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Impaired cognitive control mediates the relationship between cortical thickness of the superior frontal gyrus and role functioning in schizophrenia

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ABSTRACT

Structural abnormalities in the lateral prefrontal cortex (LPFC) are well-documented in schizophrenia and recent evidence suggests that these abnormalities relate to functional outcome. Cognitive control mechanisms, reliant on the LPFC, are impaired in schizophrenia and predict functional outcome, thus impaired cognitive control could mediate the relationship between neuroanatomical abnormalities in the LPFC and functional outcome. We used surface-based morphometry to investigate relationships between cortical surface characteristics, cognitive control, and measures of social and role functioning in 26 individuals with schizophrenia and 29 healthy controls. Results demonstrate that schizophrenia participants had thinner cortex in a region of the superior frontal gyrus (BA10). Across all participants, decreased cortical thickness in this region related to decreased cognitive control and decreased role functioning. Moreover, cognitive control fully mediated the relationship between cortical thickness in the superior frontal gyrus and role functioning, indicating that neuroanatomical abnormalities in the LPFC adversely impact role functioning via impaired cognitive control processes.

1. Introduction

Deficits in social and role functioning are pervasive and disabling impairments in schizophrenia (APA, 2000; Couture et al., 2006). Effective management of the complex demands of daily life requires engagement of top-down inhibitory and facilitatory processes necessary to maintain task-relevant processing and coordinate appropriate behavioral responses. Impairments in these self-regulatory processes, involving cognitive control mechanisms reliant on a fronto-parietal network (Duncan and Owen, 2000; Bush and Shin, 2006; Lesh et al., 2011), may contribute to poor social and role functioning (Heatherton and Wagner, 2011). Neurofunctional and morphological abnormalities in the cognitive control network are well-established in schizophrenia, particularly in the lateral prefrontal cortex (LPFC; Shenton et al., 2001; Barch, 2005), such that LPFC dysfunction has been proposed as a biomarker for the illness (Woodward et al., 2009; Lesh et al., 2011). However, the relationship between LPFC abnormalities and functional impairment has received limited attention, thus how they impact functioning remains unknown. One proposal is that LPFC abnormalities reflect a neurobiological vulnerability that affects functioning via impaired cognitive control.

Individuals with schizophrenia consistently show abnormal activation in the LPFC during cognitive control tasks (Minzenberg et al., 2009), paralleling well-documented impairments on behavioral measures (Heinrichs and Zakzanis, 1998). Damage to these brain regions is associated with similar deficits in response inhibition and cognitive control (Burgess et al., 2000; Miller, 2000), suggesting that the observed neurofunctional abnormalities in the cognitive control network in schizophrenia may be rooted in neuroanatomical abnormalities. Consistent with this, structural neuroimaging studies routinely demonstrate abnormalities in the LPFC (e.g. Shenton et al., 2001; Kuperberg et al., 2003; Honea et al., 2005; Wisco et al., 2007; Venkatasubramanian et al., 2008; Janssen et al., 2009). Moreover, recent findings show a pattern of reduced cortical thickness/gray matter volume in lateral prefrontal regions relating to increased symptoms (Zierhut et al., 2013) and decreased global functioning (Chemerinski et al., 2002; Prasad et al., 2005; Kasparek et al., 2009), indicating a relationship between LPFC morphology and core clinical characteristics of schizophrenia. Given the role of LPFC regions in cognitive control, it is possible that impaired cognitive control mediates this relationship.

Prior research indicates a relationship between LPFC structure and performance on tasks assessing executive functioning and cognitive control in schizophrenia. Reduced gray matter volume (GMV) relates to poor performance on the Wisconsin Card Sorting Task (WCST; Seidman et al., 1994; Ho et al., 2003), the continuous performance task (Salgado-Pineda et al., 2004), the N-back (Zierhut et al., 2013) and the Controlled Oral Word Association Test (COWAT; Minatogawa-Chang et al., 2009)—tasks that involve the core aspect of cognitive control (i.e. the ability to inhibit prepotent responses in favor of subdominant ones), and are known to predict functional outcome

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(Green, 1998; Addington and Addington, 2000; Milev et al., 2005). Collectively, these data suggest that structural abnormalities in the LPFC affect functioning through cognitive control processes.

This study had two aims: first, we sought to compare cortical thickness and surface area between groups, with particular interest in hypothesized group differences in the LPFC. Second, we sought to examine the relationship between identified group differences in cortical thickness and/or surface area to behavioral measures of cognitive control and functioning. Specifically, we investigated whether cognitive control mediates the relationship between disease-related variations in LPFC thickness/surface area and measures of functioning. We used surface-based morphometry (SBM) methods to investigate the neuroanatomical characteristics of the cortical surface in a sample of schizophrenia and healthy control participants. SBM offers the ability to examine cortical thickness and surface area independently, which despite sharing high heritability, are believed to be determined by separate genetic mechanisms (Panizzon et al., 2009; Winkler et al., 2010). Therefore examining them separately in relation to putative cognitive endophenotypes may be a more sensitive measure of neurobiological substrates of functional impairments in schizophrenia than the more commonly used measure of GMV. Moreover, since cortical volume is derived from both thickness and surface area, the averaging of these two features could obscure pathophysiological characteristics present independently in each feature (Fornito et al., 2008), and their relationship to functioning measures. Here we use Freesurfer, an SBM analysis suite (http://surfer.nmr.mgh.harvard.edu), that measures cortical thickness within an accuracy of .2 mm (Rosas et al., 2002) and has been well validated across MRI protocols (Fischl and Dale, 2000).

For our measure of cognitive control we used the category fluency animal naming test (Spreen and Strauss, 1991). Although primarily classified as a verbal fluency task testing semantic processing, the category fluency task has long been considered an index of frontal lobe executive functioning (Baddeley et al., 1997) given the task's demands for a directed, cognitive control dependent search for words, facilitation of efficient set switching between sub-categories of words, and inhibition of non-category items (Rende et al., 2002). Poor performance on category fluency task has been associated with abnormal neural function (Kubota et al., 2005; Azechi et al., 2010) and structure (Minatogawa-Chang et al., 2009) in the LPFC in schizophrenia, indicating that the task is a sensitive assessment of LPFC dependent cognitive control processes.

Our hypotheses are as follows: 1) Compared to healthy participants, schizophrenia participants will have reduced cortical thickness and surface area in the LPFC; 2) Reduced cortical thickness and/or surface area in regions with identified group differences will be related to decreased cognitive control and decreased functioning; 3) Cognitive control will mediate the relationship between cortical thickness/surface area and functioning.

2. Methods

2.1. Participants

26 individuals with schizophrenia or schizoaffective disorder and 29 healthy controls matched for age, gender, years of education and IQ were recruited from the Greater Boston area (Table 1). Inclusion criteria for all participants are as follows: age 18–65, IQ above 70, primary English speaker, no history of head trauma, neurological or major medical illness, no substance abuse within six months, and no current/past substance dependence. Inclusion criteria for schizophrenia participants are as follows: diagnosis of schizophrenia or schizoaffective disorder, no comorbid axis I disorders, and no history of electroconvulsive therapy. Inclusion criteria for healthy participants are as follows: no current/past axis I disorders, no first-degree relative with a psychotic disorder, and scores within 1.5 standard deviations of the population mean on five measures of schizotypal personality: the perceptual aberration scale (Chapman et al., 1976), magical ideation scale (Eckblad and Chapman, 1983), referential thinking scale (Lenzenweger et al., 1997), physical anhedonia scale (Chapman et al., 1976), and revised social anhedonia scale (Eckblad et al., 1982). Psychopathology was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 2002). PhD-level clinical psychologists (LMT, SHL) conducted clinical assessments, supervised by a licensed clinical psychologist (CIH).

Harvard University Institutional Review Board approved the study. Participants gave written informed consent and were paid for their participation.

2.2. Assessments

2.2.1. Cognitive control

We assessed cognitive control using the category fluency animal naming task (Spreen and Strauss, 1991) in which participants have 60 s to generate as many animal names as possible. Although typically classified as a verbal fluency task testing semantic processing, optimal task performance also requires intact lateral prefrontal mediated cognitive control processes to direct and maintain semantic activation in a task appropriate context (Rende et al., 2002). Therefore the outcome measure – the total number of animals named – can be interpreted as a measure of cognitive control processes; higher scores reflect better cognitive control.

2.2.2. Social and role functioning

Clinician rated social and role functioning was obtained using the Global Functioning: Social Scale (GFS; Auther et al., 2006) and Global Functioning: Role Scale (GFR; Niendam et al., 2006). The GFS assesses four main areas of social functioning: involvement with family members, age appropriate intimate relationships, quantity and quality of peer relationships, and level of peer conflict. The GFR assesses functioning in school, work, or as a homemaker, depending on age and the primary role of the individual. Scores range from 1 to 10 on both scales; higher scores indicate better functioning.

2.3. Magnetic resonance imaging

High resolution anatomical brain images were acquired on a Siemens 3T TimTrio scanner (Siemens Sonata, Erlangen, Germany) with a 32 channel whole-head coil using a 3-dimensional T1-weighted multi-echo magnetization-prepared rapid acquisition of gradient-echo (MEMPRAGE) sequence (176 contiguous 1 mm anterior commissure–posterior commissure slices; acceleration factor of 2; voxel size, 1 mm × 1 mm × 1 mm; flip angle, 7 degrees; TR, 2530 ms; TE, 7.22 ms; FOV, 256 mm × 256 mm; matrix size, 256 × 256; total acquisition time = 6 min, 44 s). Head movement was minimized using foam padding in the head coil and subjects wore earplugs to muffle scanner noise.

2.4. Statistical analysis

All variables were screened for normalcy and outliers. Two variables identified as significantly skewed (role functioning and mean cortical thickness in the superior frontal gyrus) were log transformed. Two participants in the healthy control group did not complete the category fluency task; missing scores were replaced with the mean of the group.

Analysis of behavioral data was conducted in IBM SPSS v. 20.0. We used chi-square and independent *t*-tests to assess group differences on demographic and behavioral variables, and Pearson correlations to assess relationships between measures of cognitive control and functioning.

2.4.1. SBM analysis

Cortical thickness and surface area were calculated for each subject in Freesurfer (version 5.1.0), using procedures detailed in prior publications

Table 1
Demographics and behavioral data.

	SZ group	Control group	Differences between groups
N	26	29	
Gender (M/F)	16/10	20/9	$X^2(1) = 0.33, p = 0.56$
Age	38.69 (10.28) [21–58]	33.76 (12.38) [18–55]	$t(53) = 1.60, p = 0.12$
Education	14.69 (2.15) [10–18]	14.59 (2.64) [11–21]	$t(53) = 0.16, p = 0.87$
IQ[a]	108.08 (13.32) [82–133]	110.69 (11.60) [87–130]	$t(53) = 0.78, p = 0.44$
Diagnosis[b]			
Schizophrenia N (%)	20 (77%)		
Schizoaffective N (%)	6 (23%)		
Age of illness onset	22.24 (4.94) [13–34]		
Length of illness	16.40 (12.02) [1–42]		
Antipsychotic medication[c]			
Atypical N (%)	19 (73%)		
Typical N (%)	3 (12%)		
None N (%)	3 (12%)		
CPZ equivalent[d]	461.11 (416.91) [0–1600]		
Cognitive control[e]			
Category fluency	47.08 (9.21) [32–66]	55.00 (8.61) [39–74]	$t(53) = 3.30, p < 0.01, d = 0.91$
Functioning			
Social functioning	6.08 (1.79) [3–9]	8.66 (1.26) [6–10]	$t(53) = 6.23, p < 0.001, d = 1.71$
Role functioning	5.31 (1.89) [2–8]	8.38 (1.18) [6–10]	$t(53) = 7.31, p < 0.001, d = 2.01$

Note: data represent mean (SD) [range] unless otherwise indicated.
[a] Full scale IQ scores were estimated using the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI).
[b] Subtypes of the 20 participants with schizophrenia were: 16 paranoid, 3 residual, and 1 undifferentiated. Subtypes of the 6 participants with schizoaffective disorder were: 3 bipolar and 3 depressive.
[c] One patient did not report medication.
[d] CPZ = chlorpromazine equivalents calculated using methods described in Woods (2003).
[e] Cohen's d effect size.

(Dale et al., 1999; Fischl et al., 1999). Cortical thickness and surface area group statistical maps were created by mapping each subject's surface data to a common spherical coordinate system and smoothed using a 10 mm full-width-half-maximum Gaussian filter. To examine group differences in cortical parameters we conducted general linear models (GLMs) comparing cortical parameter maps (thickness/surface area) between healthy and schizophrenia individuals at every vertex over the whole cortex for each hemisphere (i.e. whole cortex vertex-by-vertex analysis). For all analyses left and right hemispheres were tested separately.

We corrected for multiple comparisons using Monte-Carlo permutation cluster analyses conducted in Freesurfer (Hagler et al., 2006) with a vertex threshold of $p < 0.05$ (two-tailed) and a cluster-wise threshold (p_{cw}) of $p_{cw} < 0.025$ (i.e. $p_{cw} < 0.05$ Bonferroni corrected across two hemispheres). This statistical approach has been used in prior publications using SBM methods in schizophrenia samples (e.g. Wisco et al., 2007). Statistics for identified clusters, including cluster size (mm^2) and number of vertices, MNI coordinates, and p_{cw} are reported.

To account for confounding effects of variables known to influence SBM the following covariates were entered into all models: age, gender, and mean cortical parameter for the given hemisphere in the given analysis (i.e. mean cortical thickness for the whole left hemisphere was entered into models testing group/variable related effects on cortical thickness in the left hemisphere; idem for surface area analyses).

2.4.2. Mediation analysis

We conducted mediation analysis across all participants using bootstrapping, a nonparametric resampling procedure that constructs confidence intervals for the indirect effect of the proposed mediator (Hayes, 2009). We used the SPSS macro PROCESS from Hayes (2013) to obtain estimates of the total, direct, and indirect effects and associated 95% confidence intervals using the recommended 5000 bootstrap samples. PROCESS also produces two measures of effect size: R^2_{med}, which accounts for the portion of variance in the outcome variable that the predictor and mediator share, and κ^2 ("kappa squared") which expresses the size of the indirect effect in terms of a ratio to the maximum possible indirect effect that could have been found. For κ^2 a small effect is 0.01, a medium effect is 0.09, and a large effect is 0.25 or above (Preacher and Kelley, 2011).

3. Results

There were no group differences in age, gender, IQ, or years of education (Table 1). Consistent with prior literature, schizophrenia participants performed significantly worse than healthy individuals on category fluency ($t(53) = 3.30, p = 0.002$), indicating impaired cognitive control capabilities. Schizophrenia participants also demonstrated expected deficits in social ($t(53) = 7.31, p < 0.001$) and role ($t(53) = 6.23, p < 0.001$) functioning.

Hypothesis 1. Schizophrenia participants have abnormalities in cortical thickness and cortical surface area.

Group comparisons of cortical thickness maps identified one cluster where schizophrenia participants had thinner cortex compared to healthy controls in the left superior frontal/middle frontal gyral region of BA10 (MNI: x = −10.4, y = 60.9, z = 19.6; $p_{cw} = 0.017$; surface area = 811.78 mm^2) (Fig. 1). No clusters showing group differences were detected in the right hemisphere. There were no clusters detected in either hemisphere where schizophrenia participants had increased thickness compared to healthy individuals. Results did not change with the inclusion of antipsychotic medication dose and duration of illness as covariates.

No clusters showing significant group differences in cortical surface area were identified in either direction, in either hemisphere. No further analyses using cortical surface area were conducted.

Hypothesis 2. Reduced cortical thickness in regions with identified group differences will be related to decreased performance on behavioral measures of cognitive control and decreased functioning.

To test our second hypothesis we extracted mean cortical thickness data from the cluster in the superior frontal gyrus (SFG) where schizophrenia patients had thinner cortex compared to healthy controls and conducted Pearson correlations with our behavioral measures (Table 2).

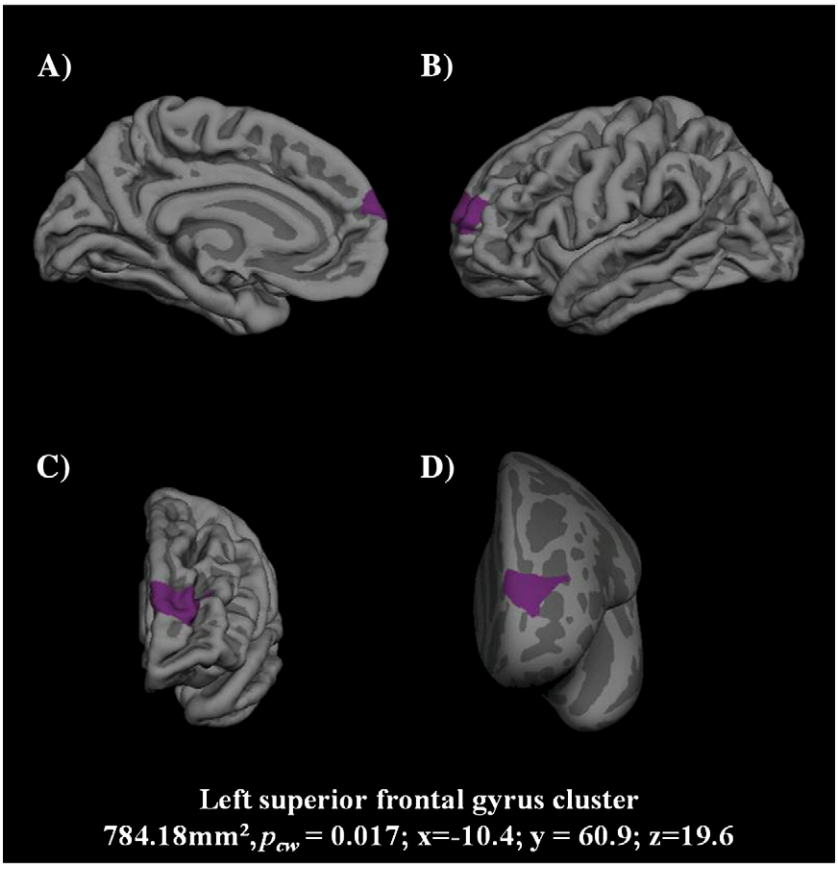

Fig. 1. Left hemisphere views of group differences in cortical thickness presented on average cortical surface template overlayed with curvature map (light gray regions area are gyri; dark gray regions are sulci). A, medial; B, lateral; C, anterior; and D, anterior inflated. Purple region represents cluster identified in the superior frontal gyrus (BA10) where schizophrenia participants (n = 26) had thinner cortex compared to healthy controls (n = 29). Cluster size = 784.18 mm^2; clusterwise *p*-value = 0.017; MNI coordinates of peak F-ratio value: x = −10.4; y = 60.9; z = 19.6. Statistical analysis was performed fitting a general linear model at every vertex, with age, gender, and mean cortical thickness of the left hemisphere as covariates. Correction for multiple comparisons was done with Monte Carlo permutation analyses (see Methods).

Within healthy controls, increased performance on category fluency was related to increased SFG cortical thickness and increased social functioning, but social functioning was not related to SFG cortical thickness. SFG cortical thickness correlated with category fluency in the predicted direction; increased cortical thickness was related to increased performance on the category fluency test. Although there were no significant relationships between role functioning and SFG cortical thickness or category fluency, correlations were moderately sized in the predicted direction. Within schizophrenia participants, no relationships between the SFG, category fluency, and social or role functioning were observed; however, SFG cortical thickness showed a moderately sized relationship with category fluency in the predicted direction. Across all participants, increased SFG cortical thickness was related to increased role functioning, and showed a trend level ($p = 0.057$) relationship with increased performance in category fluency. Increased category fluency was also related to increased social functioning, but social functioning was not related to SFG cortical thickness.

For mediation analysis to be justified, the predictor, mediator, and outcome variables must all be inter-related (MacKinnon, 2008). Because role functioning was the only functioning measure shown to relate to both SFG thickness and our measure of cognitive control (category fluency), we entered SFG cortical thickness, category fluency, and role functioning into a single mediator model to test our third hypothesis that cognitive control mediates the relationship between cortical thickness and functioning.

Hypothesis 3. Cognitive control will mediate the relationship between cortical thickness and functioning.

To test our third hypothesis we assessed a single mediator model in which cognitive control (as measured by category fluency) is

Table 2
Correlations between cortical thickness in superior frontal gyrus and measures of cognitive control and functioning.

	SZ group			HC group			All participants		
	SFG thickness	Category fluency	Role	SFG thickness	Category fluency	Role	SFG thickness	Category fluency	Role
Category fluency	0.15	–		0.38*	–		**.26**†	–	
Role	0.34	0.08	–	0.28	0.27	–	**.29***	**.41***	–
Social	0.07	0.06	0.55**	0.30	0.42*	0.60**	0.18	.41**	.75**

Note: Bold values indicate variable relationships entered into mediation analysis to test hypothesis three (see Methods).
** $p < 0.001$.
* $p < 0.05$.
† Trend level significant, $p = 0.06$.

postulated to mediate the relationship between cortical thickness in the SFG and role functioning. All four paths were in the predicted direction (Fig. 2). SFG cortical thickness had a positive effect on role functioning ($\beta = 2.43$, $p = 0.033$) and cognitive control ($\beta = 80.79$, $p = 0.057$); cognitive control had a positive effect on role functioning ($\beta = 0.01, p = 0.007$). Bootstrap analysis of the indirect effect revealed a bias corrected confidence interval excluding zero ($\beta = 0.77$; SE = 0.55; $CI_{.95} = 0.09, 2.34$), representing a medium effect size ($\kappa^2 = 0.09$; $CI_{.95} = 0.02, 0.23$). Importantly, the direct effect of SFG cortical thickness on role functioning, controlling for cognitive control, was no longer significant ($\beta = 1.59$, SE = 1.08; $p = 0.15$) indicating that cognitive control abilities fully mediate the relationship between cortical thickness in the SFG and role functioning. The overall regression model with SFG cortical thickness and cognitive control as predictors of role functioning accounted for 20% of the variance in role functioning ($F(2,52) = 6.63$, $p = 0.003$, $R^2 = 0.20$). The R^2 of the indirect effect size, R^2_{med} (i.e. the variance in role functioning that is shared by SFG thickness and cognitive control) indicates that SFG cortical thickness and cognitive control share 5% of the variance in role functioning ($R^2_{med} = 0.05$, $CI_{95} = 0.05, 0.16$).

4. Discussion

We report three main findings: first, we identified a region in the superior frontal gyrus (SFG; BA10) where schizophrenia participants had reduced cortical thickness compared to healthy individuals. This replicates prior findings (Janssen et al., 2009; Gutiérrez-Galve et al., 2010; Schultz et al., 2010b) and provides further evidence that abnormalities in the cortical sheet, particularly in lateral/dorsomedial prefrontal regions, are characteristic of schizophrenia. Second, decreased cortical thickness in this region of the SFG was related to decreased role functioning, demonstrating a direct relationship between neurobiological characteristics of schizophrenia and directly observable functioning impairments. Third, performance on the category fluency task – our proxy for cognitive control – fully mediated the relationship between cortical thickness in the SFG and role functioning, indicating that disease-related abnormalities in cortical thickness affect real-world functioning through impaired cognitive control processes.

These findings have implications for understanding the specific role of SFG abnormalities in role functioning impairments in schizophrenia. Here, we found schizophrenia participants to have reduced cortical thickness in a region of the SFG located in the anterior portion of the dorsomedial PFC (BA10). This region is known to be involved in a range of processes reliant on cognitive control, including set-switching (Koechlin et al., 1999), working memory (Braver and Bongiolatti, 2002), and complex problem solving (Burgess et al., 2000). Consequently, BA10 is primarily thought to implement higher-order control processes when multiple cognitive operations must be coordinated to respond appropriately to rapidly changing demands in the environment (Burgess et al., 2000; Ramnani and Owen, 2004). Given that successful performance in the work or school environment is reliant on these higher-order control processes in order to maintain context appropriate behavior and achieve desired/required goals, it seems intuitive that neural structure in this region impacts role functioning. Our finding that cognitive control fully mediates the relationship between cortical thickness in the SFG begins to illuminate *how* SFG cortical structure influences role functioning. Optimal performance on the category fluency task not only requires the directed retrieval of words from long-term memory, but also efficient set-switching, the maintenance in working memory of words already generated, and inhibition of irrelevant items (Rende et al., 2002; Henry and Crawford, 2004); that is, processes reliant on overarching cognitive control mechanisms at least partly implemented in the SFG. Prior studies have shown that category fluency predicts functional outcome in schizophrenia (Green et al., 2004). Our findings provide direct evidence to support this; the results from mediation analysis clearly demonstrate that cognitive control is one of the mechanisms underlying the relationship between cortical thickness in the SFG and role functional impairment.

This study adds to a growing body of literature linking the neural indicators of schizophrenia to the neurocognitive and clinical indicators of the disease. Several studies have shown relationships between executive or cognitive control tasks and neuroanatomical abnormalities in schizophrenia (Seidman et al., 1994; Ho et al., 2003; Minatogawa-Chang et al., 2009; Zierhut et al., 2013), and functional neuroimaging studies are increasingly demonstrating a relationship between neural function to real-world behavior (e.g. Berkman et al., 2011). Directly relevant to this study, Takizawa et al. (2008) found a relationship between activation in BA10 during category fluency tasks and global functioning; moreover, LPFC connectivity during cognitive control and working memory tasks has been shown to predict global functioning (Yoon et al., 2008; Sanz et al., 2009). Our findings extend this literature to understanding the neurocognitive mediators that link brain to behavior, and demonstrate that the "brain-as-predictor" approach (Berkman et al., 2011) can be extended from studies of neural function to meaningfully connect neuroanatomical indicators of psychological processes to behavior.

Study limitations must be acknowledged. While our finding of group differences in the SFG is consistent with prior studies, we did not replicate oft-reported findings of differences in temporal and parietal regions (e.g. Schultz et al., 2010b). Several factors could account for this, including sample size and analysis methods. Existing studies reporting additional regions of group-related differences in cortical thickness tend to have larger sample sizes (e.g. Goldman et al., 2009; Schultz et al., 2010a,b; Ehrlich et al., 2012; Sasamoto et al., 2013), or employ different statistical analysis methods (e.g. region of interest versus whole brain analyses; different approaches for

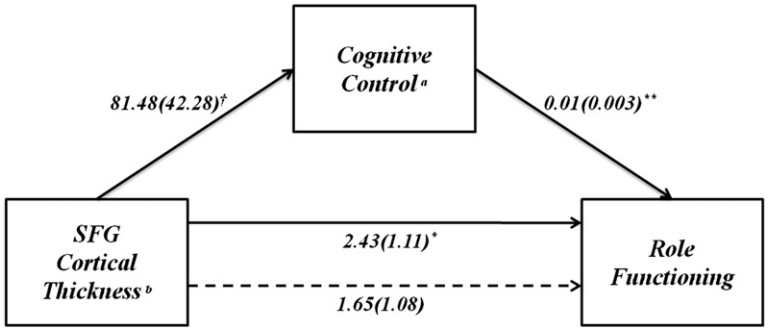

Fig. 2. The effect of cortical thickness in the superior frontal gyrus on role functioning through cognitive control. When cognitive control was included in the model the direct effect of cortical thickness in the superior frontal gyrus on role functioning (dashed line) was no longer significant, indicating a fully mediated effect. Unstandardized path coefficients (SE) shown for each path. SFG = superior frontal gyrus. *$p < 0.01$; **$p < 0.05$; †$p = 0.057$; [a]Cognitive control was measured by the category fluency animal naming task. [b]Mean cortical thickness in the SFG for each participant was extracted from the cluster where group differences in cortical thickness were identified in whole brain vertex-by-vertex analysis in Freesurfer (see Methods).

correcting for multiple comparisons) (e.g. Kuperberg et al., 2003; Goldman et al., 2009; Gutiérrez-Galve et al., 2010; Li et al., 2012). The cluster-based approach used here is relatively conservative (Schultz et al., 2010a), and although our sample size is sufficient to detect medium differences (0.5–1 mm differences in thickness), it is underpowered to detect small differences (e.g. <=0.25 mm differences in thickness) in temporal and limbic structures (Pardoe et al., 2012), thus we could have missed small clusters of group differences. Indeed, studies using the same methods with similar sample sizes also report few or no group differences in cortical thickness (e.g. Janssen et al., 2009; Gutiérrez-Galve et al., 2010; Murakami et al., 2011), further suggesting that methodological differences could account for our findings. Individual differences in sulcal and gyral variations could also be a factor; for example, individual variation in the incidence of the paracingulate sulcus can obscure group differences in the anterior cingulate (Fornito et al., 2008). Finally, although antipsychotic medication and duration of illness did not account for these findings, other secondary disease-related factors, such as number of previous psychotic episodes, may be at play. A second limitation is that the age range of our groups spans both developmental and aging-related decline periods in brain morphology. To address this potential confound we matched groups by age and included age as a covariate in all cortical analyses. However, further examination of groups with more tightly defined neurodevelopmental periods could further illuminate cortical thickness abnormalities in schizophrenia. Finally, although social functioning was also related to the category fluency measure of cognitive control, we did not find a relationship between social functioning and cortical thickness in the SFG. Given the inherently affective nature of social interactions, it is possible that social functioning is more strongly related to prefrontal regions involved in affective processes, such as the ventrolateral prefrontal cortex (VLPFC), and that this relationship is mediated by cognitive control of emotional information. In functional neuroimaging studies the VLPFC has been shown to relate to cognitive control of emotional information and social interactions in healthy individuals (Hooker et al., 2010) and people with high-levels of schizotypal traits (Hooker et al., 2013). Next steps include investigating the relationship between neuroanatomical abnormalities in the LPFC, cognitive control in relation to emotional information, and social functioning.

This study demonstrates that reduced cortical thickness in the superior frontal gyrus contributes to role functioning deficits in schizophrenia through impaired cognitive control. These findings provide insight into how the underlying neuroanatomical indicators of schizophrenia affect clinical and behavioral presentations of the illness.

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Contributors

Laura M. Tully and Christine I. Hooker designed the study and managed analyses. Laura M. Tully, Nadia Liyanage-Don, and Sarah Hope Lincoln recruited participants, conducted magnetic resonance imaging scans, managed literature searches and undertook statistical analyses. Laura M. Tully wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors have no financial disclosures or conflicts of interest.

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