Psychiatry Research: Neuroimaging 174 (2009) 97–104

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Efficiency of working memory encoding in twins discordant for schizophrenia ☆

Peter Bachman[a,*], Junghoon Kim[b], Cindy M. Yee[a,c], Sebastian Therman[d], Marko Manninen[d], Jouko Lönnqvist[d], Jaakko Kaprio[d,e], Matti O. Huttunen[d], Risto Näätänen[f,g], Tyrone D. Cannon[c]

[a]Department of Psychology, University of California, Los Angeles (UCLA), 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563, United States
[b]Moss Rehabilitation Research Institute, 1200 W. Tabor Rd., Philadelphia, PA 19141, United States
[c]Department of Psychiatry and Biobehavioral Sciences, UCLA, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563, United States
[d]Department of Mental Health and Alcohol Research, National Public Health Institute, Mannerheimintie 166, FIN-00300 Helsinki, Finland
[e]Department of Public Health, Faculty of Medicine, P.O. Box 41, Mannerheimintie 172, FIN-00014 Helsinki, University of Helsinki, Finland
[f]Cognitive Brain Research Unit, Department of Psychology, P.O. Box 9, Siltavuorenpenger 20 C, FIN-00014 Helsinki, University of Helsinki, Finland
[g]Helsinki Brain Research Centre, P.O. Box 9, Siltavuorenpenger 20 C, FIN-00014 Helsinki, University of Helsinki, Helsinki, Finland

ARTICLE INFO

Article history:
Received 27 May 2008
Received in revised form 24 April 2009
Accepted 24 April 2009

Keywords:
Electrophysiology
ERP
Performance
Hyperactivation
CNV
P3

ABSTRACT

It has been proposed that patients with schizophrenia and some of their relatives suffer from reduced neurocognitive efficiency, increasing their sensitivity to experimental task demands. The present study evaluated such a possibility during performance of a working memory task by schizophrenia patients and their co-twins along with a healthy control sample. Electrophysiological data were obtained from sets of nine twin pairs (monozygotic and dizygotic pairs collapsed) discordant for a diagnosis of schizophrenia and from nine matched healthy control twin pairs, during administration of a variable-load spatial working memory task. Event-related potentials (ERPs) were measured immediately after memory set onset and during a delay period. For correctly performed trials, slow-wave ERP activity measured during the late stimulus encoding and delay periods exhibited a significant Diagnostic Group-by-Memory Load interaction, with schizophrenia patients showing a differentially strong load effect. Patients' co-twins displayed an intermediate level of load sensitivity while healthy controls showed no significant load effect. These results support an inefficiency model of neurocognitive dysfunction in schizophrenia, a pattern that appears to be related to the pathogenesis and inheritance of the disorder. Furthermore, this inefficiency appeared during the late stimulus encoding stage of working memory functioning, possibly reflecting disruptions in stimulus representation consolidation.

1. Introduction

Impaired spatial working memory (WM) has been observed consistently among schizophrenia patients (Park and Holzman, 1992; reviewed, Piskulic et al., 2007), and to a lesser extent, among individuals diagnosed with other schizophrenia spectrum disorders (Park et al., 1995; Saperstein et al., 2006) and among non-schizophrenic relatives of patients (Glahn et al., 2003), suggesting that it may serve as an endophenotypic indicator of genetic liability to the disorder (Gottesman and Gould, 2003).

Functional neuroimaging of the affected WM system has generated findings that are generally consistent with the hypothesis that the neurocognitive mechanisms supporting successful WM performance operate with less efficiency in schizophrenia patients (Callicott et al., 2003; Manoach, 2003; Tan et al., 2005; Van Snellenberg et al., 2006; Schlösser et al., 2008) and their first-degree relatives (Thermenos et al., 2004; Karlsgodt et al., 2007). For instance, studying a particularly large sample of schizophrenia patients, Potkin et al. (2009) demonstrated that regions of prefrontal cortex are hyper-responsive to increases in WM load, including under circumstances in which patient and control groups are matched on task performance. Here neural inefficiency is operationalized as a relatively increased, task-dependent brain response engaged in the service of achieving a constant behavioral criterion.

Published reports are not unanimous in support of this inefficiency hypothesis, though. At least two studies (Tan et al., 2005; Schlösser et al., 2008) demonstrate that physiological evidence of inefficiency may be restricted to only a subset of cortical regions associated with WM performance. Furthermore, a number of earlier reports describe results that may be better summarized by a simple hypoactivation model of abnormal neural activity in patients (reviewed, Barch, 2005). A final source of ambiguity involves the nature of the relationship

☆ Previous presentation: Portions of this work were presented at the meeting of the Society for Psychophysiology Research in Vancouver, BC, October 25–29, 2006.

* Corresponding author. Tel.: +1 310 206 7174; fax: +1 310 206 5895.
E-mail addresses: bachman@psych.ucla.edu (P. Bachman), kimj@einstein.edu (J. Kim), yee@psych.ucla.edu (C.M. Yee), sebastian.therman@ktl.fi (S. Therman), marko.manninen@ktl.fi (M. Manninen), jouko.lonnqvist@ktl.fi (J. Lönnqvist), jaakko.kaprio@helsinki.fi (J. Kaprio), matti.huttunen@konsmoh.inet.fi (M.O. Huttunen), risto.naatanen@helsinki.fi (R. Näätänen), cannon@psych.ucla.edu (T.D. Cannon).

0925-4927/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2009.04.010

between neural activity and the associated hemodynamic response, and the manner in which neural inefficiency may be reflected in observed cerebrovascular activity (e.g., Rypma et al., 2006; Mangia et al., 2008).

Electrophysiology has the potential to provide a complementary test of the inefficiency hypothesis, given its direct demonstration of large-scale neural activity (Birbaumer et al., 1990; Nunez and Srinivasan, 2006), and its reflection of both event-related phasic responses (e.g., to stimulus onset) and more tonic activity corresponding to periods of information maintenance over a delay period (e.g., Muller and Knight, 2002). One event-related potential (ERP) in particular, the contingent negative variation (CNV; Walter et al., 1964), has been shown to index neural activity associated with information maintenance over a several-second delay period. Specifically, CNV amplitude during a delay period *decreases* – or becomes *more positive* – with increasing memory load (Roth et al., 1975; McEvoy et al., 1998). Although CNV amplitude has been measured at least three times previously in schizophrenia patients performing WM tasks (Klein et al., 1996; Low et al., 2000; Cameron et al., 2003), none of these experimental protocols manipulated WM demand in a parametric manner, which is necessary to permit characterization of WM system efficiency; instead, they convolved engagement of additional cognitive processes with increases in task difficulty.

Alternatively, if information maintenance demands are varied parametrically, load-dependent decreases in CNV amplitude should reflect the WM memory system's level of efficiency, as evidenced by a greater physiological response associated with accurate task performance in less efficient subjects. Stated differently, less efficient subjects would be expected to incur a relatively greater depletion of resources in order to reach the same level of performance as that of more efficient subjects (Kahneman, 1973; Hockey, 1997). Formally, this prediction parallels the inefficiency argument as delineated in the functional magnetic resonance imaging (fMRI) literature (e.g., Callicott et al., 2003; Manoach, 2003; Van Snellenberg et al., 2006), and discussed above with respect to the demonstration by Potkin et al. (2009) that schizophrenia patients display greater prefrontal cortex activation than controls do when behavioral performance is matched between groups. The translation of this model to electrophysiology, however, allows the hypothesis that schizophrenia patients suffer from decreased efficiency of neurocognitive WM mechanisms to be tested using a direct measure of ensemble neural activity (Birbaumer et al., 1990; Nunez and Srinivasan, 2006).

With respect to more phasic ERP activity, the visually evoked P1 and N1 components reflect relatively early perceptual encoding demands (Handy and Mangun, 2000). Moreover, P3 amplitude has been shown to be associated with the allocation of cognitive resources to support less perceptually-bound processes (Sirevaag et al., 1989), such as working memory encoding and maintenance processes (Jeon and Polich, 2003), possibly including representation consolidation (Vogel and Luck, 2002) and subsequent updating (Donchin and Coles, 1988). Even without assuming that these ERP components reflect entirely discrete, independent processing stages (e.g., Smulders et al., 1995), the P1, N1, P3, and CNV taken collectively provide temporal resolution adequate to parse the observed physiological response into cognitively meaningful components, potentially isolating the information-processing stage at which inefficiency or other abnormalities begin to emerge.

In light of evidence that WM deficits in schizophrenia patients may be attributable largely to degraded encoding of perceptual information into durable mental representations that can be maintained over a delay (Lee and Park, 2005) – or more specifically, the representation consolidation phase of stimulus encoding – it might be expected that evidence of neurocognitive inefficiency in patients would arise during the consolidation stage of task performance (Fuller et al., 2005), coinciding with the development of the P3 component of the ERP (Vogel and Luck, 2002).

We predicted that schizophrenia patients and, to an intermediate extent, their non-schizophrenic co-twins would exhibit increased load sensitivity relative to healthy control twin pairs during performance of a spatial WM task, beginning relatively late in the stimulus encoding process as reflected by the P3 and extending through the development and resolution of the delay-period-specific CNV. Although auditory P3 amplitude reductions (especially over frontal electrodes) are a well-replicated finding among patients and their relatives (e.g., Bramon et al., 2005; Sumich et al., 2008), visually induced P3 amplitude findings are less readily available (one example is Groom et al., 2008). Nevertheless, these findings, in addition to the aforementioned behavioral and BOLD results showing patients' relatives performing similar to patients, but at a less severe level, suggest that patients' co-twins should show a P3 abnormality similar to, but less severe than, patients' abnormalities.

2. Methods

2.1. Sample ascertainment and assessment

Participants were recruited from the cohort of same-sex twin pairs born in Finland between 1940 and 1957 and in which one co-twin received a DSM-III-R diagnosis of schizophrenia or schizoaffective disorder (not predominantly affective type) and the other did not meet criteria for any psychotic disorder. Diagnoses were confirmed using the Structured Clinical Interview for DSM-III-R Disorders (Spitzer et al., 1979). Patients also were rated using the Scale for the Assessment of Positive Symptoms (Andreasen, 1984a) and the Scale for the Assessment of Negative Symptoms (Andreasen, 1984b). Mood and anxiety disorders were diagnosed in a minority of patients, co-twins, and controls, but the prevalence of non-psychotic disorders did not differ among the three groups. None of the study participants displayed evidence of neurological abnormality other than those potentially associated with schizophrenia vulnerability and illness in patients and their co-twins. No participant had an estimated total IQ score at or below 70. Additional subject identification, recruitment, and assessment details are provided elsewhere (Cannon et al., 1998; Kaprio and Koskenvuo, 2002).

Twenty-nine of these discordant pairs (selected to maintain the distributions of demographic variables present in the larger, overall sample) participated, although upon inspection of the raw EEG data, it became apparent that technical factors had introduced significant noise to a substantial portion of subjects' data sets. Session notes indicated that large-scale subject and hardware movement (including loss of contact between subject and sensors and possibly between leads and amplifiers) associated with construction nearby the laboratory accounted for the majority of the contamination. Additionally, although the testing equipment is located in a shielded room and has an extensive history of collecting clean data, artifacts consistent with episodes of electromagnetic interference were apparent. These particular instances of interference are difficult to account for definitively; however, they are evenly distributed across diagnostic groups and task conditions.

Since only intact twin pairs were included, patients and their non-schizophrenia co-twins were eliminated from the study sample at equivalent rates. Another four discordant pairs were excluded because their behavioral performance fell below chance, leaving nine discordant pairs. After screening for any psychotic disorder, Cluster A diagnosis (Personality Disorders Examination; Loranger et al., 1985), or history of psychosis-related treatment or work disability in any first-degree relatives, nine demographically matched control twin pairs were recruited from the same database. The data contamination discussed above did not affect the discordant and control pairs differentially (16 discordant sets and 14 control sets eliminated).

All patients except one had long-standing treatment with conventional neuroleptics, with daily chloropromazine equivalents ranging as high as 800 mg (mean $\pm$ 1 S.D. $= 243 \pm 170$ mg). The patient not on neuroleptic medication at the time of testing did have a