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Error detection failures in schizophrenia: ERPs and FMRI

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ABSTRACT

Self-monitoring of actions, critical for guiding goal-directed behavior, is deficient in schizophrenia. Defective error-monitoring may reflect more general self-monitoring deficiencies. Prior studies have shown that the error-related negativity (ERN) component of the event-related potential (ERP) is smaller in patients with schizophrenia. Other studies using functional magnetic resonance imaging (FMRI) have shown the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC), both critical for error detection, to be less responsive to errors in patients with schizophrenia.

In the present study, both ERP and FMRI data were collected while 11 patients with schizophrenia and 10 healthy controls performed a Go–NoGo task requiring a button press to Xs ($p = .88$) while withholding responses to Ks ($p = .12$). We measured the ERN and ACC and DLPFC activations to false alarms.

The task elicited a robust ERN and modest activations in ACC and DLPFC to false alarms. As expected, ERN was larger in controls than patients. However, ACC and DLPFC activations were not greater in controls than patients. Surprisingly, DLPFC was more activated by errors in patients than controls.

ERPs may be superior to fMRI for assessing error processing abnormalities in schizophrenia because (1) ERNs can be measured precisely without needing to control for the multiple comparisons of FMRI, and (2) ERPs have the temporal precision to detect transient activity necessary for error detection and on-the-fly behavioral adjustments.

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1. Introduction

Self-monitoring of thoughts and actions is critical for distinguishing self-initiated from externally generated stimuli and for guiding goal-directed behavior. Defective self-monitoring may be a core feature of schizophrenia (Feinberg, 1978; Frith and Done, 1989). Indeed, self-monitoring deficits have been demonstrated in schizophrenia, particularly in patients with Schneiderian first-rank symptoms performing tasks calling for self-willed actions (Mlakar et al., 1994). Defective error-monitoring may reflect this more general self-monitoring deficiency. We (Turken et al., 2003) and others (Frith and Done, 1989; Malenka et al., 1982, 1986) have shown that patients with schizophrenia show error-correction deficits when exteroceptive feedback is withheld such that internal monitoring of action is needed.

While behavioral studies highlight the deficits in self-monitoring in schizophrenia, brain imaging provides important details about the temporal course of error monitoring and its precise neuroanatomical underpinnings. Two in-vivo, non-invasive brain-imaging methods have been used to understand neural responses to errors, electrophysiological and hemodynamic. Electroencephalogram (EEG) based methods are relatively direct ways of measuring neuronal activity with millisecond temporal resolution. Individual EEG trials are averaged to produce an event-related potential (ERP), whose components develop and resolve within tens or hundreds of milliseconds. A less direct measure of neural activity is hemodynamic brain imaging, the most common of which is functional magnetic resonance imaging (fMRI). While fMRI operates on a much more delayed time scale than EEG, taking about 4 to 6 s to develop and another 8 to 10 s to resolve (Buckner, 1998), it has superior spatial resolution, allowing a more precise delineation of brain structures and circuits involved in specific sensory and cognitive processes.

1.1. ERP studies of error monitoring

Almost simultaneously, two laboratories reported a unique brain response to errors, referred to as the error-related negativity (ERN) (Gehring et al., 1993) and the negativity associated with errors (Ne) (Falkenstein et al., 1991). This is a negative component of the ERP starting at the onset of error responses, peaking at about 100 ms after the error, and being maximal at frontocentral midline scalp sites. Although ERN is typically elicited in situations where the subject knows the correct response but fails to execute it (Dehaene et al., 1994), it can also be elicited in the absence of error awareness (Nieuwenhuis et al., 2001). Also, it is independent of corrective motor responses, occurring after errors of commission in Go–NoGo tasks even though no corrective actions are possible (e.g. Ford et al., 2004b; Mathalon et al., 2003) and occurring in response to external error feedback (Badgaiyan and Posner, 1998; Luu et al., 2000; Miltner et al., 1997). It has been described as part of the feed

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forward system in which awareness of the error occurs before the error is executed; such an error monitoring system was proposed by Rabbitt (1966) to enable us to correct our errors "in flight" before they are complete.

1.2. ERP studies of error monitoring in schizophrenia

Using a flanker task, Kopp and Rist (1999) were the first to report that the ERN was smaller in patients with schizophrenia, a finding that we and others replicated using a variety of tasks (Alain et al., 2002; Bates et al., 2002, 2004; Mathalon et al., 2002; Morris et al., 2008, 2006). In addition to abnormally small ERNs on error trials in patients, some (Alain et al., 2002; Kopp and Rist, 1999; Mathalon et al., 2002), but not all (Bates et al., 2002) investigators have reported abnormally large ERNs on correct trials, sometimes referred to as the correct-response negativity (CRN), in patients with schizophrenia.

1.3. Hemodynamic studies of error monitoring

While most researchers have interpreted the ERN as a reflection of an early error detection system involving the anterior cingulate cortex (ACC) (Coles et al., 1995; Dehaene et al., 1994; Falkenstein et al., 1995, 1991, 2000; Gehring et al., 1995, 1993; Holroyd et al., 1998; Leuthold and Sommer, 1999; Scheffers and Coles, 2000), some have pointed to the contribution of conflict-related processing to the error-related responses (Carter et al., 1998). Although Carter et al. (1998) showed that the same region of the ACC was activated by conflict and errors, others have shown distinct areas of the ACC to be activated by conflict and by errors, suggesting potentially dissociable processes (Braver et al., 2001; Kiehl et al., 2000; Ullsperger and von Cramon, 2001).

1.4. Hemodynamic studies of error monitoring in schizophrenia

FMRI studies provide evidence of a diminished ACC response to errors in patients with schizophrenia compared to controls (Carter et al., 2001; Kerns et al., 2005; Laurens et al., 2003; Polli et al., 2008). Involvement of ACC with error monitoring is consistent with dipole localization analyses of the ERN (Badgaiyan and Posner, 1998; Dehaene et al., 1994; Holroyd et al., 1998; Luu et al., 2000; Miltner et al., 1997; Van Veen and Carter 2002) as well as with a literature showing patients with ACC lesions to have reduced error awareness (Turken and Swick, 1999) and diminished or absent ERNs following errors (Stemmers et al., 2000). Although these studies focus on ACC, ACC is large and different sub-regions within the ACC show group differences across studies. For example, Manoach and colleagues recently distinguished between dorsal ACC (dACC) and rostral ACC (rACC), with hypoactivity in the dACC reflecting deficient updating of context in response to errors, and hypoactivity in the rACC network reflecting diminished concern regarding behavioral outcomes (Polli et al., 2008).

1.5. Dopamine, reward processing, and the ERN

Holroyd and Coles (2002) formulated a model of the ERN based on the neurobiology of reward processing. Midbrain dopamine neurons project to the ventral striatum, prefrontal cortex, and ACC. Reward anticipation is associated with an increase in dopamine release in the ventral striatum, and reward prediction errors (i.e., outcomes worse than expected) are associated with transient inhibition of dopamine release in the ventral striatum(Schultz, 2007). Holroyd and Coles theorized that the ACC is subject to similar regulation by midbrain dopaminergic input, with ACC neurons being tonically inhibited by midbrain dopaminergic input, and with phasic inhibition of dopamine release following reward prediction errors leading to transient increases in ACC neuronal activity that give rise to the ERN. This ACC signal is thought to recruit greater input from other brain regions, including the DLPFC, to enhance performance, facilitate learning, and maximize rewards.

1.6. Abnormal error processing and the pathophysiology of schizophrenia

Based on the Holroyd and Coles (2002) model, abnormalities in dopaminergic neurotransmission associated with schizophrenia, either as part of its primary pathophysiology (Davis et al., 1991; Laruelle and Abi-Dargham, 1999; Moore et al., 1999) or secondary to its treatment with dopamine-blocking antipsychotic medications (Laruelle et al., 2005), would be expected to disrupt reward processing signals, including the ERN and possibly the CRN. However, exactly which mechanisms are disrupted by the illness, and how these disruptions account for the pattern of ERN/CRN abnormalities observed in schizophrenia, have yet to be elucidated. Importantly, although dopamine D2-receptor antagonists have been shown to reduce ERN amplitudes acutely in healthy volunteers (Zirnheld et al., 2004), ERN amplitude reduction has been shown to be more pronounced in acutely hospitalized, variably medicated, schizophrenia patients than when they were clinically stabilized after 6 weeks of optimized antipsychotic treatment (Bates et al., 2004). Thus, it is unlikely that antipsychotic effects alone could fully account for the ERN abnormalities in schizophrenia.

While neuropathological (Benes, 2000; Honer et al., 1997; Suhara et al., 2002) and functional (Carter et al., 1997; Holcomb et al., 1996, 2000; Mulert et al., 2001) abnormalities of the ACC have been reported in schizophrenia, suggesting that local pathology of the ACC itself could contribute to ERN and CRN abnormalities in the disorder, other regions have also been implicated. In particular, the dorsolateral prefrontal cortex (DLPFC), which has rich connections with the ACC (Bush et al., 2000), has been implicated in both error processing (Carter et al., 1998) and in the pathophysiology of schizophrenia (e.g., Goldman-Rakic and Selemon, 1997; Weinberger and Berman, 1996). Of note, the DLPFC appears to play an important role in modulating the ACC's differential response to errors and correct responses, as indicated by a study showing patients with DLPFC lesions to have normal amplitude ERNs but equally (and abnormally) large CRN amplitudes following correct responses (Gehring and Knight, 2000). This similarity between ERN and CRN amplitudes has sometimes been observed in patients with schizophrenia (Kopp and Rist, 1999; Mathalon et al., 2002), consistent with compromised DLPFC function. Based on these findings, it is likely that with normal input from DLPFC, the CRN will be minimal.[1]

1.7. Goals of this experiment

In order to compare the sensitivity of neurophysiologic and hemodynamic measures of brain responses to errors, the same subjects were subjected to identical Go–NoGo paradigms with both imaging modalities. To increase the likelihood of errors, we attempted to establish a strong prepotent bias to respond to Go stimuli. To build up expectancy for Go stimuli, we skewed stimulus probabilities (Go stimuli = 88%, NoGo stimuli = 12%). In addition, we pre-trained subjects to respond to the stimulus that subsequently became the NoGo stimulus, and we emphasized speed over accuracy.

2. Methods

2.1. Participants

In separate sessions, we recorded ERPs and fMRI while 11 patients with DSM-IV schizophrenia and 10 healthy comparison subjects

[1] There is also a positivity following errors, the Pe. Because of its insensitivity to schizophrenia (Mathalon et al., 2002; Bates et al., 2002; Alain et al., 2002), the Pe data were not analyzed for this report.