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Frontal brain volume correlates of impaired executive function in schizophrenia

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ABSTRACT

Cognitive impairments affect functional capacity in individuals with schizophrenia (SZH), but their neural basis remains unclear. The Wisconsin Card Sorting Test (WCST), and the Stroop Task (SCWT), are paradigmatic tests which have been used extensively for examining executive function in SZH. However, few studies have explored how deficits on these tasks link to brain volume differences commonly seen in SZH. Here, for the first time, we tested associations between FreeSurfer-derived frontal brain volumes and performance on both WCST and SCWT, in a well-matched sample of 57 SZH and 32 control subjects. We also explored whether these associations were dissociable from links to symptom severity in SZH. Results revealed correlations between volumes and task performance which were unique to SZH. In SZH only, volumes of right middle frontal regions correlated with both WCST and Stroop performance: correlation coefficients were significantly different to those present in the control group, highlighting their specificity to the patient group. In the Stroop task, superior frontal regions also showed associations with Stroop interference scores which were unique to SZH. These findings provide important detail around how deficits on these two paradigmatic executive function tasks link to brain structural differences in SZH. Results align with converging evidence suggesting that neuropathology within right middle frontal regions (BA9 and BA46) might be of particular import in SZH. No volumetric associations with symptom severity were found, supporting the notion that the structural abnormalities underpinning cognitive deficits in SZH differ from those associated with symptomatology.

1. Introduction

Schizophrenia is a debilitating psychotic disorder affecting approximately 1% of the global population (Velligan and Rao, 2023). The overall cost of Schizophrenia and other psychotic disorders has been estimated at £11.8 billion per year in the United Kingdom alone (Ride et al., 2020). In addition to the economic burden, the impact on well-being and functional capacity is severe (Harvey and Strassnig, 2012), with broader consequences for society as a whole. Although cognitive impairment is not one of the diagnostic criteria, cognition is impaired in most individuals with schizophrenia (SZH), and this affects daily functioning (Bowie and Harvey, 2006). These cognitive impairments are persistent and largely unresponsive to pharmacological therapy (Tripathi et al., 2018), and cognitive training is not always effective (Best et al., 2019). The brain structural differences in SZH are well studied, but the brain structural underpinnings of cognitive impairment in SZH are still uncertain.

One common structural alteration in SZH is a progressive reduction in Gray Matter Volume (GMV), predominantly observed in frontal and temporal brain regions (Jiang et al., 2018; Vita et al., 2012). Previous studies have linked this GMV reduction to the key cognitive domains impaired in SZH, including executive function (Guo et al., 2014), attention (Gur et al., 2000), verbal learning (Antoniades et al., 2018), and visual memory (Nestor et al., 2007). Amongst these, executive dysfunction is of particular importance since there is considerable evidence showing that executive functioning predicts functional outcome in SZH (Berberian et al., 2019; Lysaker et al., 1995; Velligan et al., 2000); this is unsurprising as it encompasses processes critical for goal-directed behaviours, such as planning, flexible thinking, and cognitive inhibition.

There are various well-established measures of executive functioning. The Wisconsin Card Sorting Test (WCST), in which subjects

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must detect, follow and switch rules for sorting cards into categories, is perhaps the most widely used task-based instrument amongst these (Nelson, 1976). Many studies have shown that SZH demonstrate poorer performance on the WCST (Hartman et al., 2003; Prentice et al., 2008; Singh et al., 2017), failing to achieve as many categories as control subjects, and showing an elevated rate of perseverative errors, reflecting a difficulty in updating a previously-correct rule after receiving negative feedback. A handful of studies have looked at links with brain structure: in chronic SZH, poorer WCST performance was linked to volume in left dorsolateral prefrontal cortex, measured using voxel-based morphometry (VBM) (Rüsch et al., 2007); this was not seen in the control group. Likewise, Bonilha et al. (2008), found correlations between WCST performance measures and volume (again measured using VBM) in frontal regions BA9 and BA46 in SZH, but correlations in controls were not assessed. This accords with functional MRI studies in SZH showing reduced activity in left dorsolateral prefrontal cortex during WCST performance (Wilmsmeier et al., 2010); fMRI studies also implicate the anterior cingulate cortex (ACC) since activity in that region in particular has been associated with better WCST performance in SZH (Pedersen et al., 2012). In contrast, other studies could not find any significant relationships between GMV and WCST performance in chronic SZH (Frascarelli et al., 2015; Nestor et al., 2019). However, Frascarelli et al. (2015) used a sample that comprised patients with a wide range of duration of illness. Nestor et al. (2019) found that in the control group, total left PFC volume correlated with WCST measures of categories completed and both nonperseverative and perseverative errors, but for the patient group, PFC volumes did not correlate with any of these measures. However, the sample size was small (27 SZH, 17 controls); indeed, the aforementioned studies have often been hampered by small samples. Thus, the relationship between frontal GMV and WCST performance in SZH requires further investigation and clarification.

Another impaired executive function in SZH is cognitive inhibition and interference/conflict resolution: this is often measured via the classic Stroop task (Krabbendam et al., 2009). The Stroop Colour and Word Test (SCWT) is a widely employed neuropsychological assessment tool that measures one's capacity to resolve the cognitive interference which arises from colour-word incongruence (the Stroop Effect) (Scarpina and Tagini, 2017). SZH exhibit an increased Stroop interference effect both in terms of response time and accuracy (Westerhausen et al., 2011), suggesting a deficiency in inhibition; fMRI studies of the Stroop task have linked this to a failure to deactivate medial frontal cortex in SZH (Salgado-Pineda et al., 2021). Only a few studies have looked at links to brain volumes. Better Stroop performance has been linked to higher GMV in right middle frontal gyrus in early-onset SZH (Guo et al., 2022), and upper frontal, middle and medial frontal regions in first-episode SZH (Zhang et al., 2018). In chronic SZH, associations with dorsomedial prefrontal cortex volume have been shown (Premkumar et al., 2008a). However, none of these studies contrasted with a control group so it is uncertain as to whether relationships are unique to SZH.

Thus, current evidence suggests GMV reductions in various brain regions within frontal and temporal lobes are associated with WCST and Stroop task impairments in SZH, but there are major inconsistencies and limitations to the existing evidence base. Of the aforementioned studies, many are hampered by small sample sizes of less than 35 patients, with some as low as 14 (Bonilha et al., 2008; Chu et al., 2016; Dempster et al., 2017; Frascarelli et al., 2015; Zhang et al., 2018); further, some studies did not contrast with healthy controls. A well-matched control group is essential so as to determine the specificity and uniqueness of GMV-cognition relationships in SZH. Also, much of the previous work is based on VBM techniques rather than modern FreeSurfer-based approaches. Importantly, no study to date has investigated relationships with brain volumes on both the WCST and Stroop in a single sample, so it uncertain the extent to which structure-performance relationships compare and overlap across the two tasks. As these are perhaps the most well-used and well-established tests of executive function, both with robust deficits demonstrated in SZH, ascertaining and contrasting their neural underpinnings in a single sample would provide important insights. Therefore, the current study investigated associations between GMV and performance on the WCST and Stroop, focusing on the frontal brain areas implicated by previous work, and contrasting with a well-matched control group. In patients, we also interrogated whether these relationships are dissociable from links to symptom severity. Leveraging the advanced parcellation methods available within the FreeSurfer package, we took a region of interest (ROI) approach that encompassed medial and inferior frontal areas, divided by subregion, as well as anterior cingulate.

2. Material and methods

2.1. Participants

The sample included 57 SZH (16 females, aged between 21 and 49, mean age 37.21, see Table 1), and 32 age and gender-matched healthy controls (CON) (10 females, aged between 20 and 65, mean age 33.19, see Table 1). The exclusion criteria for both groups consisted of the following: any neurological conditions, head injuries resulting in a loss of consciousness, prior exposure to the current neuropsychological assessments, and substance abuse; for SZH, having an additional Axis I disorder diagnosis; for controls, having a personal history of DSM-IV Axis I and II disorders or a family history of psychosis. This was assessed using SCID-I (First and Gibbon, 2004) and Structured Clinical Interview for DSM-IV Axis II Disorders Research Version (SCID-II) (First and Gibbon, 2004). Schizophrenia was diagnosed by an experienced psychiatrist using the SCID-I. The evaluation of symptoms was conducted using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). With the exception of five individuals (who were not medication-naïve), all patients were receiving traditional antipsychotic medications, either in oral form or through depot injections; the mean chlorpromazine equivalent dosage was 453.4 (standard deviation = 300.2), range was 100–1600 mg per day. The study procedures received approval from the ethics committee at the Institute of Psychiatry and

Table 1
Demographic and clinical characteristics of the sample.

	All Subjects (N = 89)	Healthy Controls (N = 32)	SZH (N = 57)	*p*
Age, M (SD)	35.76 (9.53)	33.19 (11.43)	37.21 (8.02)	0.055[a]
Female (N, %)	26 (27.4%)	10 (31.3%)	16 (25.4%)	0.355[b]
Education (years) (SD)	14.37 (2.72)	15.34 (2.62)	13.82 (2.65)	0.011[a]
WASI total (Mean/SD)	109.00 (20.1)	120.09 (13.86)	103.35 (20.38)	<0.001[a]
NART Premorbid IQ (Mean/SD)	110.23 (9.83)	114.62 (8.47)	107.83 (9.77)	.002
Medication (Chlorpromazine equivalents mg/day) (SD)	N/A	N/A	453.40 (300.23)	N/A
PANSS (7 items) positive symptoms (mean) (SD)	N/A	N/A	16.49 (4.87)	N/A
PANSS (16 items) general psychopathology (mean) (SD)	N/A	N/A	32.75 (6.75)	N/A
PANSS (7 items) negative symptoms (mean) (SD)	N/A	N/A	17.97 (5.01)	N/A
PANNS Total (mean, SD)	N/A	N/A	67.21 (13.98)	N/A

Abbreviations. SZH, Schizophrenia; SD, standard deviation; PANSS, Positive and Negative Syndrome Scale; N/A, Not Applicable.
[a] Independent sample *t*-test.
[b] Pearson Chi-Square.

Maudsley Hospital. Additionally, all participants provided written consent after being informed about the study and were compensated for their time and travel expenses.

2.2. MRI acquisition

Structural images were acquired using a 1.5 T GE NV/i MR Signa System (General Electric, Milwaukee, Wisconsin).

Visual inspection of all images was carried out, followed by cortical reconstruction using FreeSurfer 6.0.0 (http://surfer.nmr.mgh.harvard.edu). Cortical parcellation was determined using the Destrieux atlas (Destrieux et al., 2009). To calculate intracranial (ICV)-adjusted volumes, we divided the volume in each region of interest (ROI) by the total intracranial volume (ICV) and then multiplied the result by 100.

2.3. ROI approach

The regions of interest (ROIs) encompassed various frontal areas, based on previous research implicating these areas in structural-executive functioning relationships in SZH (Bonilha et al., 2008; Chu et al., 2016; Dempster et al., 2017; Frascarelli et al., 2015; Guo et al., 2014, 2022; Nestor et al., 2019; Premkumar et al., 2008a; Rüsch et al., 2007; Zhang et al., 2018), these were: left/right superior frontal, left/-right caudal middle frontal, left/right rostral middle frontal, left/right pars opercularis, left/right pars orbitalis, left/right pars triangularis, and left/right anterior cingulate (14 regions in total).

2.4. Executive function measures

WCST (Heaton et al., 1993)- Participants sorted 64 cards and the number of completed categories (WCST categories), the % of non-perseverative errors, and % perseverative errors were recorded.

SCWT (Stroop) (Golden et al., 1978)- The standard SCWT test (three cards, 100 items each) was used. Full details are in the Supplementary Materials. Stroop Interference scores were calculated for each participant, with higher scores reflecting better performance.

We also used the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) as a measure of general Intelligence. Additionally, we used the National Adult Reading Test (NART) (Nelson, 1991) as a measure of premorbid intelligence.

2.5. Statistical analysis

We conducted statistical analyses using IBM SPSS Statistics 28.0. For demographic variables, group comparisons were made using independent sample t-tests for age and education, and a $\chi 2$ test for gender distribution. We used ANCOVA to test for group differences in GMV of the ROIs. Checks for normality (Kolmogorov-Smirnov) indicated that neither the WCST subscales nor the Stroop interference scores followed a normal distribution. Therefore, Mann-Whitney U tests were used for group comparisons, and Spearman's correlations (between executive function measures and GMVs) were computed separately for controls and SZH. Significance of difference between the correlation coefficients for controls and SZH was assessed using the Fisher r-to-z transformation (http://vassarstats.net/rdiff.html). In the SZH group, we also performed Pearson's correlations to test the relationship between symptom severity and GMVs, and Spearman's correlations to test the relationship between symptom severity and executive function measures. Corrections for multiple comparisons were performed using false discovery rate (FDR) with the Benjamini- Hochberg method (Benjamini and Hochberg, 1995), and the significance level was set at.05.

2.6. Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

3. Results

3.1. Participant characteristics

Summary demographic data are presented in Table 1. There were no statistically significant differences between the SZH and healthy control groups in terms of age and sex (all p values $> .05$), but controls had a significantly higher level of education ($M = 15.34$, $SD = 2.62$) compared to SZH ($M = 13.82$, $SD = 2.65$, $p = .011$). On WASI, controls ($M = 120.09$, $SD = 13.86$) also had significantly higher premorbid IQ scores (NART) compared to SZH ($M = 103.35$, $SD = 20.38$).

3.2. Neurocognitive measures

Means and standard deviations for all executive function scores are reported in Table 2. SZH, compared to controls, had significantly lower performance on all measures, with the exception of Stroop Interference, where a strong trend was present (1- tailed $p = .055$).

3.3. Correlations between symptom severity and executive function measures

We tested associations between symptom severity (PANNS positive, negative, and general psychopathology) and each of the executive function measures. After FDR correction, WCST performance correlated significantly with PANSS Negative, in terms of higher % Perseverative Errors, and lower Categories performance (Supplementary Table 1). No other associations were found.

3.4. MRI–GMV differences between SZH and controls

We found reduced GMVs in SZH, in left superior frontal ($p_{FDR} = .039$), right caudal middle frontal ($p_{FDR} = .035$), right pars opercularis ($p_{FDR} = .035$), and right anterior cingulate ($p_{FDR} = .037$), after FDR correction for multiple comparisons (see Supplementary Table 2). Uncorrected, there were also reduced GMVs in SZH evident in right superior frontal (unadjusted $p = .031$), left caudal middle frontal (unadjusted $p = .037$), left pars opercularis (unadjusted $p = .030$), and bilateral pars triangularis (unadjusted right: $p = .033$, unadjusted left: $p = .021$), No significant differences were observed in left/right rostral middle frontal, left/right pars orbitalis, left anterior cingulate (all p values $> .05$).

3.5. Correlations between executive function and GMV

WCST % Perseverative Errors: In SZH, WCST perseverative error scores negatively correlated with GMV in left caudal middle frontal (unadjusted $p = .004$) and right rostral middle frontal (unadjusted $p = .018$), however, neither of these relationships survived FDR correction. No associations were seen in healthy controls, but Fisher's Z test indicated that only the correlation coefficient for right rostral middle frontal was significantly different between SZH and controls (Supplementary Table 3).

WCST % Non-Perseverative Errors: In SZH, there was an (uncorrected) negative relationship between right hemisphere rostral middle frontal GMV and WCST non-perseverative errors (unadjusted $p = .019$). However, this relationship did not survive FDR correction. No associations were seen in healthy controls, but Fisher's Z test indicated that the correlation coefficients for right rostral middle frontal was not significantly different between SZH and controls (Supplementary Table 4).

WCST Categories: In SZH, WCST categories scores positively correlated with GMV in right hemisphere caudal middle frontal ($p_{FDR} = .042$, Fig. 1a) and right hemisphere rostral middle frontal ($p_{FDR} = .042$, Fig. 1b) after FDR correction. Uncorrected, there was also a positive

Table 2
Group differences in executive function performance.

Executive Function	Controls		Schizophrenia		Group Comparisons	
	Mean Rank	**Sum of Ranks**	**Mean Rank**	**Sum of Ranks**	***z***	***P (1-tailed)***
WCST % Perseverative Errors	26.81	724	49.93	2846	−4.062	<.001[a]
WCST % non-perseverative errors	31.44	849	47.74	2721	−2.863	.002[a]
WCST categories	53.93	1456	37.09	2114	−3.202	<.001[a]
Stroop interference score	47.48	1282.00	38.56	2121	−1.594	.055

Z scores are from Mann-Whitney *U* test used as the variables were not normally distributed.
*p < .05.
[a] p < .01.

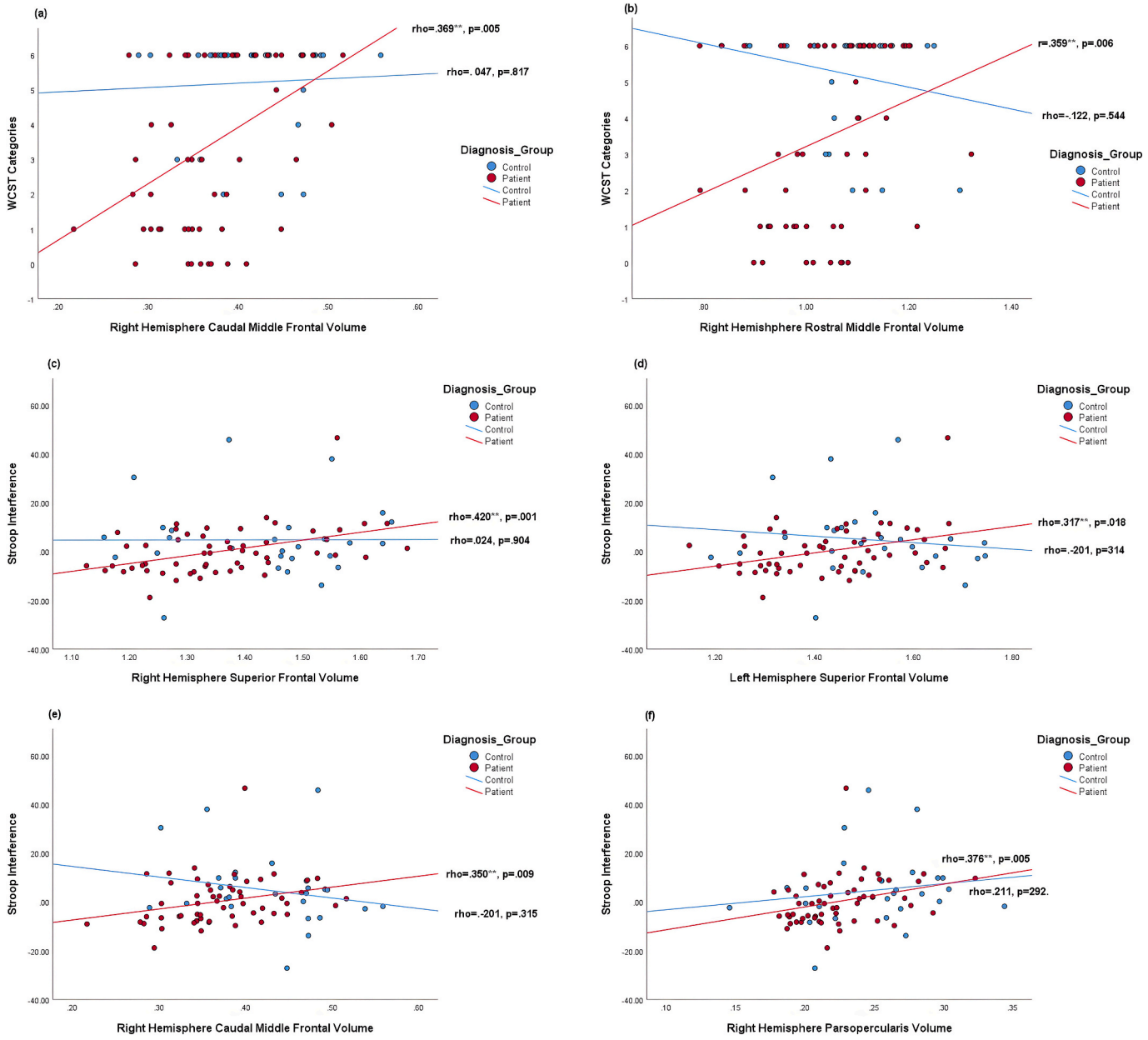

Fig. 1. The relationship between GMV and executive functioning tasks. (a) GMV in right hemisphere caudal middle frontal region correlated with WCST Categories performance in SZH (*rho* = .369, *p* = .005). (b) GMV in right hemisphere rostral middle frontal region correlated with WCST Categories performance in SZH (*rho* = .359, *p* = .006). (c) GMV in right hemisphere superior frontal correlated with Stroop Interference in SZH (*rho* = .420, *p* = .001). (d) GMV in left hemisphere superior frontal correlated with Stroop Interference in SZH (*rho* = .317, *p* = .018). (e) GMV in right hemisphere caudal middle frontal correlated with Stroop Interference in SZH (*rho* = .350, *p* = .009). (c) GMV in right hemisphere pars opercularis correlated with Stroop Interference in SZH (*rho* = .376, *p* = .005). Note that higher Stroop Interference scores indicate better performance.

correlation between WCST categories and right hemisphere pars orbitalis GMV (unadjusted p = .044) in SZH. No associations were seen in healthy controls, but Fisher's Z test indicated that only the correlation coefficient for right rostral middle frontal was significantly different between SZH and controls (Supplementary Table 5).

Stroop Interference: In SZH, Stroop Interference scores positively correlated with GMV in bilateral superior frontal (right: p_{FDR} = .014, left: p_{FDR} = .049, Fig. 1c and d), right hemisphere caudal middle frontal (p_{FDR} = .042, Fig. 1e), right hemisphere pars opercularis (p_{FDR} = .035, Fig. 1f), and left hemisphere anterior cingulate (p_{FDR} = .049). Uncorrected, there was also positive correlations between Stroop interference and left hemisphere pars triangularis GMV (unadjusted p = .048) and right hemisphere rostral middle frontal (unadjusted p = .037). No associations were seen in healthy controls, and Fisher's Z test indicated that only the correlation coefficients for left superior frontal, right rostral, and right caudal middle frontal, were significantly different between SZH and controls (Supplementary Table 6).

3.6. Correlations between symptom severity and GMV

There was no association between symptom severity (PANNS positive, negative, and general psychopathology) and GMV in any of the ROIs, even prior to FDR correction (Supplementary Table 7).

4. Discussion

This study set out to clarify the frontal lobe GMV correlates of WCST and Stroop task performance in SZH. Although previous studies in patients have linked impaired performance on these well-used tasks to brain volumetric reductions, no previous imaging study has investigated associations for both of these tasks within the same sample, so the current work provides valuable insights into how regional brain volumes reductions contribute differentially to each task. Further, previous work has often neglected to include a control sample. This is important so as to ascertain whether volume-performance associations are specific and unique to patients. Here, we derived volume estimates using FreeSurfer (offering better accuracy than older studies using VBM approaches) and investigated links to performance, across SZH and control groups, within a pre-defined set of frontal ROIs implicated by previous work.

SZH and control groups were well matched in terms of age and sex, although it should be noted that the control group were better educated and scored higher on IQ. As expected, reduced volumes were observed across most of the ROIs in patients, in line with the neuroimaging literature (Haijma et al., 2013). The patient group performed significantly worse on all the WCST measures, in accordance with the literature (Hartman et al., 2003; Prentice et al., 2008; Singh et al., 2017), but the Stroop deficit was present only as a strong trend (p = .055). In line with previous work showing that it is negative symptoms in particular that correlate with poorer reasoning and set shifting, higher negative symptoms were associated with worse WCST performance in the SZH group (Tyburski et al., 2021).

Regarding links to volume, a number of interesting associations were observed, although not all survived multiple comparison correction. Amongst patients only, the number of WCST categories successfully completed correlated positively with volumes of right caudal and rostral middle frontal regions, and these remained significant after FDR correction; in the rostral subdivision, the correlation coefficient was significantly different to that of the control group. To derive the ROI volumes, we used FreeSurfer, which automatically parcellates the middle frontal gyrus into rostral and caudal subdivisions (Desikan et al., 2006). The caudal part of the middle frontal gyrus includes BA9 as well as the premotor area and the frontal eye fields (Bruno et al., 2022), while the rostral portion encompasses BA46 and a portion of BA9 (Kikinis et al., 2010). Our finding of links between WCST performance and volumes within dorsolateral prefrontal (DLPFC) regions accords with a VBM study (Bonilha et al., 2008) which found that WCST performance measures correlated with volume in regions BA9 and BA46 (although a control group was not included); also, Hartberg et al. (2010) found correlations between WCST performance and right inferior and superior frontal cortical thickness, but the relationship did not differ between SZH and controls.

A meta-analysis of fMRI executive task studies (Buchsbaum et al., 2005) in healthy individuals concluded that right middle frontal is responsible for the inhibitory aspects of WCST performance. Given that we found volumes in these regions to correlate with number of categories completed on the WCST, this suggests that integrity of BA9 and BA46 might be of particular importance in SZH, with regard to inhibitory control, allowing better set-switching and category completion. Work by Wilmsmeier et al. (2010) supports this: they focused on set-shifting within the WCST, contrasting SZH with controls, using fMRI. After negative feedback events, controls showed activation in both left and right BA46, whereas patients showed activation in right BA46 only, again suggesting a critical role for right middle frontal in patients (Wilmsmeier et al., 2010). Relatedly, a concurrent TMS/fMRI study found that TMS stimulation of left BA9 led to less activation of right BA9 in SZH vs. healthy controls, pointing to impaired interhemispheric connectivity in patients, suggesting perhaps that SZH rely more on right-lateralised middle frontal as a compensatory strategy. Interestingly, Nestor et al. (2019) found that total left PFC volume correlated with WCST performance in controls but could find no associations with PFC volumes in SZH. Here, in a larger sample and a higher degree of frontal regional parcellation, we found right-lateralised volumes to be important in SZH but not controls. Taken together, these findings could be seen as an indicator of reduced lateralisation of function in SZH, as shown by various imaging studies, albeit usually in the domains of language and sensorimotor processing (Walter et al., 2003).

These dorsolateral prefrontal regions BA9 and 46 are also implicated in working memory (Owen et al., 2005), which is central for good performance on the WCST due to the need to keep track of feedback information while simultaneously updating and maintaining sorting rules. Abnormal frontal activity within dorsolateral prefrontal regions has been consistently shown in SZH performing working memory tasks (Glahn et al., 2005), one study found that right middle frontal activity was the only feature differentiating SZH from controls during a task that required explicit manipulation of information held in memory (Cannon et al., 2005). Thus, physiological disturbances in the dorsolateral prefrontal cortex appear to be highly important in relation to cognitive impairment in SZH, for the WCST (as observed here), and for the components of executive function that contribute to WCST performance (inhibitory control, set-shifting and working memory). Studies contrasting cognitively impaired vs near-normal SZH subgroups have identified volume and cortical thickness reductions in rostral and caudal middle frontal that characterise the impaired subgroup (Van Rheenen et al., 2018). Volumes in right middle frontal (BA9) have also been shown to correlate with levels of metacognitive insight amongst SZH (Spalletta et al., 2014), again supporting the notion that loss of volume in this region is an important contributor to impaired higher-order cognitive functioning in SZH. Various other lines of evidence also support the notion that this region is of particular importance for SZH, with studies identifying genes that are differentially expressed in BA46 in SZH (Dean et al., 2007), morphological changes in that region (Larsen et al., 2022), alongside recent evidence of viral signatures in BA46 which may represent a SZH biomarker (Ghorbani, 2023). Also, BA46 volume loss is consistently reported in the literature (Aoyama et al., 2007; Kikinis et al., 2010); interestingly, it has been shown that in bipolar patients, reduced volume within (specifically) right BA46 differentiates those with a history of psychosis from those without (Ekman et al., 2017). Here, volumetric reductions vs. controls were only evident in right caudal, not rostral middle frontal, but on WCST category and perseverative error scores, correlation coefficients differed significantly between the SZH and control groups scores in the right rostral middle frontal sub-region specifically, supporting the assertion that this region

is of unique importance in SZH.

No associations with any of the ROI volumes were seen in the control group. However, one noteworthy issue in relation to the control group is that of ceiling effects on the WCST, which reduces the ability to detect correlations with structural parameters. Given their higher performance, coupled with a smaller sample size, this could explain why no significant associations were found. Rüsch et al. (2007) found volumes (from VBM) in left dorsolateral prefrontal cortex to associate with WCST performance in chronic SZH but not controls, but we did not replicate this relationship here.

Uncorrected, there was also a positive correlation between WCST category performance and right hemisphere pars orbitalis volume. This was only evident in patients, although it should be noted that the correlation coefficient was not significantly different to that of the control group. Right pars orbitalis is thought to be involved in the generation of alternative hypotheses in cognitive tasks in which a variety of solutions are possible (Vartanian and Goel, 2005), providing a theoretical explanation for the volume-performance link found here. Previous work, comparing cognitively impaired SZH to controls, identified thinner cortices in this specific ventrolateral frontal region; this thinning was not present in cognitively-spared patients (Cobia et al., 2011).

On the SCWT (Stroop) task we identified various regions whose volumes correlated with performance, in SZH only. We found positive correlations with GMV in bilateral superior frontal, right caudal middle frontal, right pars opercularis and left anterior cingulate. Right rostral middle frontal showed a relationship, but this did not survive multiple comparisons correction. Amongst these, the right caudal and rostral middle frontal regions had correlation coefficients that were significantly different to controls, as did left superior frontal (right superior frontal at trend). These findings are in accordance with the limited previous work on this subject. Using VBM, Premkumar et al. (2008a) found associations with volumes of dorsomedial prefrontal cortex (which includes BA9 and anterior cingulate) in chronic SZH. In patients with early-onset schizophrenia, Guo et al. (2022) linked Stroop performance to higher GMV in right middle frontal gyrus, as seen here. Zhang et al. (2018) found associations with upper frontal, middle and medial frontal volumes in a first-episode cohort. However, none of these studies contrasted with a control group so it was uncertain whether these relationships were specific to SZH. Here, we provide evidence that volumes of right middle frontal regions, and superior frontal regions, might of unique importance in relation to the impaired Stroop performance often observed in SZH.

The links to right middle frontal regions are in accordance with the arguments around inhibition outlined above. The Stroop task is the paradigmatic test of inhibitory control, as it requires the participant to inhibit prepotent responses in the presence of distracting stimuli. SZH exhibit an increased Stroop interference effect (Westerhausen et al., 2011) and fMRI evidence suggests that patients show reduced activation in the DLPFC and/or the ACC while performing the task (Cadena et al., 2018; Köhler et al., 2019; Reid et al., 2010). As discussed, right middle frontal gyrus (BA9 and 46) are implicated in inhibitory control (Buchsbaum et al., 2005), and these regions also seem to be of particular importance with regard to SZH neuropathology and its impact on cognitive function. The association between Stroop interference and left superior frontal volume, unique to SZH, is also noteworthy in the context of a recent connectivity imaging study suggesting that connectivity between left superior frontal and the rest of the brain might represent a possible endophenotype for SZH (Ding et al., 2019): analyses of global brain connectivity showed that both patients and unaffected siblings had enhanced functional connectivity with left superior frontal gyrus specifically. Also, Li et al. (2017) found increased functional connectivity between left superior frontal gyrus and other key regions, in first episode SZH. Further, work using machine learning to differentiate SZH from controls based on structural MRI features indicated that volume reduction in left superior frontal was the most informative classifier amongst all frontal regions (Zhu et al., 2022).

For both WCST and Stroop, no relationships between brain volumes and performance were identified in the control group. Since we focused on frontal ROIs only, it is possible that volumetric relationships were present in other regions of the brain, for example in the temporal lobe as identified by previous work studying the volumetric correlates of WCST performance (Premkumar et al., 2008b). Our approach was to study relationships within a comprehensive and fine-grained set of frontal ROIs implicated by previous work, and this necessarily restricted our analyses. It is also noteworthy that the control group was smaller in size, and had a more restricted range of cognitive scores, than the SZH group. Although this situation is common in the literature, and sample sizes still compare favourably to much previous work in the field, this could contribute to the lack of structure-cognitive effects observed in controls. Future work should address this issue; it would also be useful to investigate whether the current study findings generalise to other executive function tasks as well.

We examined associations between volumes and symptom severity for all of the ROIs under study and no relationships were identified. This accords with previous work pointing to a lack of overlap between structure-cognition and structure-symptom associations in SZH (Alkan et al., 2021; Alkan and Evans, 2022a,b; Alkan and L. H. Evans, 2022; Goghari et al., 2014), as well as evidence that trajectories of change in symptoms and cognitive function are divergent (Hughes et al., 2003). Cognitive impairments in SZH are generally more stable than symptomatology, and tend not to respond to antipsychotic treatment, which again lends support to the notion of dissociable underlying neuropathological causes.

The current findings add important detail to the literature: to date, no study has explored the volumetric correlates of these two paradigmatic and commonly-used tests of executive function within the same cohort. Also, as highlighted previously, few amongst the limited number of previous studies examining volume-performance links on these tasks have included a control group, which limits interpretation around the uniqueness of the relationships identified. Thus, the current results address key knowledge gaps in the literature. Of particular significance is the finding that volumes of right middle frontal regions correlated with both WCST and Stroop performance in SZH only. This novel insight highlights the value of the approach taken,and as these relationships were unique to the patient group, points to a significant role for right middle frontal cortex in relation to executive dysfunction in SZH. This aligns well with various lines of evidence suggesting that neuropathology within right middle frontal regions (BA9 and BA46) might be of particular import in SZH. Further, no overlap regarding volumetric associations with symptom severity were observed, supporting the notion that the neuropathological processes underlying cognitive deficits are independent from those associated with other aspects of symptomology in SZH.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Erkan Alkan: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Veena Kumari:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Simon L. Evans:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.08.018.

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