Schizophrenia Research: Cognition 5 (2016) 47–55

Contents lists available at ScienceDirect

Schizophrenia Research: Cognition

journal homepage: http://www.schizrescognition.com/

Impaired retrieval processes evident during visual working memory in schizophrenia

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ARTICLE INFO

Article history:
Received 29 March 2016
Received in revised form 7 July 2016
Accepted 10 July 2016
Available online 11 August 2016

Keywords:
Working memory
Schizophrenia
Event-related potential
Endophenotype
Relatives

ABSTRACT

Prominent working memory (WM) deficits have been observed in people with schizophrenia (PSZ) across multiple sensory modalities, including the visuospatial realm. Electrophysiological abnormalities noted during early visual processing as well as later cognitive functions in PSZ may underlie deficiencies in WM ability, though the mechanisms linking behavior to neural responses are not well understood. WM dysfunction has also been observed in biological relatives of PSZ (REL) and therefore may be a manifestation of genetic liability for the disorder. We administered a delayed response visuospatial WM task to 23 PSZ, 30 of their REL, and 37 healthy controls (CTRL) to better understand the contributions of neural abnormalities to WM performance deficits associated with schizophrenia. PSZ performed more poorly on the WM task and failed to effectively process distractor stimuli as well as CTRL and REL. N1 electrophysiological responses to probes during retrieval differentiated the type and locations of stimuli presented during encoding in CTRL. Retrieval N1 responses in PSZ, however, failed to do so, while retrieval responses in REL showed more pronounced differentiation of stimulus features during encoding. Furthermore, neural responses during retrieval predicted behavioral performance in PSZ and REL, but not CTRL. These results suggest that retrieval processes are particularly important to efficient visuospatial WM function in PSZ and REL, and support further investigation of WM retrieval as a potential target for improving overall WM function through clinical intervention.

1. Introduction

Working memory (WM) dysfunction in people with schizophrenia (PSZ) has been demonstrated across various sensory modalities (Fleming et al., 1997; Haenschel et al., 2007; Lee and Park, 2005). WM deficits have likewise been observed in the unaffected first-degree relatives of PSZ (Conklin et al., 2000; Park et al., 1995; Pirkola et al., 2005; Seidman et al., 2012), suggesting that WM impairment may represent an endophenotypic marker for schizophrenia (Gottesman and Gould, 2003; Haenschel and Linden, 2011).

In addition to WM performance deficits, related neurophysiological abnormalities have been demonstrated in PSZ and their unaffected relatives. Deficient early visual processes have been repeatedly observed in PSZ during WM tasks (Dias et al., 2011; Haenschel et al., 2007; Zhao et al., 2011), and related deficits have been observed in unaffected relatives who presumably carry genetic liability for the disorder (Yeap et al., 2006). Electrophysiological correlates of later cognition, including WM functions (Haenschel et al., 2007; Zhao et al., 2011), have likewise been shown to be abnormal in PSZ. Some abnormalities in later processes have similarly been reported in unaffected relatives (Lee et al., 2010; Sponheim et al., 2006). Recent work in WM has focused on the role of distracting stimuli in preventing efficient encoding which may compromise the amount or content of material in WM in PSZ (see Eich et al., 2014; Erickson et al., 2014). However, researchers have yet to understand the mechanisms linking these neural abnormalities to observed behavioral deficits during WM in PSZ and their unaffected relatives.

We analyzed event-related potentials (ERPs) elicited during WM encoding and retrieval from PSZ, their unaffected relatives, and non-psychiatric controls to better understand the contribution of neural responses to WM dysfunction associated with the disorder. To understand neural mechanisms associated with WM performance deficits, we examined electrophysiological responses to task manipulations related to distracting stimuli, amount of material (i.e., load), and the

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http://dx.doi.org/10.1016/j.scog.2016.07.002

location of the probe stimulus. If, for example, PSZ and/or relatives showed abnormal modulation of neural responses to distractors versus target stimuli, this would support the notion that distracting stimuli may be particularly important in explaining WM deficits in these populations. Similarly, examination of responses during encoding and retrieval would allow for isolation of neural deficits to a particular component of WM. We expected to see ERP abnormalities in PSZ and their first-degree relatives as compared to controls, as have been previously observed in studies outside the realm of WM and only scarcely investigated in visuospatial WM, especially in unaffected relatives. Specifically, we hypothesized that PSZ alone would show increased late potential amplitudes, thought to index WM load, for distractor stimuli during encoding, suggesting that PSZ were encoding task-irrelevant information. In addition, we hypothesized that REL would show stronger abnormalities in neural indices than behavioral indices.

2. Methods

2.1. Participants

Participants ($n = 90$) were 23 PSZ, 30 first-degree biological relatives of PSZ (REL), and 37 healthy controls (CTRL; Table 1). They were enrolled as part of a family study of severe psychopathology based at the Minneapolis Veterans Affairs Medical Center. PSZ were recruited through a mental health clinic and past research rosters, other current studies of severe psychopathology, referrals from physicians, as well as community-based mental health facilities and the medical center. REL were recruited using contact information provided by PSZ, and CTRL were recruited primarily through advertisement in the medical center and community, as well as from past research rosters. Enrolled participants underwent clinical assessments, the results of which were subjected to a consensus diagnosis process in which two or more Ph.D. clinicians or advanced doctoral students reviewed participants' study materials to form jointly agreed upon diagnoses. Full inclusion and exclusion criteria and clinical assessments are described in the supplementary materials.

2.2. Spatial working memory task, EEG acquisition and processing

Participants were administered a spatial WM task derived from Park's (1997) delayed response task; see Fig. 1 for further description. EEG was recorded using a BioSemi Active-Two *AgCl* electrode system (BioSemi Inc., Amsterdam, The Netherlands). Recordings utilized a 128-channel, full scalp dense array sampled at 1024 Hz. Recordings were down-sampled offline to 512 Hz, high-pass filtered at 0.5 Hz, and transformed to a linked earlobe reference. Data were preprocessed using a custom independent component analysis (ICA) based method for ocular, muscular and cardiac artifact removal; see supplementary materials for details.

2.3. ERPs

To investigate whether memory stimuli were differentially processed during encoding, ERPs were computed for stimulus type (target vs. distractor). To examine neural processes associated with increasing WM load during encoding, we computed ERPs for order of stimulus presentation (first vs. second vs. third). Finally, to study neural processes associated with retrieval as modulated by encoding manipulations, we computed ERPs for probe location based on the type of encoding stimulus that appeared in the same location ("encoded type": probe at previous target vs. previous distractor location vs. elsewhere), as well as probe location based on the sequential position of the encoding stimulus ("encoded order": probe at first vs. second vs. third stimulus position vs. elsewhere). ERPs were time-locked to the relevant stimulus and epoched from −150 ms to 850 ms with stimulus onset designated as 0 ms; subject averages were low-pass filtered at 20 Hz for ERP component analysis.

ERP components of interest included the P1, N1, and a late positive potential (LPP) encompassing the P300 but extending as far as 850 ms after stimulus onset. P1 and N1 were measured by computing peak amplitudes between 100 and 175 ms and 125–225 ms respectively. The LPP was assessed by computing mean amplitudes within 50 ms time windows between 200 and 850 ms after stimulus onset. For each independent variable (stimulus type, order of stimulus presentation, probe location/stimulus type and probe location/presentation order), P1 and N1 were measured at electrode sites PO4 and PO8, and the LPP was measured at sites FC1, C2, and CP1. All reported findings are for these electrode sites because they contained the greatest component amplitudes.

2.4. Statistical analyses

To examine the effects of group status and task manipulations on participants' performance of the WM task, separate repeated measures ANOVAs were run for independent variables of number of trial stimuli (two vs. three), trial type (with vs. without distractor), probe location based on encoded stimulus type (probe at previous target vs. distractor location vs. elsewhere), and probe location based on presentation order of encoded stimulus (probe at first vs. second vs. third stimulus location vs. elsewhere); diagnostic group (CTRL, PSZ or REL) was included in each ANOVA as an additional factor.

ERP measures were analyzed using mixed model ANCOVAs. Separate ANCOVAs were run for independent variables of stimulus type, order of stimulus presentation, probe type, and probe order. Each model included as fixed factors the relevant independent

Table 1
Participant characteristics.

	CTRL ($n = 37$)	PSZ ($n = 23$)	REL ($n = 30$)	Test Statistic (Degrees of Freedom)	p-value
% Female	35.1%	4.3%	63.3%	$\chi^2(2) = 19.6$	$p < .001$
Age (years)	46.7 (11.1)	42.9 (10.2)	45.3 (10.7)	$F(2, 87) = 0.9$	$p = .42$
Years of education	15.1[a] (1.9)	13.6[a] (1.7)	14.6 (2.2)	$F(2, 87) = 4.7$	$p = .01$
Estimated IQ	106.1[a] (14.9)	90.3[a,b] (19.9)	105.0[b] (14.5)	$F(2, 87) = 7.7$	$p < .001$
BPRS Total Score	28.4[a] (4.2)	43.8[a,b] (11.1)	32.7[b] (7.7)	$F(2, 87) = 29.6$	$p < .001$
Positive Symptoms	5.1[a] (0.4)	13.3[a,b] (6.9)	5.7[b] (1.7)	$F(2, 87) = 41.1$	$p < .001$
Negative Symptoms	3.1[a] (0,3)	5.5[a,b] (2.8)	3.4[b] (1.0)	$F(2, 87) = 17.7$	$p < .001$
Disorganized Symptoms	5.2[a] (1.4)	7.0[a] (2.7)	6.2 (1.7)	$F(2, 87) = 6.4$	$p = .003$

Parentheses indicate standard deviations unless noted otherwise. p-values indicate differences in measures across diagnostic categories: schizophrenia probands (PSZ), controls (CTRL) and relatives of PSZ (REL). Paired superscripts indicate differences between groups for a given measure, $p < .05$. BPRS = Brief Psychiatric Rating Scale (24 item version).