Schizophrenia Research 109 (2009) 182–190

Contents lists available at ScienceDirect

Schizophrenia Research

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

Abnormal prefrontal cortical activity and connectivity during response selection in first episode psychosis, chronic schizophrenia, and unaffected siblings of individuals with schizophrenia

Neil D. Woodward [a,*], Barb Waldie [b], Baxter Rogers [c], Phil Tibbo [b], Peter Seres [b], Scot E. Purdon [b]

[a] Psychiatric Neuroimaging Program, Vanderbilt University School of Medicine, Nashville, TN, United States
[b] Edmonton Early Psychosis Intervention Clinic & Bebensee Schizophrenia Research Unit, University of Alberta Hospital, Edmonton, AB, Canada [1]
[c] Vanderbilt University Institute of Imaging Sciences, Vanderbilt University, Nashville, TN, United States

ARTICLE INFO

Article history:
Received 9 October 2008
Received in revised form 23 November 2008
Accepted 25 November 2008

Keywords:
Schizophrenia
First episode psychosis
Endophenotype
Response selection
fMRI

ABSTRACT

The search for genes conferring liability for schizophrenia may be aided by the identification of endophenotypes. Response selection is a heritable cognitive function that is impaired in patients with schizophrenia and their unaffected siblings. The abnormalities in cerebral function that presumably underlie the deficit in patients and unaffected siblings remain to be elucidated. Cerebral neurophysiology during performance of a 4-choice reaction time (CRT) task in 25 patients with schizophrenia (15 medication free first episode (FEP) and 10 chronic patients), 32 controls, and 12 unaffected siblings of individuals with schizophrenia was investigated using fMRI. CRT was impaired in both medication free FEP and chronic patients with schizophrenia, and unaffected siblings. FEP patients, chronic patients, and unaffected siblings demonstrated greater BOLD response in the right dorsolateral prefrontal cortex (dlPFC) during CRT task blocks. The nature of the altered activation in the dlPFC was further examined using functional connectivity analysis. This revealed marked reductions in connectivity between the right dlPFC and multiple brain regions in both patient groups and, to a lesser degree, unaffected siblings. The magnitude of connectivity between right dlPFC and inferior parietal lobule correlated with task performance in the combined patient/unaffected siblings group, but not controls suggesting that the network of brain regions recruited to perform the task differed as a function of genetic liability for schizophrenia. The findings suggest that altered activity and connectivity of the right dlPFC appears to be related to genetic vulnerability for schizophrenia and may represent a potential endophenotype of the disorder.

1. Introduction

Schizophrenia is a highly heritable disorder (Cardno and Gottesman, 2000; Shields and Gottesman, 1972). The search for liability genes for complex disorders such as schizophrenia may be aided by identifying endophenotypes (Gottesman and Gould, 2003). Endophenotypes are quantifiable markers of an illness that are, presumably, closer to the underlying biological causes and genetic basis of a disorder along the genotype–phenotype pathway and include biochemical, structural, and functional brain changes, including neuropsychological impairment (Braff et al., 2007; Turetsky et al., 2007; Cannon et al., 2002). To be useful an endophenotype must be: 1) associated with the illness; 2) heritable to some degree; 3) state independent in affected individuals (i.e. present regardless of the stage of the illness); and 4) observed in unaffected family members to a greater extent than the general population (Gottesman and Gould, 2003).

* Corresponding author. Psychiatric Neuroimaging Program, Vanderbilt Psychiatric Hospital, Suite 3057, 1601 23rd Ave. S., Nashville, TN 37212, United States. Tel.: +1 615 322 8361; fax: +1 615 936 3563.
E-mail address: neil.woodward@vanderbilt.edu (N.D. Woodward).
[1] Location of work.

0920-9964/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2008.11.028

Impaired response selection is one of several promising neuropsychological endophenotypes of schizophrenia (Nuechterlein, 1977; Krieger et al., 2001; Krieger et al., 2005; Pellizzer and Stephane, 2007). The prototypical response selection task, choice reaction time (CRT), requires subjects to execute one of several possible motor responses following presentation of a specific stimulus cue, the spatial location of a target for example. CRT is impaired in both first episode medication naïve and chronic patients and it has been hypothesized that the deficit relates to altered connectivity between brain regions involved in response selection (Krieger et al., 2001, 2005; Pellizzer and Stephane, 2007). More importantly from an endophenotype standpoint are findings from twin studies in controls and schizophrenia indicating that CRT is heritable, and, along with deficits in divided attention, working memory, and verbal learning, is more impaired in unaffected monozygotic than dizygotic twins discordant for schizophrenia (Cannon et al., 2000; Wright et al., 2001). Thus, in addition to being associated with the illness, impaired CRT meets several additional endophenotype criteria including: 1) heritability; 2) state-independence in patients; and 3) impairment in unaffected relatives of patients.

Surprisingly, the alterations in cerebral function associated with impaired CRT in patients with schizophrenia and their unaffected relatives have not been investigated; although many of the paradigms employed in imaging studies of cognition in schizophrenia rely heavily on response selection. For example, commonly used paradigms of procedural learning, working memory, and cognitive control require subjects to select from one of several motor responses following presentation of a specific stimulus cue (Zedkova et al., 2006; Callicott et al., 2003b; Becker et al., 2008). Typically, additional demands are placed on subjects by varying working memory load or perceptual/stimulus–response conflict. Consequently, examination of the neural correlates of response selection in many functional magnetic resonance imaging (fMRI) studies is often precluded by the fact that CRT, in one form or another, is used as a baseline control condition. Indeed, prior imaging studies of procedural learning and working memory employed a typical CRT task as the baseline condition (Reiss et al., 2006; Woodward et al., 2007; Zedkova et al., 2006; Callicott et al., 2003b,a). Failure to examine the neural correlates related to response selection may have important consequences for interpreting results related to other cognitive abilities given evidence that at least part of the behavioral deficits observed in executive functions and working memory in schizophrenia relates to impaired response selection (Krieger et al., 2001; Krieger et al., 2005). Reports of greater activation in the prefrontal cortex (PFC) during a CRT baseline condition, relative to the procedural learning condition, in patients and their unaffected siblings, but not control subjects, suggest that at least some of the changes observed in cerebral function during procedural learning may reflect alterations in the neural circuitry underlying the basic cognitive process of response selection (Zedkova et al., 2006; Woodward et al., 2007; Reiss et al., 2006).

In order to examine the neural correlates of CRT in schizophrenia and determine the extent to which abnormalities in brain function during CRT relate to genetic vulnerability for schizophrenia, we took advantage of the fact that our imaging investigations of procedural learning included a fixation period thereby allowing us to examine neural activity during a CRT task that served as the baseline condition in our prior studies. In addition to performing a novel imaging analysis, we further expanded upon our earlier investigations by including a group of medication-free first episode psychosis patients. The goals of this experiment were to: 1) replicate previous demonstrations of impaired CRT in first episode psychosis, chronic schizophrenia, and unaffected relatives of patients; 2) extend these findings by determining if impaired CRT performance in patients is associated with alterations in brain activation; and 3) determine if the exact same regional changes in brain function observed in patients are also present in unaffected relatives of patients.

2. Methods

2.1. Subjects

This study was approved by the institutional review boards of the University of Alberta Hospital and Alberta Hospital Edmonton. All subjects were provided a verbal and written description of the study prior to solicitation of written informed consent to participate. 75 right-handed subjects were initially recruited to participate in the study; however, 4 patients (1 FEP and 3 chronic patients) were excluded due to excessive head motion and 2 control subjects were excluded due to periods of sleep during scanning. The final sample consisted of 25 patients with schizophrenia (15 medication-free first episode psychosis (FEP) and 10 chronic patients), 32 healthy control subjects, and 12 unaffected siblings of patients with schizophrenia. Due to the fact that FEP patients were younger than chronic patients and the well established association between reaction time and age, controls were partitioned into two groups, denoted young adult (YA) and middle aged (MA), that were matched to the FEP and chronic patient sub-groups, respectively. Unaffected siblings were age-matched to the MA control group and all groups were matched on gender distribution and parental socio-economic status (Myers et al., 1965). 15 controls, 10 chronic patients, and 12 siblings were included in our prior reports (Woodward et al., 2007; Zedkova et al., 2006); however, this is a novel analysis of their data. Demographic data for the subjects is presented in Table 1. Complete details on subject characteristics and recruitment procedures are presented in the Supplemental material.

2.2. Behavioral paradigm and statistical analysis of behavioral data

The task has been described in detail previously (Woodward et al., 2007; Zedkova et al., 2006) and is virtually identical to CRT tasks used in prior behavioral and functional neuroimaging studies (Tuch et al., 2005; Schumacher et al., 2003). During scanning subjects were required to identify the location of a target that could appear in one of four boxes arranged horizontally by pressing one of four response keys on each trial. The outer and inner left stimulus locations corresponded to the middle and index finger of the left hand, and the inner and outer right locations corresponded to the index and middle finger of the right hand, respectively. Subjects were requested to respond as quickly and accurately as possible. Sixty trials comprised a block and there were two block conditions referred to as 'sequenced', during which the location of the target followed a 12-element sequence that repeated five times, and 'random', hereafter