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Impaired target detection in schizophrenia and the ventral attentional network: Findings from a joint event-related potential–functional MRI analysis

Target stimulus ERP/fMRI analysis in schizophrenia

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ABSTRACT

Schizophrenia patients have abnormal neural responses to salient, infrequent events. We integrated event-related potentials (ERP) and fMRI to examine the contributions of the ventral (salience) and dorsal (sustained) attention networks to this dysfunctional neural activation. Twenty-one schizophrenia patients and 22 healthy controls were assessed in separate sessions with ERP and fMRI during a visual oddball task. Visual P100, N100, and P300 ERP waveforms and fMRI activation were assessed. A joint independent components analysis (jICA) on the ERP and fMRI data were conducted. Patients exhibited reduced P300, but not P100 or N100, amplitudes to targets and reduced fMRI neural activation in both dorsal and ventral attentional networks compared with controls. However, the jICA revealed that the P300 was linked specifically to activation in the ventral (salience) network, including anterior cingulate, anterior insula, and temporal parietal junction, with patients exhibiting significantly lower activation. The P100 and N100 were linked to activation in the dorsal (sustained) network, with no group differences in level of activation. This joint analysis approach revealed the nature of target detection deficits that were not discernable by either imaging methodology alone, highlighting the utility of a multimodal fMRI and ERP approach to understand attentional network deficits in schizophrenia.

1. Introduction

Schizophrenia patients have deficits in many cognitive abilities, including the basic ability to separate important from distracting stimuli, such as distinguishing targets from nontargets. One widely-used task to examine dysfunctional target processing is the oddball task, in which infrequent target ("oddball") stimuli are embedded in a stream of frequent nontarget ("standard") stimuli. Schizophrenia patients have impairments on oddball tasks (Ford, 1999; Ford et al., 1994; Kiehl et al., 2005; Kim et al., 2009), as they do on similar tasks of target detection, including the continuous performance task (Cornblatt and Erlenmeyer-Kimling, 1985; MacDonald, 2008; Nuechterlein and Dawson, 1984), and visual search tasks (Silverstein et al., 2010). Efforts have been made to better understand the specific nature of the attentional impairment involved in this task (Ford et al., 2010). In the current study we examined the neural networks associated with dysfunctional oddball detection in schizophrenia using converging evidence from functional magnetic resonance imaging (fMRI) and event-related potentials (ERPs).

Two separate attentional processes are involved in target detection in oddball tasks: 1) maintaining attentional readiness, and 2) detecting an infrequent change in the environment. Dorsal and ventral attentional networks have been implicated in these separate processes (Corbetta and Shulman, 2002; Kim, 2014). The dorsal network includes activations in the inferior frontal junction (IFJ), medial intraparietal sulcus (IPS), superior parietal lobule (SPL), and middle temporal area (MT+). This network is thought to orient attention to the task in general, responding to both targets and nontargets (Kim, 2014). In contrast, the ventral network includes activations in the temporal parietal junction (TPJ), anterior insula (AI), anterior middle frontal gyrus (aMFG), bilateral anterior cingulate cortex (ACC), and supplementary motor area (SMA). This network is involved in detecting salient changes within the

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task (Corbetta and Shulman, 2002), and is specifically associated with detection of targets, but not nontargets. When presented with a task-relevant stimulus the ventral network is associated with attentional allocation to that stimulus to initiate an action (Palaniyappan and Liddle, 2012). Importantly, the Kim (2014) meta-analysis found the same ventral attention network activated across both auditory and visual oddball tasks.

Oddball studies yield a highly characteristic ERP, the P300, elicited by rare, cognitively-relevant (target) stimuli. The P300 is a positive deflection occurring approximately 300–600 ms after target presentation, and is largest over parietal areas. Source localization, though not as precise as fMRI, and intracranial studies have identified P300 neural generators located in several regions that partially overlap with the ventral attentional network, including the TPJ, posterior superior parietal regions, ACC, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and medial temporal regions (Bledowski et al., 2004; Jeon and Polich, 2003; Kiss et al., 1989; Machado et al., 2014; McCarthy and Wood, 1987; Mulert et al., 2004). Attention has also been shown to increase amplitudes of earlier, primarily sensory components, including the visual P100 and N100 (for review, see Herrmann and Knight, 2001) as well as components at Pz occurring earlier than the P300 (e.g., Clementz et al., 2008; Sponheim et al., 2006). These findings indicate that attention can enhance neural responses to targets, and thus salience detection, in early stages of processing.

There are well established fMRI (Gur et al., 2007; Kiehl et al., 2005) and P300 ERP (Bramon et al., 2004; Ford, 1999; Jeon and Polich, 2003) findings of deficits in schizophrenia on oddball tasks. Schizophrenia patients also exhibit deficits in early sensory ERP components (P100, N100) (Foxe et al., 2001; Martinez et al., 2012; Schechter et al., 2005), though they are less consistent than those seen for the P300. Thus, problems in target detection could possibly arise earlier in the processing stream, leading to down-stream deficits.

Despite the deficits seen within each imaging method, the relationship between abnormal ERP components and dysfunctional fMRI activation during oddball tasks in schizophrenia patients is not established (Kiehl et al., 2005). Examining this relationship between ERP and fMRI would allow us to discern which attentional network is specifically contributing to impairments in target detection. For example, fMRI alone implicates both dorsal and ventral systems in schizophrenia as abnormal in oddball tasks, but only one might be responsible for the problems in target detection.

Recent advances in computational neuroimaging have utilized a joint independent components analysis (jICA) approach to determine underlying neural structures and chronometry associated with a task by combining the temporal resolution of EEG with the spatial resolution of fMRI (Calhoun et al., 2006). One study examined EEG and fMRI in the same sample of patients using jICA, but it did not focus on P300 (Calhoun et al., 2010). No study to our knowledge has integrated visual oddball ERP and fMRI data in the same sample of patients and controls. Without such integration, we cannot know whether deficits in oddball tasks in schizophrenia are specific to the ventral or dorsal attentional networks, or whether they arise in early, primarily sensory brain regions.

The goal of the current study is to utilize fMRI and ERPs to examine whether schizophrenia is associated with a dysfunctional ventral and/or dorsal network during a visual oddball task. We hypothesized that: 1) patients will show reduced fMRI neural activation to targets relative to controls, 2) patients will show reduced ERP responses to targets relative to controls, and 3) that a joint ERP–fMRI analysis will reveal that dysfunctional P300 ERP in schizophrenia is associated with abnormalities in the ventral attention network.

2. Methods

2.1. Participants

EEG and fMRI data were collected from 21 schizophrenia patients and 22 healthy controls in separate sessions, with a median of 14 days between sessions. Patients were recruited from outpatient treatment clinics at the Greater Los Angeles VA (GLA) and the community. All patients were receiving second generation antipsychotic medication, mean (SD) chlorpromazine equivalent of 307 (153) mg/day (Andreasen et al., 2010). Patients met diagnostic criteria for schizophrenia based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1996b). Psychiatric symptoms were evaluated using the 24-item University of California Los Angeles (UCLA) version of the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1995); we report total scores and means for the "positive symptom," "negative symptom," "agitation/mania," and "depression/anxiety" factors (Kopelowicz et al., 2008). Healthy controls were recruited through internet postings, interviewed with the SCID-I and portions of the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II; First et al., 1996a), and excluded if they had any of the following Axis II disorders: avoidant, paranoid, schizoid, or schizotypal. Additional inclusion and exclusion criteria for both groups can be seen in the Inline Supplementary Methods.

Table 1
Demographic information, symptom ratings, and oddball task behavioral and ERP results.

	Schizophrenia patients (n = 21)		Healthy controls (n = 22)	
	Mean	SD	Mean	SD
Age	46.2	10.9	41.5	7.7
Education*	12.6	1.1	14.4	1.8
Parental education	13.7	3.3	14.2	3.0
Male:female	19:2	–	19:3	–
BPRS				
Total score	40.1	7.6		
Factors (mean score per item)				
Positive symptoms	1.8	0.6		
Negative symptoms	1.6	0.8		
Depression/anxiety	1.8	0.6		
Agitation/mania	1.3	0.3		
Behavioral performance				
EEG accuracy (% out of 60)	84.6	28.1	96.3	5.5
fMRI accuracy (% out of 54)	84.9	19.4	93.7	9.8
EEG d-prime*	3.97	1.40	4.79	0.62
fMRI d-prime*	3.71	0.97	4.44	0.78
Number EEG trials accepted				
Targets	53.8	8.5	51.5	12.4
Nontargets	390.7	63.5	375.3	93.4
P300 amplitude (μV)				
Targets*	2.36	1.34	4.40	2.37
Nontargets	1.27	1.20	1.71	0.95

* $p < 0.05$ difference between groups.

All participants had the capacity to give and provided written informed consent after all procedures were explained in accordance with procedures approved by the Institutional Review Boards at UCLA and GLA.

2.2. Procedures

2.2.1. fMRI task

Participants viewed images of two letters, X and K, that served as targets or nontargets. The target and nontarget letters were counterbalanced across subjects and recordings (i.e., EEG and fMRI). Stimuli were presented in a fast event-related design in three separate blocks using magnet-compatible goggles (Resonance Technology, Northridge, CA). Stimuli were displayed for 100 ms with an interstimulus interval that varied between 900 and 2900 ms. Participants were instructed to push a button on an MRI-compatible button box whenever they detected the target and had 3000 ms to make a response. Within each block a total of 150 stimuli were presented: 12% were targets (n = 18) and 88% were nontargets (n = 132). Null trials were