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Neural correlates of global and specific cognitive deficits in schizophrenia

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ABSTRACT

Cognitive deficits are a core feature of schizophrenia, but the neural mechanisms that contribute to these characteristics are not fully understood. This study investigated whether volume of the dorsal lateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), hippocampus, and white matter were associated with impairment in specific cognitive domains, including executive functioning, working memory, verbal memory, verbal fluency, processing speed, versus global functioning. The multi-site data used in this study was collected from the Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP), and consisted of 206 healthy controls and 247 individuals with either schizophrenia or schizoaffective disorder. The neuroimaging data was segmented based on the Destrieux atlas in FreeSurfer. Linear regression analyses revealed that global cognition, executive functioning, working memory, and processing speed were associated with all brain structures, except the DLPFC was only associated with executive fucntion. When controlling for the global cognitive deficit, executive function was trending significance with white matter, but continued to be associated with the DLPFC and IFG, as did the association between processing speed and the hippocampus. These findings suggest that volumes of the DLPFC, IFG, hippocampus, and white matter are associated with the global cognitive impairment seen in schizophrenia, but some brain structures may also be specifically related to domain-specific deficits (primarily executive function) over-and-beyond the global cognitive deficit.

1. Introduction

Cognitive impairments among individuals with schizophrenia have been widely elucidated, with deficits apparent at the first-psychotic episode (Hoff et al., 1999) and remaining relatively stable throughout the chronic state (Meier et al., 2014), making them a core feature of schizophrenia. Understanding these deficits is particularly important given that cognitive ability has been associated with every-day functioning and quality of life for schizophrenia patients (Nuechterlein et al., 2011; Tolman and Kurtz, 2012). Furthermore, antipsychotic medications have minimal effects on cognitive impairments (Goldberg et al., 2007), indicating the need for further research into putative mechanisms underlying cognitive deficits.

Decades of research have revealed the presence of both specific and global cognitive deficits in schizophrenia (Dickinson et al., 2004; Schaefer et al., 2013; Sheffield et al., 2014; Shmukler et al., 2015). Evidence of the global deficit was highlighted by Dickinson et al. (2004, 2008), who showed that deficits in a multitude of cognitive domains (e.g. working memory, episodic memory, executive functioning, processing speed, verbal fluency, and attention) were mediated through a common factor that explained a significant proportion of diagnosis-related variance. The presence of a global deficit has been replicated by several other researchers (Mohamed et al., 1999; Keefe et al., 2006). There is also evidence to suggest differential impairments occur in areas of cognitive control (Lesh et al., 2011), episodic memory (Saykin et al., 1991), and processing speed (Schatz, 1998), even in the context of this global impairment. In fact, some researchers have suggested that these domain-specific deficits may contribute to a global deficit because they have wide-spread influences on other domains (Gold et al., 2009). Therefore, both global and specific deficits are core features of the cognitive impairment in schizophrenia, and both are critical to our understanding of the neural mechanisms underlying the complex deficits observed in psychotic disorders.

One potential mechanism contributing to such cognitive deficits are alterations in brain structure in schizophrenia (Steen et al., 2006; Fusar-Poli et al., 2013; Haijma et al., 2013). Volumetric reductions in schizophrenia have been attributed to abnormalities in dendritic spines and synapses, which can disrupt the neural circuitry underlying cognition (Flashman and Green, 2004). Some aspects of brain structure that exhibit volumetric reductions include the dorsolateral prefrontal cortex (Volpe et al., 2012), hippocampus (Nelson et al., 1998), and total white matter (Haijma et al., 2013). Importantly, these brain structures

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have been found to be critical contributors to the types of cognitive deficits found among individuals with schizophrenia (Barch and Ceaser, 2012; Watson et al., 2012). For instance, numerous studies have suggested that the DLPFC is involved in executive functioning and working memory (Kawada et al., 2009; Ehrlich et al., 2012), as well as some aspects of episodic memory (Minatogawa-Chang et al., 2009) and processing speed (Eckert et al., 2010). Further, a number of studies have suggested that the IFG is important for verbal memory and verbal fluency (Iwashiro et al., 2016). Multiple studies report that the hippocampus plays a critical role in executive functioning (Guo et al., 2014), working memory, verbal episodic memory, and verbal fluency (Schobel et al., 2009; Ehrlich et al., 2012; O'Shea et al., 2016). Additional studies show that white matter integrity may also be important for verbal fluency (Lee et al., 2007) and processing speed (Karbasforoushan et al., 2015).

The goal of the current study was to investigate whether brain volume of the DLPFC, hippocampus, IFG, and white matter are associated with domain-specific and/or global deficits in cognitive ability, as well as determine whether brain volume relationships are specific to any cognitive domain, above and beyond the global deficit. Based on previously reported associations, we hypothesized that 1) Global cognition and executive functioning would be associated with all brain structures. 2) Working memory would be associated with DLPFC and hippocampal volume. 3) Verbal episodic memory would be associated with hippocampal and IFG volume. 4) Verbal fluency would be associated with hippocampal, IFG, and white matter volume. 5) Processing speed would be associated with DLPFC and white matter volume. 6) Executive functioning would remain associated with all brain structures, even after controlling for global cognition.

To test this, we use a relatively large sample of individuals with schizophrenia and healthy controls in addition to a well-established comprehensive cognitive assessment: the Brief Assessment of Cognition in Schizophrenia (BACS). Although previous studies have examined general IQ versus specific cognitive domains (Antonova et al., 2005), the innovation of the current work is to investigate the magnitude of correlations between the generalized cognitive deficit and domain-specific deficits. Delineating the differences between distinct structure-function relationships is essential for understanding how structural brain abnormalities contribute to the complex constellation of cognitive impairments in schizophrenia.

2. Methods

2.1. Participants

The data used in this study was collected from the B-SNIP (Tamminga et al., 2013), and consisted of 206 healthy controls and 247 individuals with either schizophrenia (59.1%) or schizoaffective disorder (40.9%). Participants were recruited from the following six sites: Baltimore MD, Boston MA, Chicago IL, Dallas TX, Detroit MI, and Hartford CT. All sites used identical protocols and test assessments were approved by their local Institutional Review Board. Researchers from all sites underwent initial training and attended monthly cross-site meetings to maintain reliability (Tamminga et al., 2013). Structural MRI and cognitive data was collected from all participants included in the current study.

The recruitment of healthy controls was initiated through flyers, electronic advertisements, and research registries. Patients with schizophrenia or schizoaffective disorder were recruited through mental health providers, electronic advertisements, and talks at community organizations (Hill et al., 2013). All patients were required to have a diagnosis of schizophrenia or schizoaffective disorder with a history of psychosis to meet inclusion criteria. The Structured Clinical Interview for DSM-IV (SCID, (First et al., 1995) was used to assess clinical diagnosis. Exclusion criteria for all subjects included: no history of seizures, neurological disorders that affect cognition, or head injuries with a loss of consciousness >10 min. Participants could not have a diagnosis of substance abuse in the past 30 days or substance dependence in the past 6 months, and all participants were required to pass a urine drug screen on the day of testing. Additional exclusion criteria for healthy controls included: history of recurrent depression or a psychotic disorder, and immediate family members with a history of these disorders.

The demographic characteristics of all participants are displayed in Table 1.

2.2. Cognitive measures

Cognitive function of all participants was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS, (Keefe et al., 2008), which is a valid and reliable assessment that has been widely used in schizophrenia research. This cognitive assessment is approximately 30 min long and consists of tests pertaining to five different cognitive domains including executive functioning, working memory, verbal episodic memory, verbal fluency, and processing speed. Executive functioning was measured by the Towers Task, which asks participants to rearrange a set of balls using the lowest amount of moves possible. Working memory was assessed by the Digital Sequencing task, which asks participants to remember a random order of numbers and recall them from smallest to largest. Verbal episodic memory was assessed by the List Learning task, which asks participants to read fifteen words and repeat as many as possible. Verbal fluency was assessed by the Semantics Fluency and Letter Fluency tasks, which asks participants to generate as many words possible given a certain category or letter. Processing speed was measured by the Symbols Coding task, which asks participants to use a key to match as many letters and numbers together within 90 s. Global cognition was defined as the first factor in a principal axis factor analysis that included all BACS subtests (Hochberger et al., 2016), which was done on this sample and explained 61% of the variance in cognitive function. Scores on the BACS were age-normed and z-scored. *Z*-scores ≥ |4.0| were truncated to limit the impact of outliers.

2.3. Neuroimaging measurements

Structural MRI data was acquired from T_1–weighted structural brain scans at all six sites. Specific imaging protocols differed slightly across sites (Table S1), however, all T1 images included $1 \times 1 \times 1.2$ mm voxels (Meda et al., 2015). The neuroimaging data was volumetrically segmented and analyzed in an automated manner using the Destrieux

Table 1
Demographic characteristics of healthy controls and schizophrenia patients.

Demographics mean (standard deviation)	Healthy controls $n = 205$	Schizophrenia $n = 247$	Statistics
Age (years)	36.4(11.7)	33.48(11.6)	$f(1,450) = 0.9$, $p = 0.008$
Gender (male/female)	87/118	154/93	$X2 = 17.8$, $p < 0.001$
Ethnicity (Caucasian/African American)	62%/28%	53%/39%	$X2 = 5.8$, $p = 0.02$
Subject education (years)	14.8(2.3)	13.1(2.2)	$f(1,445) = 2.0$, $p < 0.001$
Father education (years)	13.6(2.1)	13.9(3.6)	$f(1,375) = 0.01$, $p = 0.42$
Mother education (years)	13.2(3.2)	13.5(3.0)	$F(1,413) = 0.9$, $p = 0.38$

atlas (Destrieux et al., 2010) in the FreeSurfer software (Fischl, 2012). The cortical regions used to define the DLPFC were the sum of the Middle Frontal Gyrus and the Middle Frontal Sulcus, which corresponds to parcellation units 15 and 53, respectively. The cortical regions used to define the IFG were the sum of the opercular and triangular part of the IFG, which corresponds to parcellation units 12 and 14, respectively. Hippocampus volume was generated using the ASEG segmentation file, and Total White Matter volume was taken from ASEGWM segmentation. FreeSurfer data from all subjects was visually inspected by a single rater (J.M.S) to assess accuracy of white/gray matter automatic segmentation. Six subjects had poor segmentation and when excluding these six participants the results remained consistent. Given differences in neuroimaging parameters across sites, analyses were performed that included B-SNIP site as a covariate, with the same results as our main findings.

2.4. Statistical analyses

All statistical analyses were completed with SPSS software version 24. Before computing primary analyses, data was tested for normality using Q-Q plots, and multivariate outliers were identified using the Mahalanobis distance. A total of six multivariate outliers (4 patients and 2 healthy controls) were excluded from the data set before statistical analysis began. Linear regressions were used to assess relationships between cognition and brain volume. Cognitive function was always the dependent variable and predictors included: region of interest (ROI) brain volume, age, gender, and diagnosis group (when analyzing all subjects together). Total brain volume (minus the ROI for that analysis) was also included as a predictor, to assess the specificity of the relationship between ROI and cognition. For white matter, total gray matter volume was included as a predictor. Interaction variables were included to assess differences between groups in the relationship between brain volume and cognition. A second level of linear regressions were conducted, which included global cognition as an additional predictor in order to determine if associations between specific cognitive domains and brain volume remained significant even when controlling for general cognition. Post-hoc tests were performed to assess differences in correlation magnitude between brain ROIs and specific cognitive tasks for all subjects, while controlling for age and gender, using methods from Meng et al. (1992). Additional linear regressions were performed with site dummy codes included as predictors, and all significant associations reported in the results section remained consistent.

3. Results

3.1. Group difference in cognition and brain volume

As previously reported (Tamminga et al., 2014), patients were significantly impaired in all cognitive domains, including executive functioning ($F(1, 431) = 46.8$, $p < 0.001$), working memory ($F(1,432) = 85.9$, $p < 0.001$), verbal memory, ($F(1, 432) = 90.4$, $p < 0.001$), verbal fluency ($F(1,432) = 56.5$, $p < 0.001$), processing speed ($F(1,433) = 190.3$, $p < 0.001$), and global cognitive functioning ($F(1,432) = 206.9$, $p < 0.001$).

Patients had significantly reduced hippocampal volume compared to controls ($F(1,449) = 6.5$, $p = 0.011$) but did not have significant volumetric reductions in the DLPFC ($F(1,449) = 0.2$, $p = 0.62$), IFG ($F(1,449) = 0.2$, $p = 0.62$), or total white matter ($F(1,449) = 0.1$, $p = 0.78$).

3.2. Global cognition

As shown in Table 2 and Fig. 1, global cognition was significantly associated with all brain regions of interest (trend level for DLPFC) even when controlling for brain volume outside the regions of interest. No significant interactions were found between any brain structure and diagnostic group (Table 2), suggesting that these associations were present across patients and controls. To confirm this, we conducted follow up analyses within groups. Global cognition was associated with the IFG, hippocampus and white matter in both controls and patients.

3.3. Executive functioning

As shown in Table 2, executive functioning was significantly associated with all brain regions of interest even while controlling for brain volume outside the regions of interest. When controlling for the global cognitive deficit, executive functioning was no longer significantly associated with the hippocampus ($p > 0.10$), but continued to be associated with the other three brain structures (Fig. 2): DLPFC ($\beta = 0.09$, $t = 2.2$, $p = 0.03$), IFG ($\beta = 0.14$, $t = 3.23$, $p = 0.001$), and a trend for white matter ($\beta = 0.08$, $t = 1.76$, $p = .08$). There were no significant interactions between brain structures and diagnostic group in the prediction of executive functioning (Table 2), again suggesting that these associations were present across patients and controls. To confirm this, we conducted follow up analyses within groups, and executive function was related to all brain metrics in both groups individually.

3.4. Working memory

Working memory (Table 2) was significantly associated with the IFG, hippocampus and white matter, but not with the DLPFC. However, working memory did not remain significantly associated with these

Table 2
Regional brain volume predicting cognitive function while controlling for age, gender, total brain volume, and diagnostic group (between-group only).

Regression analyses including groups				Analyses within each group	
Cognitive domain	Brain area	Main effect (β)	Interaction (β)	Healthy controls (β)	Schizophrenia (β)
Global cognition	DLPFC	0.10$^{\sim}$	0.01	0.08	0.12
	IFG	0.19***	−0.08	0.25***	0.20***
	Hippocampus	0.17***	0.02	0.19**	0.21**
	White matter	0.18***	0.01	0.25*	0.19*
	Gray matter	0.15***	−0.04	0.27***	0.11
Executive functioning	DLPFC	0.17***	0.06	0.18*	0.19*
	IFG	0.27***	0.30	0.33***	0.28***
	Hippocampus	0.19***	0.04	0.22***	0.20***
	White matter	0.21***	0.02	0.28***	0.20*
	Gray matter	0.17***	−0.07	0.29***	0.08
Working memory	DLPFC	0.04	0.01	NA	NA
	IFG	0.11*	−0.17	0.13	0.10
	Hippocampus	0.12*	−0.01	0.14$^{\sim}$	0.13$^{\sim}$
	White matter	0.14*	−0.03	0.20$^{\sim}$	0.11
	Gray matter	0.13**	−0.08	0.25***	0.05
Verbal episodic memory	DLPFC	0.04	0.05	NA	NA
	IFG	0.11*	0.06	0.13	0.12
	Hippocampus	0.10*	0.07	0.06	0.16*
	White matter	0.05	0.03	NA	NA
	Gray matter	0.06	−0.02	NA	NA
Verbal fluency	DLPFC	0.06	−0.08	NA	NA
	IFG	0.10$^{\sim}$	−0.35	0.06	0.10
	Hippocampus	0.06	−0.02	NA	NA
	White matter	0.08	0.01	NA	NA
	Gray matter	0.09	−0.01	NA	NA
Processing speed	DLPFC	0.08	0.01	NA	NA
	IFG	0.17***	0.16	0.23**	0.17*
	Hippocampus	0.18***	0.01	0.20**	0.23***
	White matter	0.19***	−0.01	0.25**	0.20**
	Gray matter	0.13***	0.02	0.13	0.02

$^{\sim}$ $p \le 0.10$.
* $p \le 0.05$.
** $p \le 0.01$).
*** $p \le 0.005$.

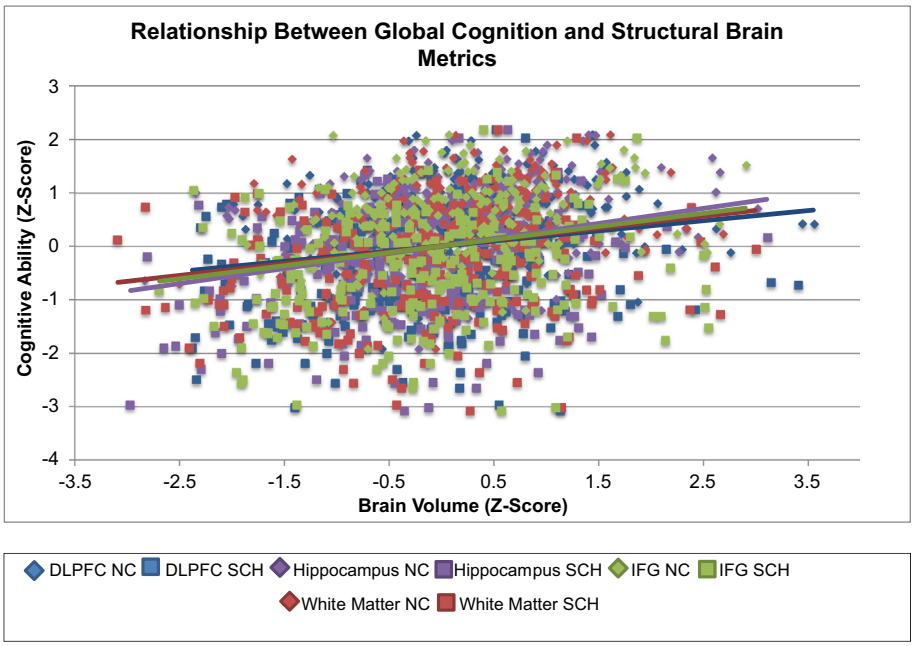

Fig. 1. Positive associations between global cognition and brain structure, controlling for age, sex, and gray matter volume. Larger Hippocampal volume ($\beta = 0.19$, $p < 0.005$), IFG volume ($\beta = 0.19$, $p < 0.005$), white matter volume ($\beta = 0.18$, $p < 0.005$) were significantly associated with better cognitive ability in all participants, while DLPFC volume was associated at a trend-level ($\beta = 0.10$). NC = normal control; SCH = schizophrenia. DLPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus.

three regions when controlling for the global cognitive deficit ($p's > 0.19$).

3.5. Verbal episodic memory

Verbal episodic memory (Table 2) was associated with IFG and hippocampal volume, and not with the DLPFC or white matter, but theses relationship did not hold when controlling for the global cognitive deficit ($p's > 0.26$).

3.6. Verbal fluency

Verbal fluency (Table 2) was not associated with any brain region of interest, except trend level with IFG, nor were there any significant interactions.

3.7. Processing speed

Processing speed (Table 2) was not associated with the DLPFC, but was associated with the IFG, hippocampus, and white matter even when controlling for brain volumes outside the regions of interest. However, none of these relationships remained significant when controlling for the global cognitive deficit except for the hippocampus ($\beta = 0.07$, $t = 2.28$, $p = 0.02$).

3.8. Total gray matter covariate

The covariate total gray matter volume (Table 2) was correlated with global cognition, executive function, working memory and processing speed, but not verbal memory or verbal fluency. There were

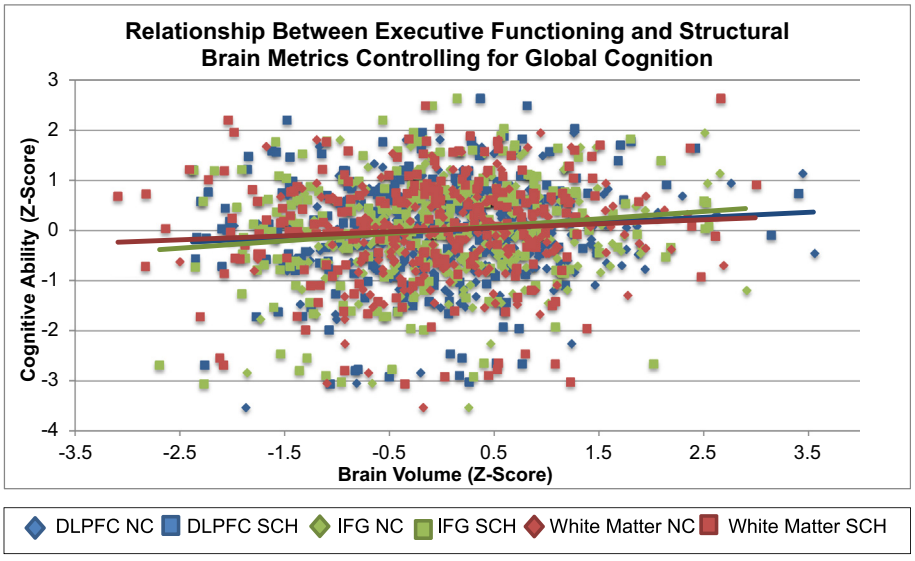

Fig. 2. Executive functioning ability was positively associated with DLPFC ($\beta = 0.17$, $p < 0.005$), IFG ($\beta = 0.27$, $p < 0.005$) and white matter volume ($\beta = 0.21$, $p < 0.005$) in all participants, controlling for age, sex, and global cognition. NC = normal control; SCH = schizophrenia. DLPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus.

no significant interactions with group, but separate analyses within group showed significant relationships only in controls and not in patients.

4. Discussion

The findings of this study provide evidence that volume of the DLPFC, IFG, hippocampus, and white matter are associated with global cognition, and with executive function after controlling for global cognition (except for hippocampus). Further, these associations were significant when controlling for total gray matter volume and demographic variables, suggesting that these specific brain structures are critical for cognitive functioning. These structure-function relationships (other than total gray matter) were observed in both healthy controls and schizophrenia patients, indicating that regardless of diagnostic group, brain volume of these structures appears to be associated with cognitive functioning. However, hippocampal volume was significantly reduced in schizophrenia, suggesting the potential for particular vulnerability in schizophrenia to the cognitive impairments associated with hippocampal volume.

Consistent with the previously reported results from the full B-SNIP sample (Tamminga et al., 2014), patients were significantly impaired across all domains, in line with the conceptualization that a global deficit is present in schizophrenia (Dickinson and Gold, 2008). Furthermore, a global deficit, as measured by the shared variance in performance across multiple cognitive domains, was associated with volume of all investigated brain structures, indicating that a more severe global cognitive deficit is associated with volumetric reductions in the DLPFC, IFG, hippocampus, and white matter. Further, these relationships remained even when controlling for brain volume outside the regions of interest, suggesting some specificity of these relationships. These findings are consistent with the hypotheses that the global deficit would be associated with multiple neural mechanisms and widespread volumetric reductions of gray matter (Antonova et al., 2004) and white matter (Kubicki et al., 2005).

We also observed some evidence of specificity of relationships between brain structure and cognition, beyond the generalized deficit. Post-hoc analysis revealed that volumetric reductions in the DLPFC, IFG, and white matter were specifically related to deficits in executive functioning, above and beyond the global deficit. The brain-behavior relationship between the DLPFC, IFG, white matter, and executive functioning has been consistently reported both functionally (Hampshire et al., 2010) and structurally (Premkumar et al., 2008; Kawada et al., 2009; Guo et al., 2014). However, this is one of the first reports demonstrating specific associations between brain volume of these structures and executive function, while controlling for general cognitive ability. Executive function is a critical facet of general cognitive ability believed to facilitate continuous interactions between multiple cognitive processes, in order to support goal-directed behavior (Gilbert and Burgess, 2008). Therefore, these results suggest that DLPFC, IFG, and white matter volumes are not only important for overall cognition, but may more specifically contribute to cognitive ability through distinct support of executive functions. In addition, we saw a specific relationship between hippocampal volume and processing speed, even controlling for the global deficit. While unexpected, this finding is consistent with the literature in aging suggesting that hippocampal function and structure may be important for this cognitive domain (Papp et al., 2014).

Several limitations exist within the current study. One potential limitation is that the BACS cognitive assessment, although reliable and well-validated, may be less robust at identifying isolated domain-specific deficits relative to other types of tasks designed to specifically isolate particular cognitive functions, such as those developed by the Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia Consortium (Gold et al., 2012). Additionally, the neuroimaging data was segmented using the Destrieux atlas in Freesufer, but this parcellation may not capture important subdivisions of the DLPFC that might show more fine grained relationships. Lastly, the majority of schizophrenia patients in this study were taking antipsychotic medications. Although there is evidence that cognitive deficits are not the consequence of medications (Goldberg and Weinberger, 1996), the effects of medications on brain changes are still being investigated (Ho et al., 2011).

Considering that this study is one of the first to investigate the structural neural correlates of global and domain specific deficits, it is important that our findings are replicated and expanded on by examining whether other brain regions might show evidence of more specific relationships to domains such as verbal episodic memory or verbal fluency. Additionally, future research is necessary to determine if these associations between brain volume and cognitive impairments are similar in first-psychotic episode patients and treatment-naïve patients, or whether they change with time.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.06.017.

Conflict of interest

RJJ has no conflicts to report. JMS has no conflicts to report. DMB has received grants from the Brain & Behavior Research Foundation and the National Institutes of Health (NIH), and is a consultant for Pfizer, Amgen, Upsher-Smith and Takeda on studies related to the treatment of negative symptoms in schizophrenia.

Contributors

JMS & DMB have access to the study data and take responsibility for the integrity of the data and accuracy of the data analysis. RJJ and JMS drafted the initial manuscript and DMB provided critical revision. All authors developed the analysis concept and design and aided in interpretation and provided critical revisions. All authors approved the final version of the paper for submission.

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The funding source had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

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