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Abnormal early brain responses during visual search are evident in schizophrenia but not bipolar affective disorder

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ABSTRACT

People with schizophrenia show deficits in processing visual stimuli but neural abnormalities underlying the deficits are unclear and it is unknown whether such functional brain abnormalities are present in other severe mental disorders or in individuals who carry genetic liability for schizophrenia.

To better characterize brain responses underlying visual search deficits and test their specificity to schizophrenia we gathered behavioral and electrophysiological responses during visual search (i.e., Span of Apprehension [SOA] task) from 38 people with schizophrenia, 31 people with bipolar disorder, 58 biological relatives of people with schizophrenia, 37 biological relatives of people with bipolar disorder, and 65 non-psychiatric control participants. Through subtracting neural responses associated with purely sensory aspects of the stimuli we found that people with schizophrenia exhibited reduced early posterior task-related neural responses (i.e., Span Endogenous Negativity [SEN]) while other groups showed normative responses. People with schizophrenia exhibited longer reaction times than controls during visual search but nearly identical accuracy. Those individuals with schizophrenia who had larger SENs performed more efficiently (i.e., shorter reaction times) on the SOA task suggesting that modulation of early visual cortical responses facilitated their visual search. People with schizophrenia also exhibited a diminished P300 response compared to other groups. Unaffected first-degree relatives of people with bipolar disorder and schizophrenia showed an amplified N1 response over posterior brain regions in comparison to other groups.

Diminished early posterior brain responses are associated with impaired visual search in schizophrenia and appear to be specifically associated with the neuropathology of schizophrenia.

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1. Introduction

To better understand how brain abnormalities result in schizophrenia, researchers have used visual search tasks to describe attentional impairments, which contribute to the disorder (e.g., Silverstein et al., 2010). Individuals with schizophrenia have generally been shown to have difficulty controlling attention when required to efficiently identify a behaviorally relevant target object grouped with several visually similar objects (Luck and Gold, 2008). Difficulty with guiding attention to better deal with distractors results in a less efficient search process, which has been estimated as 39 ms per item for people with schizophrenia as compared to 23 ms per item for health controls (Gold et al., 2007). There is some evidence that the difficulty with efficiently searching objects stems for people with schizophrenia having a small visual span (i.e., a narrow spotlight of attention) which is manifest in terms of greater difficulty with wide visual angle displays (Elahipanah et al., 2010). It has also been suggested that inefficient visual search stems from dysregulation in the magnocellular visual system (Elahipanah et al., 2011) and failure to effectively discount peripheral distractors that tap magnocellular mechanisms (Leonard et al., 2014). Finally, impaired visual search or limited visual span have been documented in brain conditions other than schizophrenia, including attention deficit disorder (Karatekin and Asarnow, 1998), late life depression (Potter et al., 2013), and bipolar affective disorder (Addington and Addington, 1997). In order to test whether visual span deficits are specific to schizophrenia and mark genetic liability for the disorder, we carried out a five-group analysis testing whether search deficits were evident in schizophrenia and bipolar affective disorder patient groups, as well as in their first-degree biological relatives who are generally at increased genetic liability for the mental disorders. To better isolate brain abnormalities that underlie inefficient visual search we used electroencephalography (EEG) to record brain electrical activity during the visual search task and contrasted these brain responses to those during a reaction time sensory control condition.

Because a goal of the current study was to examine whether visual search deficits and associated brain abnormalities serve as markers of genetic liability (e.g., an endophenotype; Gottesman and Gould, 2003) the Span of Apprehension (SOA) task was employed since it has been

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the most widely used visual search task in endophenotype oriented studies. Although people with schizophrenia typically perform less accurately on the SOA task (Asarnow et al., 1983, 1991; Granholm et al., 1996; Ito et al., 1997) some investigations have failed to demonstrate the deficit (Bedwell et al., 2006; Harvey et al., 1985; Laurent et al., 2000; Miller et al., 1990).

Prior research on the SOA task (Strandburg et al., 1991) has revealed a negative potential called the Span Endogenous Negativity (SEN), which is thought to reflect posterior cortical activity necessary to visually search for an object of interest. To reveal the negative potential, waveforms of a reaction time control trials to letter arrays (i.e. low attention) are subtracted from the SOA trials where a search of the array is performed (i.e. high attention). The subtraction results in a negative component between 160 milliseconds (ms) and 360 ms after stimulus onset. A decrease in SEN amplitude is thought to indicate a reduction of attention resources that are in part controlled by executive search functions (Strandburg et al., 1991). Several studies have identified diminished SEN responses in people with schizophrenia compared to non-psychiatric controls (Davenport et al., 2006; Strandburg et al., 1991, 1994) suggesting that those affected by the disorder have difficulty deploying visual attentional resources during visual search.

To determine if behavioral and electrophysiological deficits during visual search are unique to people with schizophrenia, we used the SOA task to compare performance (i.e. accuracy and reaction time) and event-related potential (ERP) brain responses (e.g., SEN) in people with schizophrenia, bipolar affective disorder, their first-degree relatives and a non-psychiatric control group. To date, no published work has described the neural correlates of visual search in such a wide array of psychopathology.

2. Methods

2.1. Participants

Five groups were studied in this experiment: people with schizophrenia (SCZ), people with bipolar affective disorder (BP), people with no history of psychiatric issues (CTRL; i.e., healthy non-psychiatric control participants), and the first-degree biological relatives (siblings, parents, and offspring) of people with schizophrenia (SCZREL) and bipolar disorder (BPREL). Table 1 describes the characteristics of each group of participants. Additional information on recruitment, exclusion criteria, and assessment can be found in the supplemental material.

2.2. SOA task

The SOA task developed by Asarnow and Nuechterlein (1996) was used for this study. Participants were instructed to report for each trial whether they saw a "T" or an "F" amongst an array of letters using the thumb of each hand to indicate on a two-button joystick their letter choice. If the participant was uncertain about which letter was present, they were encouraged to make their best guess. The task displayed during each trial an array of three or twelve-letters (Fig. 1) within a 4×4 matrix, which covered $11.2 \times 14.8°$ of visual angle. The array of three-letters was presented 64 times, while the array of twelve-letters was presented 128 times. See supplemental information for additional task details.

2.3. Reaction time (RT) control task

An RT control task was administered prior to the SOA task to collect information about sensory and motor responses apart from the cognitive load induced by searching for target letters. The RT task was identical to the SOA task, except for the participant was simply instructed to respond to the stimuli with a single button, regardless of the letters presented. In other words, the "F" button was pressed in response to the first 64 trials, while the "T" button was pressed for the second 64 trials in the control task. Within these 128 trials, 64 presented three-letters and 64 presented twelve-letters. See supplemental information for additional details.

2.4. EEG data collection and processing, and ERP computation

Electroencephalograms (EEGs) were collected from 27 tin electrodes embedded in an elastic cap that was placed on the head so the electrode sites conformed to a 10–10 configuration. EEG was collected referenced to the left earlobe and later re-referenced to linked earlobes (A1 and A2). Vertical electro-oculogram (VEOG) data were used to remove ocular artifacts from the EEG signals (Semlitsch et al., 1986). After EEG processing (see supplemental materials for additional details) all correct trials were averaged for each individual subject for the three- and twelve-letter array conditions for the SOA task and the RT control task. The ERPs of primary interest in this study were the SEN and P300. We computed the SEN by subtracting the neural response to the RT control trials from the neural response of SOA trials for each array size (i.e., 3 letters and 12 letters) and then computing the mean negative voltage in the difference waveform between 160 ms and 360 ms post-stimulus. The P300 was quantified by taking the mean positive amplitude between 350 ms and 700 ms post-stimulus. The posterior visual

Table 1
Characteristics of participants.

Variable	Schizophrenia (SCZ)	Bipolar (BP)	Controls (CTRL)	Relatives of schizophrenia (SCZREL)	Relatives of bipolar (BPREL)	Statistic	p value
	$n = 39$	$n = 30$	$n = 65$	$n = 58$	$n = 37$		
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)				
Age (years)	45.9 (8.3)	44.6 (9.9)	45.7 (13.4)	50.2 (9.9)	49.3 (13.2)	$F(4,224) = 2.2$	0.07
Percent female	17.9[a]	26.6[a]	49.2[a]	58.6	48.6	$\chi^2(4) = 20.5$	<.001
Estimated IQ	96.2 (11.5)[b]	108.9 (16.8)[b]	110.5 (12.4)[b]	103.3 (15.9)	108.6 (12.4)[b]	$F(4,224) = 7.7$	<.001
Years education	13.9 (2.6)	14.9 (2.3)	15.2 (2.6)	14.7 (2.5)	14.4 (3.0)	$F(4,224) = 1.8$	0.13
BPRS total	42.7 (12.4)	37.7 (11.5)	NA	NA	NA	$F(1,67) = 2.9$	0.09
SANS total	29.4 (17.5)[c]	12.4 (9.5)	NA	NA	NA	$F(1,67) = 24.2$	<.001
SAPS total	21.9 (20.2)[c]	10.0 (10.9)	NA	NA	NA	$F(1,67) = 8.5$	<.01
SAS-SR mean[e]	2.97 (.78)[d]	2.48 (1.1)[d]	.88 (.52)[d]	NA	NA	$F(2,91) = 49.5$	<.001
SPQ total	NA	NA	8.7 (5.7)	11.4 (7.9)	8.7 (11.6)	$F(2,157) = 2.1$	0.13

S.D. = standard deviation; BPRS = Brief Psychiatric Rating Scale (Ventura et al., 1993); SANS = Scale for Assessing Negative Symptoms (Andreasen, 1983); SAPS = Scale for Assessing Positive Symptoms (Andreasen, 1984); SAS-SR = Social Adjustment Scale-Self Report (Weissman, 1999); SPQ = Schizotypal Personality Questionnaire (Raine, 1991).

[a] People with schizophrenia and bipolar disorder had a significantly smaller percentage of females than the non-psychiatric control group.

[b] People with schizophrenia had a significantly lower IQ than all other groups.

[c] People with schizophrenia showed significantly more positive and negative symptoms than people with bipolar disorder.

[d] People with schizophrenia and bipolar disorder both scored significantly worse on the social adjustment scale than non-psychiatric controls;

[e] Higher scores indicate lower social and occupational functioning.