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Disruption of function–structure coupling in brain regions sub-serving self monitoring in schizophrenia☆

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ABSTRACT

Deficits in self monitoring are a core feature of cognitive dysfunction in schizophrenia, and may be the basis for disturbances of self and lack of insight, ultimately impacting social functioning. However, the functional and structural neural correlates of such deficits in self monitoring are not well understood. We investigated this issue using measurements of neurophysiological and structural brain indices, i.e., error-related and correct-response negativity (ERN & CRN) of event-related potentials, and gray matter volume of the anterior cingulate cortex (ACC), and tested whether the association between these indices is altered in patients with schizophrenia. Participants consisted of 18 male patients with chronic schizophrenia and 18 healthy male controls. The 2 groups did not differ in ERN amplitude. In contrast, schizophrenia patients showed significantly larger CRN amplitudes than did healthy subjects. Although the 2 groups did not significantly differ in gray matter volume of the ACC subregions, a significant negative correlation was found between ERN amplitudes at the frontocentral electrodes and absolute gray matter volumes of the left cognitive region of ACC only in healthy controls. These results suggest a disruption of function–structure coupling of the brain regions sub-serving self monitoring in schizophrenia.

1. Introduction

Deficiency in self monitoring is a core feature of cognitive dysfunction in schizophrenia, and may be the basis for disturbances of self and lack of insight, ultimately impacting social functioning. An objective biological marker for self monitoring can be elicited by an event-related potential (ERP) component described as error negativity (Ne) (Falkenstein et al., 1991) or error-related negativity (ERN) (Gehring et al., 1993).

The ERN is theorized to be related to self-monitoring, particularly to aspects of both error detection and response conflict (Falkenstein et al., 1991; Gehring et al., 1993). The ERN can be measured during several different speeded response tasks, including the arrows version of the Erikson Flankers task, Simon task, color Stroop task, and Go/No-Go task (Olvet and Hajcak, 2008). The ERN appears as a negative deflection approximately 50–100 ms following an erroneous response, and is measured at midline frontal and central electrode sites (i.e., Fz and Cz). The interpretation of the ERN is based on the hypothesis that the ERN reflects the detection of errors. In recent years, the hypothesis has developed and the ERN is now commonly thought to reflect response conflict rather than simple errors (Carter et al., 1998; Botvinick et al., 1999, 2001; van Veen et al., 2001; van Veen and Carter, 2002; Botvinick et al., 2004).

Another ERP component that is potentially related to error processing is the correct response negativity (CRN), which is a response-related, frontocentral negative component appearing following correct trials (Ford, 1999; Falkenstein et al., 2000; Vidal et al., 2000). The CRN has a similar peak latency and topography to the ERN, but it is smaller in amplitude. Although the CRN might also reflect some aspects of response conflict, the precise nature of the CRN is not fully understood.

Patients with schizophrenia showed diminished error-related negativity (ERN) (Kopp and Rist, 1999; Alain et al., 2002; Bates et al., 2002; Mathalon et al., 2002; Bates et al., 2004; Kim et al., 2006; Morris et al., 2006, 2008), which has been interpreted as indexing self monitoring deficits in schizophrenia. These studies used several different kinds of experimental tasks, including the Erikson flanker task (Kopp and Rist, 1999; Morris et al., 2006), color Stroop task (Alain et al., 2002; Kim et al., 2006), Go/No-go task (Bates et al., 2002; Bates et al., 2004), picture-word naming task (Mathalon et al., 2002), and probabilistic learning task (Morris et al., 2008). This reduced ERN potentially reflects an abnormality in the self-monitoring system in patients with schizophrenia. On the other hand, some studies have shown that patients with schizophrenia

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exhibit an enhanced CRN compared to healthy controls (Alain et al., 2002; Mathalon et al., 2002; Kim et al., 2006; Morris et al., 2006).

The ERN has been shown to originate in the anterior cingulate cortex (ACC) by using source localization, LORETA source localization, magnetoencephalography, and functional MRI (Holroyd et al., 1998; Kiehl et al., 2000; van Veen and Carter, 2002; Miltner et al., 2003; Herrmann et al., 2004). Lesion studies have also shown that patients with ACC lesions showed diminished ERNs (Stemmer et al., 2004). The ACC is functionally subdivided into caudal cognitive, rostral affective, and subgenual subregions (Bush et al., 2000). The cognitive subregion of ACC contributes to the Stroop task without emotionally biased stimuli (Bush et al., 1999), while the emotional Stroop task specifically activates the rostral, affective subdivision of ACC (Whalen et al., 1998). FMRI studies tend to report rostral ACC activation during error processing (Kiehl et al., 2000; Laurens et al., 2003). However, EEG studies and those combined with fMRI have clarified spatiotemporal characteristics of error processing within the ACC: error monitoring process at an earlier stage is associated with a more caudal region, while the later evaluation process may be associated with a more rostral region (van Veen and Carter, 2002; Herrmann et al., 2004; Edwards et al., 2012). Thus, it may be hypothesized that the ERN detected at 100–150 ms post-stimulus would be localized to the more caudal cognitive subregion. To date, however, no study has investigated the correlation between ERN amplitudes and gray matter volumes of ACC in patients with schizophrenia. One study has investigated the relationship between ERN amplitude and cingulum bundle integrity as indexed by diffusion tensor imaging in healthy subjects, and observed an association with posterior, not anterior part of the left cingulum (Westlye et al., 2009).

Accordingly, in order to clarify the brain structural basis of self-monitoring related electrophysiological abnormalities in schizophrenia, we measured ERPs by using the color Stroop task and the ACC gray matter volumes obtained from MRI using Region of Interest (ROI) manual tracing. Correlations between the ERN/CRN and gray matter volumes of ACC subregions were examined in both patients with schizophrenia and healthy controls. In light of the inferences from previous EEG/fMRI studies (van Veen and Carter, 2002; Herrmann et al., 2004; Edwards et al., 2012), we predicted an ERN association with the cognitive subregion of the ACC in healthy subjects which would be disrupted in schizophrenia patients.

2. Methods

2.1. Subjects

The present study included 18 male patients with chronic schizophrenia and 18 healthy men, all with normal or corrected-to-normal vision, all right handed, and with an age range of 20–55 years. After a complete explanation of the study, all participants signed an informed consent form in accordance with Harvard Medical School and VA Boston Healthcare System guidelines. The exclusion criteria were (1) a history of neurological illness or major head trauma that might result in an abnormal EEG, (2) a history of electro convulsive therapy, (3) a history of alcohol or drug dependence, (4) alcohol or drug abuse within the past 5 years, and (5) a verbal IQ below 75. Healthy controls were recruited through a newspaper advertisement and were screened using the Structured Clinical Interview for DSM-III-R-Non-Patient Edition (SCID-NP). No control subjects had any axis I psychiatric disorder, nor did their first-degree relatives. The patients were recruited from the VA Boston Healthcare System, Brockton Division, and had a diagnosis of schizophrenia on the basis of their medical records and assessment with the patient edition of the SCID for DSM-IV. Mean age in the patient and control groups was 44.0 (SD 10.3) and 36.9 (SD 12.0), respectively. Handedness was assessed using the Edinburgh Inventory, and the socioeconomic status of subjects and their parents was measured by using the Hollingshead two-factor index. The Positive and Negative Syndrome Scale (PANSS) was administered to patients. All subjects underwent ERP recordings. All of the patients and 14 healthy controls underwent MRI recordings. The median interval between these recordings was 11 months. This study was approved by the VA Boston health care system and Harvard Medical School Institutional Review Boards (Table 1).

2.2. ERP recording

In order to elicit ERN and CRN, we used the Stroop task. Subjects were seated in a comfortable chair, facing a monitor, which was located 1 m from their eyes. Subjects were instructed to identify the color in which stimuli were printed by pressing 1 of 4 response-pad buttons with the index and middle fingers of both hands. Prior to the Stroop task, learning and practice sessions were conducted. In the learning session, Xs printed in 4 colors (red, green, yellow, & blue) were presented on the monitor. In the practice session, words (RED, GREEN, YELLOW, and BLUE) and Xs printed in 4 colors were presented and subjects were given feedback as to whether their response was correct. The average response time from the second half of the practice session defined the threshold for the warning sound during the actual testing session. During the actual task, congruent (e.g., RED printed in red color), incongruent (e.g., RED printed in blue color), and neutral (Xs printed in 4 colors) stimuli were presented. One block consisted of 432 stimuli (144 congruent, 144 incongruent, & 144 neutral) and 3 blocks were performed. The importance of speed and accuracy was equally emphasized. Stimuli appeared on the screen for 500 ms, followed by a blank screen with a fixation point for 1500 ms. If the subject responded slower than the individually defined threshold time, a warning sound was delivered over the headphones. The warning sound was aimed at maintaining subjects' alertness and at increasing the error rate to obtain a sufficient number of error trials for ERP analysis. The entire task required about 45 min to complete. The EEG was recorded (0.01–100 Hz, 500 Hz digitization) using 64 silver–silver chloride sintered electrodes in preconfigured caps (ElectroCap International, Eaton, Ohio). The electrode sites were as follows: Fp1/Fp2, F7/F8, F5/F6, F3/F4, F1/Fz/F2, FT9/FT10, FT7/FT8, FC5/FC6, FC3/FC4, FC1/FC2, T9/T10, T7/T8, C5/C6, C3/C4, C1/Cz/C2, TP7/TP8, CP5/CP6, CP3/CP4, CP1/CP2, P9/P10, P7/P8, P5/P6, P3/P4, P1/Pz/P2, PO9/PO10, PO7/PO8, PO1/PO2, and O1/Oz/O2, referenced to the right earlobe, with the ground electrode positioned on the forehead. The vertical electrooculogram (EOG) was recorded using 2 electrodes located medially to the right eye, one above and the other below the eye. The horizontal EOG was recorded at the outer canthi. Electrode impedances were <5 kΩ. In off-line analyses, the event-related potential responses were convolved with a zero phase shift digital low-pass filter at 16 Hz (24 dB/octave). Epochs were 800 ms in duration, including a 400-ms pre-response interval. Epochs at each electrode site were baseline corrected by subtraction of the average voltage of a 100-ms period before the response onset, and mathematically corrected for eye movement artifacts. Subsequently, epochs exceeding ± 100 μV at any electrode site were rejected. Final event-related potential responses were re-referenced off-line to the average of the left and right earlobe potentials. The ERN and CRN were measured as the average amplitude between 25 and 150 ms post-response. Because the ERN and CRN are typically largest at frontal and central sites, the analyses included the left, midline, and right frontal and central electrodes (i.e. F3, Fz, F4, C3, Cz, C4).

2.3. MR imaging procedures

The MRI protocol used 2 pulse sequences on a 1.5-T MRI system (GE Medical Systems, Milwaukee), as described in detail elsewhere (Wible et al., 1995). Briefly, a 3-dimensional Fourier transformed spoiled gradient-recalled (SPGR) acquisition sequence yielded contiguous