Schizophrenia Research 152 (2014) 358–364

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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

Laura M. Tully *, Sarah Hope Lincoln, Nadia Liyanage-Don, Christine I. Hooker

Harvard University, Department of Psychology, 33 Kirkland St., Cambridge, MA 02138, USA

ARTICLE INFO

Article history:
Received 12 August 2013
Received in revised form 28 November 2013
Accepted 5 December 2013
Available online 30 December 2013

Keywords:
Inhibitory control
Lateral prefrontal cortex
Psychosis
Surface based morphometry

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

* Corresponding author at: UC Davis Imaging Research Center, 4701 X Street, Sacramento, CA 95817, USA. Tel.: +1 916 734 7927.
E-mail address: ltully@fas.harvard.edu (L.M. Tully).

0920-9964/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.schres.2013.12.005

(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