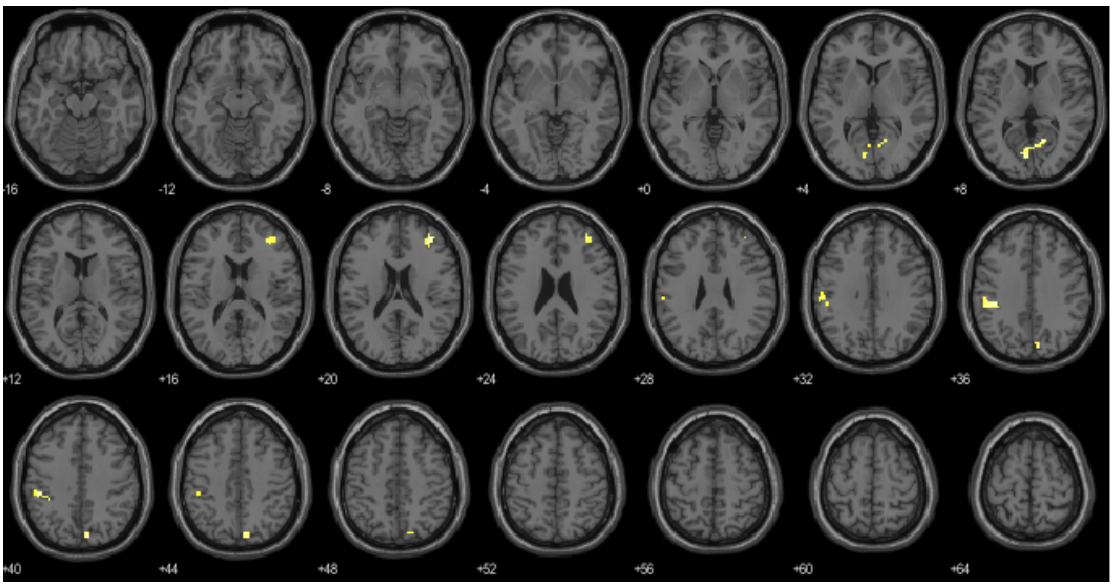


Figure 3. Location of the clusters showing significant difference between healthy individuals and patients with schizophrenia (CON > SCZ) for the positive contrast of one-sample t-test analysis (i.e., increased BOLD activation associated with larger intra-subject RT variability) ($p < 0.005$ uncorrected, cluster extent threshold 17 voxels).

Discussion

In the present study, we used an attentional choice RT task to measure the RT of patients with SCZ and HC, while recording their overall response of the brain. As it is known, patients with SCZ had larger RT and increased RT-ISV (i.e., less stable response times) compared to healthy individuals. Patients showed more trial-by-trial differences in RT than controls. Unexpectedly, we found a common neural network which was positively associated with increased RT-ISV for both groups.

The increased RT-ISV in SCZ proves to be what mainly differentiates the two groups, as it is not always necessary that patients will have larger RT than controls, but it has been suggested that they will have significantly more increased RT-ISV. This is in accordance with previous findings that even in simple tasks (e.g., visually guided saccades) patients with schizophrenia have increased RT-ISV but not larger mean RT (Smyrnis et al., 2009). The increased RT-ISV in schizophrenia has been widely replicated in several studies using various sensorimotor tasks (Theleritis et al., 2014; Karantinos et al., 2014).

The analysis of fMRI data confirmed that for the whole sample (controls and patients) several brain areas had increased activation when there was increased variability, but no regions were found to have negative association with higher variability. Thus, we did not manage to confirm previous findings of reduced activation in specific brain regions such as the dorsolateral prefrontal cortex (Panagiotaropoulou et al., 2019) or parts of the anterior cingulate (Esterman et al., 2012; Johnson et al., 2015). However, we found increased activation in the left middle cingulate gyrus related to increased RT-ISV, and we should point out how different parts of the same wider region (cingulate cortex) might subserve different functions.

However, extensive clusters of increased activation emerged, including the right inferior frontal gyrus (pars triangularis), the right supramarginal gyrus and the left insula, and less extensive clusters covering the right insula, the middle frontal gyrus and the caudate nucleus in the left hemisphere, the right middle temporal gyrus, the right and left calcarine sulcus and the left middle cingulate gyrus. The resulting set of regions have been reported in previous studies (Yarkoni et al., 2009). Most of these areas are involved in the frontoparietal network of attention, within which attentional fluctuations, as defined by changes in RT, may be predicted (Tam et al., 2014), while some of them have also been suggested to be related to selective attention and cognitive control (Arkin et al., 2020). As for the insula, Esterman et al. (2012) reported a cluster in right fronto-insular cortex that had positive correlation with RT variability. Subdivisions of the insula have been suggested that causally influence other large-scale brain networks including the central executive network which implements the maintenance and manipulation of information and decision-making (Uddin et al., 2017).

In the supplementary analysis for each separate group there were regions of increased activation related to increased variability for both groups, but areas of decreased neural activity related to increased variability were only found for the group of SCZ patients. This is perhaps the only difference concerning the engaged brain regions, besides the differences in the intensity of activation. In the comparison between the two groups, for the positive contrast (i.e., greater activation related to greater RT variability) the areas that we found were pretty much the same in both groups, differing only in the intensity of activation. Control subjects presented significantly higher activation related to increased RT variability than SCZ patients in the right middle frontal gyrus, the left calcarine gyrus, the left inferior parietal

lobule/supramarginal gyrus and the right precuneus. These differences in the intensity of activation, in addition to the decreased activation in several areas only for the group of patients, might be responsible for or at least explain somehow the fact that in schizophrenia, subjects show significantly higher RT-ISV than healthy controls.

Additionally, we refer to another master thesis conducted in the context of this Master of Science program (Clinical neuropsychology – Cognitive neurosciences). In a similar concept, increased RT-ISV and its neural correlates were also examined in patients with schizophrenia and control subjects, who performed a different task, and activation in the same brain areas proved to be positively associated with the increased RT-ISV of all participants. In a supplementary analysis we performed together, we unified our samples to check if we would find activation in the same regions with a bigger sample this time, and this was the case.

Interestingly, we conclude that there is a uniform neural network, whose activation is positively associated with increased RT-ISV for all individuals regardless of any diagnosis and what is possibly different in schizophrenia is the intensity of this association. Limitations of our study include the relatively small size of our sample. Further research is needed to investigate the interactions and how increased activation of the suggested areas might affect the increase in RT-ISV and future studies should also explore why patients with schizophrenia tend to have increased RT variability. Is it a problem with the control of attention, or most likely attributed to insufficient inhibitory control?

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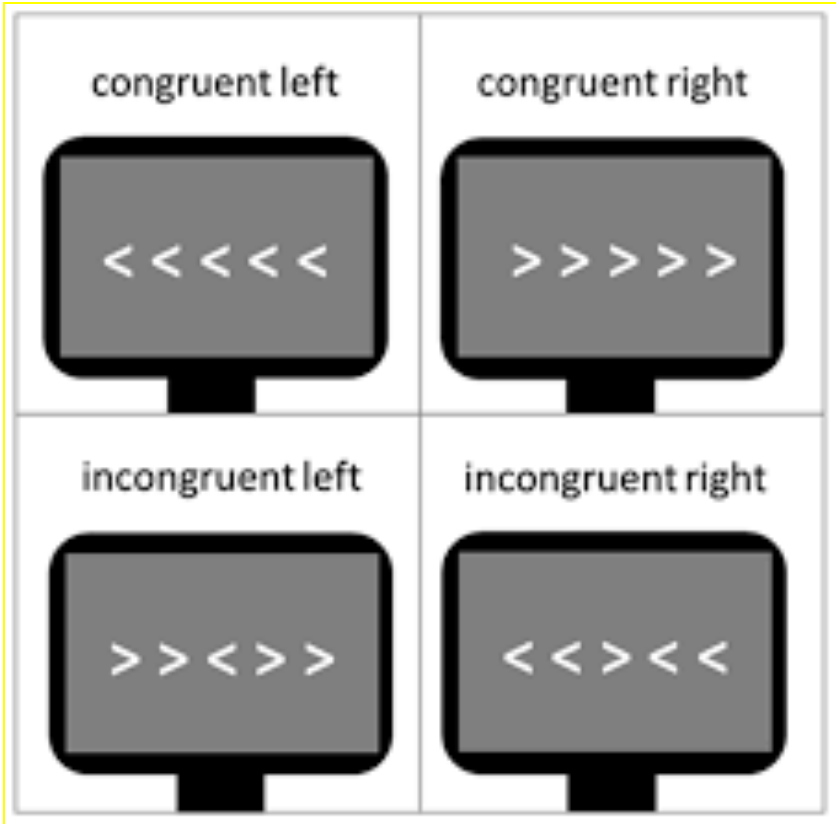
Appendix



Picture 1. The four conditions of the task.