

Rostral Anterior Cingulate Cortex Dysfunction During Error Processing in Schizophrenia

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Total number of words in text: 6560

Running head: Error processing in schizophrenia

Abstract

Previous research has demonstrated that patients with schizophrenia have an impaired ability to internally monitor erroneous responses to stimuli. Event-related potential (ERP) studies of error-eliciting tasks indicate that, in healthy adults, the commission of an erroneous response is associated with a fronto-centrally distributed negative voltage component termed the error negativity (Ne) or error-related negativity (ERN). In patients with schizophrenia, the Ne/ERN elicited by errors of commission (EoC) is reduced in amplitude compared to that elicited in healthy participants. Functional magnetic resonance imaging (fMRI) studies and source-localisation analyses of ERP data in healthy participants suggest that EoC are associated with activity in the rostral anterior cingulate cortex (ACC). Using event-related fMRI, we examined the brain activity associated with EoC in a group of 10 patients with schizophrenia and 16 matched healthy participants. Patients were stable, partially-remitted, medicated outpatients recruited from the community. Participants performed a Go/NoGo task variant that was previously shown to elicit a reduced Ne/ERN during EoC in patients with schizophrenia relative to healthy participants, as well as robust rostral ACC activation during EoC in healthy participants. Patients with schizophrenia were characterised by relative underactivity in the rostral ACC compared with healthy participants. There was also evidence for more widespread underactivity in the limbic system. In contrast to these regions of relative hypoactivity, patients with schizophrenia demonstrated hyperactivity relative to healthy participants in bilateral parietal cortex during both EoC and correctly-rejected NoGo trials. Our results are consistent with previous ERP research demonstrating functional abnormalities during error processing in schizophrenia. In light of the role of the rostral ACC and other limbic structures in mediating affective and motivational behaviour, our results suggest there may be a disturbed affective or motivational response to the commission of errors in schizophrenia.

Key words: schizophrenia, anterior cingulate cortex, error processing, limbic system, event-related functional MRI

Rostral Anterior Cingulate Cortex Dysfunction During Error Monitoring in Schizophrenia

Schizophrenia is characterised by disordered monitoring and regulation of self-generated thoughts and behaviour (Frith & Done, 1989; Leudar et al., 1994; Mlakar et al., 1994; Stirling et al., 1998, 2001; Johns et al., 2001). Research suggests that an impaired ability to internally monitor error responses to stimuli contributes to self-monitoring problems (Malenka et al., 1982, 1986; Frith & Done, 1989). Evidence for a functional abnormality associated with error monitoring in schizophrenia derives primarily from event-related potential (ERP) research investigating a fronto-central negative voltage component termed error negativity (Ne; Falkenstein, et al., 1990, 1991) or error-related negativity (ERN; Gehring et al., 1990, 1993). The Ne/ERN peaks around 50-150 ms after the commission of an erroneous response during tasks that necessitate speeded and accurate response choices, thus providing a physiological marker of internal error monitoring (see Falkenstein et al., 2000, for a review). The Ne/ERN is elicited in situations where participants know the correct answer but fail to execute the correct response (Dehaene et al., 1994), and decreases in amplitude as the participant's confidence in having committed an error decreases (e.g., in tasks in which the quality of the stimulus has been degraded; Scheffers & Coles, 2000). Several ERP studies have demonstrated that the Ne/ERN is attenuated in patients with schizophrenia compared to healthy adults (Kopp & Rist, 1999; Mathalon et al., 2002), even in paradigms in which the correct response is readily apparent and errors are easily identifiable (Bates et al., 2002). These results are consistent with the hypothesis that error responses are processed abnormally in schizophrenia.

The application of error-eliciting tasks during functional magnetic resonance imaging (fMRI) provides further neurophysiological evidence of disturbed brain function in patients with schizophrenia during error commission. Converging evidence from fMRI research (e.g.,

Carter et al., 1998; Kiehl et al., 2000; Ullsperger & von Cramon, 2001) and dipole localisation analyses of dense-array ERP data (e.g., Dehaene et al., 1994; Miltner et al., 1997; Holroyd et al., 1998; Luu et al., 2000b) in healthy individuals suggests that the commission of errors, (and the Ne/ERN), is critically associated with activity in the anterior cingulate cortex (ACC). Carter et al. (2001) recently reported attenuation of the haemodynamic response during errors of commission in patients with schizophrenia compared with healthy participants in the ACC. Taken together, the ERP and fMRI results imply that impaired error monitoring in schizophrenia relates to dysfunction in ACC. However, the nature of the error-related processes purported to underlie the Ne/ERN and ACC activity have been the subject of debate, leaving open the question as to the root of abnormal error-monitoring in schizophrenia.

Early proposals that the Ne/ERN reflects the activity of a rapid, preconscious error-detection system that compares and detects mismatch between representations of the intended response and the actual response (Gehring et al., 1993; Bernstein et al., 1995; Falkenstein et al., 2000; Scheffers & Coles, 2000) have been challenged. Functional MRI evidence that tasks involving strong response competition elicit ACC activation irrespective of response accuracy led others to hypothesise that the ACC functions to detect conflict between incompatible potential responses rather than overt errors (Carter et al., 1998; MacDonald et al., 2000; Botvinick et al., 2001). Other theorists argue that error monitoring incorporates processes related to motivation and/or affective processing of error responses (Dikman & Allen, 2000; Luu et al., 2000a; Vidal et al., 2000). For example, Luu et al. (2000a) demonstrated that the amplitude of the Ne/ERN was larger in participants who reported a propensity to experience negative affect on personality assessment scales than in participants without this propensity, and further, that the amplitude of the Ne/ERN decreased in these participants as they affectively disengaged from the task. Also consistent with the proposal

that the error response incorporates a motivational or affective processing component are a number of fMRI studies that localised activity associated with errors of commission to the rostral ACC (Kiehl et al., 2000; Braver et al., 2001; Menon et al., 2001). Activity in the rostral ACC region during errors was dissociated from activity in more superior, caudal ACC that was elicited during both response inhibition and target detection processing that included a degree of response competition. Data from a recent study reporting dipole localisation of error-related ERP components are also consistent with the idea that caudal ACC activity may reflect a conflict-detection component to error monitoring that is dissociated from an affective component mediated by activity in rostral ACC (van Veen & Carter, 2002).

Structural and functional dissociation of the ACC into rostral and caudal subregions has been described on the basis of convergent evidence from cytoarchitectural, lesion, electrophysiological, and neuroimaging data (Devinsky et al., 1995; Bush et al., 2000). The caudal ACC, termed the 'cognitive' subdivision, appears to be responsible for mediating attention and executive functions such as the detection of response conflict via strong reciprocal interconnections with dorsolateral prefrontal cortex, parietal cortex, and premotor and supplementary motor areas. The 'affective' subdivision in the rostral ACC has connections to limbic and paralimbic areas including the amygdala and hippocampus, and appears primarily involved in assessing the salience of emotional and motivational information, and in regulating emotional responses (see Bush et al., 2000 for a review). Functional subspecialisation of the ACC is also supported by neuroimaging studies that demonstrate reciprocal suppression of rostral ACC and enhancement of caudal ACC activity during attentionally-demanding cognitive tasks (e.g., divided attention, sequential learning, working memory, and response competition tasks; see review by Drevets & Raichle, 1998), as well as the converse condition of suppressed caudal ACC and enhanced rostral ACC activity during tasks employing emotional stimuli (e.g., Whalen et al., 1998). Carter et al.

(2001) demonstrated that healthy participants, but not patients with schizophrenia, showed an increase in activity in caudal ACC during the commission of errors in a task that elicited strong response conflict. This result suggests that error monitoring deficits in schizophrenia may be partially associated with a more generalised dysfunction in the detection of response conflict. However, evidence that the amplitude of the Ne/ERN is modulated by the affective or motivational response to errors (Dikman & Allen, 2000; Luu et al., 2000a) implies that the attenuated Ne/ERN in schizophrenia may reflect a disturbance in the affective or motivational component of error monitoring that is related to dysfunction in rostral ACC.

The idea that disturbed error-related processing in schizophrenia may be related to motivational or affective processing abnormalities is consistent with the clinical presentation of schizophrenia. An extensive range of disorders of emotion occur in schizophrenia, of which blunted affect and inappropriate affect are the most characteristic and tend to be the most persistent (Bleuler, 1908, 1911/1950). Disruptions of motivation and will are reflected in weakened or disjointed volition (manifest as extended periods of underactivity and poorly organised, ill-judged, impulsive activities respectively). Positron emission tomography (PET) studies have demonstrated a positive correlation between regional cerebral blood flow (rCBF) in the ACC and the severity of disorganisation symptoms (which incorporates inappropriate affect and bizarre, erratic behaviour; Liddle et al., 1992; Ebmeier et al., 1993; Yuasa, et al., 1995). Using ERPs, Bates et al. (2002) reported a significant negative correlation between psychomotor poverty syndrome (which includes the symptoms of blunted affect and underactivity) and Ne/ERN amplitude. To the extent that the error-detection signal derives from a motivational or emotional response to errors generated in rostral ACC, these results suggest that the motivational and/or affective response to errors of commission in patients with schizophrenia may be disordered.

The purpose of the present study was to employ whole-brain event-related fMRI to examine the neural response to errors of commission and correct non-responses in healthy participants and patients with schizophrenia. The Go/NoGo task used in the present study was previously employed in an ERP study that demonstrated attenuation of Ne/ERN in patients with schizophrenia compared with healthy participants (Bates et al., 2002). In fMRI, the task was shown to elicit robust activation in rostral ACC during errors of commission by healthy participants (Kiehl et al., 2000). In light of the ERP and fMRI evidence, we hypothesised that patients with schizophrenia would fail to show the same magnitude of rostral ACC activity during the commission of errors as is observed in healthy participants. Given the extensive connections between the rostral ACC and limbic and paralimbic structures, we further hypothesised that reduced activation in limbic and/or paralimbic areas would be elicited in patients with schizophrenia relative to healthy participants. To the extent that the Go/NoGo paradigm includes a degree of response conflict, it was also expected that patients with schizophrenia might show an attenuated response compared to healthy participants in caudal ACC during errors.

Methods

Participants

Sixteen healthy adults (12 male) and 10 patients with schizophrenia (9 male) participated in the experiment and provided written informed consent. All participants were right-handed (as per Annett, 1970), with normal or corrected-to-normal visual acuity. All procedures complied with University and Hospital ethical requirements.

Patients were stable, partially-remitted, medicated outpatients recruited from community mental health teams in Vancouver, BC and outpatient programs at the University of British Columbia Hospital. All patients met DSM-IV criteria for schizophrenia, as diagnosed by an institutional or University Hospital psychiatrist (APA, 1994). Mean duration of illness was 11 years (SD 3.1), with a range spanning 2 to 30 years. All patients received stable doses of atypical antipsychotics as their primary medication over the preceding 6-month period. Two patients also received a typical antipsychotic. A trained psychiatrist evaluated the symptoms of the patients with schizophrenia on the day of scanning using the Signs and Symptoms of Psychotic Illness (SSPI) interview schedule (Liddle et al., 2002). The SSPI comprises 20 symptom items scored 0 to 4 according to the severity of the symptom. Mean total score was 8.3 (SD 1.6), with a range of 1 to 18. Syndrome scores were calculated from the items according to the three-syndrome model of schizophrenia described by Liddle (1987a, 1987b). Mean syndrome scores for Reality Distortion (sum of 2 items: delusions and hallucinations), Disorganisation (sum of 3 items: thought disorder, inappropriate affect, and peculiar behaviour), and Psychomotor Poverty (sum of 3 items: blunted affect, poverty of speech, and underactivity) respectively were: 2.0 (SD 0.7), 0.9 (SD 0.4), 1.0 (SD 0.5).

Healthy participants were medication-free volunteers without history of neurological or Axis I psychiatric illness. Participant groups did not differ significantly on the demographic variables of age, gender, parental socioeconomic status (Hollingshead & Redlich, 1958), or

on estimates of premorbid (National Adult Reading Test [NART]; Nelson, 1982; Sharpe & O'Carroll, 1991) and current (Quick Test; Ammons & Ammons, 1962) intellectual functioning ($p > 0.05$; see Table 1).

Insert Table 1 about here

Procedure

A single scanning run comprising 246 visual stimuli was presented to participants using a computer-controlled visual and auditory presentation package (<http://nilab.psychiatry.ubc.ca/vapp/>). Stimuli were displayed on a rear-projection screen mounted at the entrance to the magnet bore and subtended a visual angle of approximately 3 x 5 degrees. Each stimulus appeared for 240 ms in white text within a continuously displayed rectangular fixation box. Participants viewed the screen from a distance of approximately 2 metres by means of a mirror system attached to the head coil. The scanning room and magnet bore were darkened to permit easy visualisation of the stimuli.

Participants were instructed to respond as quickly and accurately as possible with their right index finger to each presentation of the Go stimulus (the letter 'X'; occurrence probability = 0.84). They were instructed not to respond to the NoGo stimulus (the letter 'K'; occurrence probability = 0.16). Prior to scanning, participants completed a brief practice session of approximately 10 trials to promote speeded responding to the Go stimulus and thus increase the likelihood of errors of commission.

The SOA between Go stimuli varied pseudorandomly between 1000, 2000, and 3000 ms, subject to the constraint that three Go stimuli were presented within each consecutive 6-s period. In light of the protracted evolution of the haemodynamic response elicited by a single

stimulus, it was anticipated that the Go stimuli would generate a sustained, relatively constant baseline haemodynamic activity. The NoGo stimuli were interspersed among the Go stimuli in a pseudorandom manner subject to three constraints: the minimum SOA between a Go and NoGo stimulus was 1000 ms; the SOA between successive NoGo stimuli was in the range 10-15 s; and NoGo stimuli had an equal likelihood of occurring at 0, 1, or 2 s after the beginning of a 3-s acquisition period. Thus, the haemodynamic response to each NoGo stimulus occurred as a perturbation set against the relatively constant haemodynamic response to Go stimuli. By jittering stimulus presentation relative to the acquisition time, the haemodynamic response to the stimuli of interest was effectively sampled at 1-s intervals.

Motor responses were recorded using a commercially available MRI compatible fibre-optic response device (Lightwave Medical, Vancouver, BC). Reaction times to Go events were computed for trials in which the participants responded within 1000 ms of stimulus onset. Errors of commission were defined as responses that occurred within 1000 ms of the onset of a NoGo stimulus. Correctly-rejected NoGo events ('correct rejects') were determined by the absence of a motor response within 1000 ms of the NoGo stimulus.

Imaging parameters

Images were acquired on a standard clinical GE 1.5T system fitted with a Horizon Echo-speed upgrade. A custom head holder was used to prevent movement. Conventional spin-echo T₁-weighted sagittal localising images were acquired to view the positioning of the participant's head in the scanner and to prescribe the functional image volumes. Blood oxygen level dependent (BOLD) contrast images were collected with a gradient-echo sequence (TR/TE 3000/40 ms, flip angle 90°, 24 x 24 cm field of view, 64 x 64 matrix, 62.5 kHz bandwidth, 3.75 mm x 3.75 mm in plane resolution, 5 mm thickness, 29 slices) that effectively covered the entire brain (145 mm axial extent). A total of 142 brain volumes were

acquired. Four image volumes collected prior to the presentation of stimuli were discarded from subsequent analyses in order to remove the effects of the T₁ stabilisation process.

Image processing and analysis

Functional images were reconstructed offline, and realigned and motion-corrected using the procedure described by Friston et al. (1995a) and implemented in Statistical Parametric Mapping 99 (SPM99, Wellcome Department of Cognitive Neurology, London, UK. <http://www.fil.ion.ucl.ac.uk/spm/>). Corrections for translations and rotations did not exceed 3.0 mm and 2.5 degrees respectively for any participant. A Group (schizophrenic patients, healthy participants) x Movement (translation, rotation) x Displacement Axis (x, y, z) ANOVA was conducted on maximal estimated movement parameters to ensure that the groups did not differ in extent of head motion. A mean functional image was constructed in each participant and used to derive parameters for spatial normalisation into the modified Talairach stereotaxic space implemented in SPM99. Both affine and nonlinear components were used in the spatial normalisation (Friston et al., 1995b). The spatial normalisation parameters for each mean image were then applied to the corresponding functional images for each session, and the images were resampled into isotropic 4mm voxels. The normalised images were smoothed with an 8-mm full width at half-maximum Gaussian kernel to optimise the signal-to-noise ratio and compensate for intersubject anatomical variation. High frequency noise associated with alterations of the applied radio frequency field was removed using a 0.16 Hz low-pass fifth-order IIR butterworth filter applied to the fMRI time series at each voxel. While all coordinates in the present paper are reported and displayed in the modified Talairach stereotaxic space implemented in SPM99, a transformation algorithm was applied to these coordinates in order to localise activation patterns within standard Talairach space (i.e., to identify and label functional areas: Talairach & Tournoux, 1998; see <http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html> for the transformation algorithm).

Statistical analysis was performed within each voxel using the general linear model approach implemented in SPM99. Event-related responses to both errors of commission (EoC) and correct-rejects (CR) on NoGo stimuli were modeled using a synthetic haemodynamic response function comprised of two gamma functions and their temporal derivatives (Josephs et al., 1997; Friston et al., 1998). The first gamma function modelled the haemodynamic response peak at 6-s post-stimulus, and the second gamma function modelled the small ‘overshoot’ of the haemodynamic response on recovery. The occurrence of the erroneous motor response determined the timing of EoC (i.e., response-locked timing), whereas the timing of CR corresponded to the presentation of the NoGo stimulus (i.e., stimulus-locked timing). Response-locked timing for EoC was chosen for consistency with standard ERP data analysis methods. The temporal derivatives of the gamma functions were included to compensate for slight variation in the peak latency of the onset of the haemodynamic response. The response to the Go events was treated as a baseline and not explicitly modelled. A high-pass filter was applied to remove noise associated with low frequency confounds (e.g., respiratory artifact). The confounding effects of fluctuations in global signal intensity between image volumes were removed using an adjusted proportional scaling routine (Desjardins et al., 2001).

Two contrast images were specified for each participant, summarising the amplitude of the fitted response in each voxel to: (1) EoC relative to the baseline of motor responding to Go events, and (2) CR relative to the baseline of responding to Go events. These contrast images were then entered into separate independent samples t-tests at the second-level to test the null hypothesis that there was no difference between patients with schizophrenia and healthy participants in the mean amplitude of the fitted haemodynamic response for either of these event types. The contrast images were also entered into a second-level one-sample t-test for each group to test the null hypothesis that the mean of the observations on each event type

did not differ significantly from zero in either healthy participants or patients with schizophrenia.

To test the significance of the a priori hypothesis of reduced activation in rostral ACC in patients with schizophrenia compared to healthy participants during EoC, a correction for multiple comparisons at $p \leq 0.05$ within a predefined 12-mm diameter spherical region-of-interest (ROI) was applied. This ROI was centred on the rostral ACC voxel identified in Kiehl et al. (2000) as preferentially active in healthy participants during EoC compared to CR on NoGo trials (voxel coordinates $x\ y\ z = -8\ 45\ 15$). In addition to voxels within the rostral ACC, this ROI also incorporated voxels in the medial frontal gyrus (corresponding to Brodmann area 10). To ascertain whether patients with schizophrenia showed reduced activation compared to healthy participants in the region of caudal ACC that was preferentially active in healthy participants during EoC compared to CR trials in Kiehl et al. (2000), a second ROI in caudal ACC was specified (12-mm diameter sphere centred on voxel co-ordinates $x\ y\ z = 4\ 22\ 40$). To examine the specificity of the results to error trials rather than NoGo trials in general, both the rostral and caudal ROIs were also applied to the comparison of patients with schizophrenia and healthy participants on CR trials. Non-directed searches for differences between healthy participants and patients with schizophrenia on EoC and CR across the entire brain volume were implemented at the cluster level ($p \leq 0.05$ corrected for multiple comparisons, height threshold $p \leq 0.01$ uncorrected) according to the method of Worsley (1994) implemented in SPM99.

Results

Behavioural data

Mean reaction times for correct-hits to Go trials and EoC on NoGo trials for patients with schizophrenia were 393 ms (SD 60) and 349 ms (SD 48) respectively; and for healthy participants were 334 ms (SD 41) and 306 ms (SD 45) respectively. For subsequent reaction time analyses, correct-hits to Go trials were differentiated into three types; those that followed an error of commission to a NoGo trial (EoC-Go), those that followed a correct-rejected NoGo trial (CR-Go), and those that followed another correct-hit to a Go trial (Go-Go).

Reaction time (RT) data were analysed using a Group (healthy participants, schizophrenic patients) x Condition (EoC, EoC-Go, CR-Go, Go-Go) ANOVA. The analysis revealed a significant main effect of Group [$F(1, 24) = 9.18, p = 0.006$] indicating that healthy participants responded faster to the task stimuli than patients with schizophrenia. The slowed performance of patients with schizophrenia on this task is consistent with that typically observed on speeded RT tasks (e.g., Ngan & Liddle, 2000).

The main effect of Condition was also significant [$F(3, 72) = 7.40, p = 0.0002$], however, a non-significant Group x Condition interaction [$F(3,72) = 1.33, p = 0.27$] indicated that patients with schizophrenia responded more slowly than healthy participants across all trial types. The results of post-hoc Scheffé tests conducted on the RT means for the main effect of Condition are reported in Table 2. The RT for Go trials following an EoC were significantly longer than those for Go trials following a correctly-rejected NoGo stimulus, demonstrating that participants modified their response behaviour after committing an error. This was particularly true for patients with schizophrenia. A planned comparison between EoC-Go trials versus CR-Go trials confirmed that the increase in RT following errors was significant within the schizophrenic patient group [$F(1,24) = 7.90, p = 0.0097$]. The RT to Go trials

following correctly-rejected NoGo trials was less than that to Go trials following other correct Go trials, which may reflect the fact that NoGo trials were always followed by Go trials. As expected, our results replicate previous research demonstrating that EoC are associated with faster responding than occurs on correct-hits to Go trials, possibly reflecting premature or impulsive response decisions on error trials (e.g., Pailing et al., 2002).

Both healthy participants and patients with schizophrenia correctly identified the majority of Go stimuli (99.6% and 98.7% respectively), although patients responded to significantly fewer Go stimuli than healthy participants: $t(24) = 2.42$, $p = 0.024$. On NoGo trials, healthy participants and patients with schizophrenia did not differ significantly on accuracy of responding [mean EoC on NoGo trials were 16.6 (SD 7.2) and 16.3 (SD 6.4) in healthy participants and patients respectively; $t(24) = 0.94$, $p = 0.93$].

 Insert Table 2 about here

Imaging data

The non-significant main effect and interactions for Group in the ANOVA examining head motion [main effect: $F(1,24) = 0.613$, $p = 0.44$] indicates that the healthy participant and schizophrenic patient groups did not significantly differ on any estimated maximum head motion parameter, suggesting that movement did not contribute differentially to the haemodynamic results across groups.

Errors of commission. Within the ROI centred in the rostral ACC, direct comparison of the magnitude of the fitted response in the two groups during EoC revealed significantly greater activation in healthy participants compared to patients with schizophrenia (coordinates of voxel of peak activation: $x\ y\ z = -8\ 52\ 16$, $t(24) = 3.11$, $p = 0.043$ corrected for multiple comparisons within the volume of interest). Examination of the magnitude of the

fitted response at this peak voxel in the healthy participant and schizophrenic patient groups separately provided clarification of the nature of this effect (see Figure 1, solid lines).

Consistent with the findings of Kiehl et al. (2000), healthy participants showed significant recruitment of the rostral ACC/medial frontal gyrus during EoC (co-ordinates of voxel of peak activation: $x\ y\ z = -8\ 52\ 16$, $t(24) = 4.39$, $p = 0.009$ corrected for multiple comparisons within the volume of interest). By contrast, in the patients with schizophrenia, EoC were associated with a failure to activate this region.

 Insert Figure 1 about here

Direct comparison of the magnitude of the fitted response in the two groups during EoC in the ROI centred in caudal ACC revealed no significant difference between patients with schizophrenia and healthy participants at $p \leq 0.05$ corrected for multiple comparisons within the ROI volume. Inspection of the magnitude of the fitted response within the ROI for the healthy participant and schizophrenic patient groups separately provided some evidence that both groups recruited caudal ACC during EoC (co-ordinates of voxel of peak activation for healthy participants: $x\ y\ z = 0\ 24\ 36$, $t(24) = 1.88$, $p = 0.0392$ uncorrected for multiple comparisons; for patients with schizophrenia: $x\ y\ z = 8\ 28\ 40$, $t(24) = 3.20$, $p = 0.0054$ uncorrected).

A non-directed search of the entire brain to identify additional regions in which healthy participants demonstrated significantly greater activation than patients with schizophrenia during EoC failed to identify any clusters satisfying the criteria of correction for multiple comparisons. The four largest clusters of activation were located in the posterior cingulate gyrus (24 voxels; peak voxel co-ordinate and statistics: $x\ y\ z = 0\ -44\ 12$, $t(24) = 4.43$, $p = 0.001$ uncorrected for multiple comparisons across the entire brain), the rostral ACC/medial

frontal gyrus (24 voxels, peak voxel co-ordinate and statistics: $x\ y\ z = -12\ 60\ 0$, $t(24) = 3.18$, $p = 0.001$ uncorrected), the left hippocampus (14 voxels, peak voxel co-ordinate and statistics: $x\ y\ z = -32\ -20\ -12$, $t(24) = 3.37$, $p = 0.001$ uncorrected), and the left angular gyrus (14 voxels, peak voxel co-ordinate and statistics: $x\ y\ z = -48\ -72\ 32$, $t(24) = 3.21$, $p = 0.002$ uncorrected). Although none of these clusters satisfied stringent criteria for significance after correction for multiple comparisons in the entire brain volume, it is noteworthy that the three most significant clusters were located in limbic or paralimbic cortex. These clusters are illustrated in Figure 2.

 Insert Figure 2 about here

In the converse comparison that sought to identify brain regions in which patients with schizophrenia showed significantly greater activation than healthy participants during EoC, two clusters of 165 and 157 voxels respectively were observed (see Table 3 and Figure 3). These clusters were located bilaterally in the superior parietal lobule/precuneus, and the larger cluster in the left hemisphere extended into inferior parietal lobule and postcentral gyrus.

 Insert Table 3 and Figure 3 about here

Correctly-rejected trials. The ROI analysis directly comparing the magnitude of the fitted response in healthy participants and patients with schizophrenia in rostral ACC for CR trials did not reveal any significant voxel satisfying the correction within the specified small volume of interest. For the purposes of comparison, the magnitude of the fitted response for CR trials at the peak voxel identified for EoC is provided in the healthy participant and

schizophrenic patient groups separately in Figure 1 (hashed lines). The figure indicates that neither the healthy participants nor the patients with schizophrenia showed significant recruitment of the rostral ACC during CR trials.

Similarly, the ROI analysis that directly compared the magnitude of the fitted response between groups in caudal ACC for CR trials revealed no significant voxel satisfying correction within the volume of interest. Neither healthy participants nor patients with schizophrenia showed significant recruitment of this region of the caudal ACC during CR trials.

The non-directed search of the entire brain for regions showing greater activation in healthy participants compared to patients with schizophrenia during correctly-rejected NoGo trials failed to identify any clusters satisfying the criteria of correction for multiple comparisons. However, as for EoC, a large cluster of 34 suprathreshold voxels was located in posterior cingulate gyrus (peak voxel $x\ y\ z = 0\ -52\ 12$, $t(24) = 3.80$, $p = 0.001$ uncorrected for multiple comparisons across the entire brain; see Figure 2).

Four clusters were significantly more active in patients with schizophrenia than in healthy controls during CR trials (see Table 3 and Figure 3). As for EoC, two of these clusters were located bilaterally in the parietal cortex, with the two further clusters located in middle occipital cortex and in middle frontal cortex (premotor area).

Discussion

Our results demonstrate that schizophrenia is characterised by relative underactivity of the rostral ACC during commission of errors. While errors elicited increased haemodynamic activity in this region in healthy participants, patients with schizophrenia failed to recruit this area during EoC. The rostral ACC activation in healthy participants was not observed during correct non-response to NoGo stimuli, which is consistent with previous research indicating that this region is specifically involved in error processing (Kiehl et al., 2000; Braver et al., 2001; Menon et al., 2001). In caudal ACC, the haemodynamic activity elicited in the patient and healthy groups did not differ significantly during either EoC or CR. While there was some evidence that both groups activated this area of the caudal ACC during EoC, no significant activity was observed in this region in either group during CR to NoGo trials. ERP research has demonstrated an attenuation in the amplitude of the fronto-centrally distributed Ne/ERN in patients with schizophrenia relative to healthy participants (Kopp & Rist, 1999; Bates et al., 2002; Mathalon et al., 2002). Our fMRI results suggest that a failure to sufficiently activate the rostral ACC during error commission may contribute to the attenuated Ne/ERN observed in patients with schizophrenia.

The observation of aberrant activity in rostral ACC during EoC is consistent with the hypothesis that patients with schizophrenia experience a disturbed affective and/or motivational response to having committed an error. As an interface between limbic-paralimbic areas and widespread frontal cortex, the ACC would be expected to mediate the influence of the motivational and emotional state of an individual on the processing of, and response to, sensory stimuli. Disturbances in affect and motivation are common and persistent symptoms of schizophrenia. Bates et al. (2002) demonstrated that the expression of psychomotor poverty symptoms (including blunted affect and underactivity) is particularly associated with the attenuation of Ne/ERN. Thus, the attenuation of rostral ACC activity

during EoC in patients with schizophrenia may reflect a relative diminution of the affective or motivational response associated with their realisation that an error has been committed.

Relative underactivity in patients with schizophrenia compared to healthy participants was not apparent in the caudal ACC region identified by Kiehl et al. (2000) as being preferentially active during EoC compared to CR trials in healthy participants. This finding contrasts with that of Carter et al. (2001), who demonstrated diminished haemodynamic activity in the caudal ACC of patients with schizophrenia during errors that were elicited in a task that used degraded stimuli to increase error rates. As well as impaired caudal ACC function, the patients with schizophrenia in that study exhibited significantly reduced slowing of RT after error commission. In healthy individuals, RTs typically increase and fewer errors are committed following an erroneous response, which is consistent with the adoption of a more conservative response strategy following detection of an error (Rabbitt, 1966). Carter et al. (2001) interpreted the decreased error-related activity in caudal ACC and reduced post-error performance adjustment as evidence for impaired internal monitoring function in schizophrenia. The present Go/NoGo paradigm employed stimuli that were relatively easier to discriminate than the degraded stimuli employed in Carter et al. (2001), and errors were easily identifiable. The behavioural data obtained in this simple task revealed that patients with schizophrenia exhibited as great an increase in RT as was exhibited by healthy participants for Go trials following EoC relative to Go trials following CR, indicating that they modified their response behaviour following the commission of an error. This observation implies that they appropriately detected their error responses. Taken together, the results of the present study and those of Carter et al. (2001) suggest that there may be dissociable rostral and caudal ACC contributions to error processing, the relative strength of which may be modulated by task paradigm. Impairments in an internal monitoring component in schizophrenia appear to be reflected in caudal ACC underactivity, whereas

disturbance in a subjective affective error assessment process may be associated with relative decreases in rostral ACC activity in schizophrenia.

The question of the relative contributions of rostral and caudal ACC dysfunction to the attenuated Ne/ERN observed in schizophrenia is unresolved. A recent report of source-localisation of high-density ERP data from healthy participants modelled the Ne/ERN as having a caudal ACC generator (van Veen and Carter, 2002). The rostral ACC was also active during error processing, but later in time, and related to a positive error-related ERP component termed the error-positivity or Pe (Falkenstein et al., 2000). The current temporal resolution of fMRI does not allow the identification of differential Ne/ERN- and Pe-related contributions to ACC activity, and either component might be related to the rostral ACC activity elicited in healthy participants during error responses in the present study. However, previous research has failed to observe differences in Pe amplitude between patients with schizophrenia and healthy participants in spite of detecting a reduction in Ne/ERN amplitude in schizophrenia (Mathalon et al., 2002). Unpublished ERP data from a study in our laboratory that employed the same task as in the present study also failed to identify a difference in Pe amplitude between a small sample of acutely-ill patients with schizophrenia and healthy participants during EoC, in spite of observing a reduction in Ne/ERN amplitude in patients compared to healthy participants.

In addition to the error-related failure to activate rostral ACC, there was some evidence for relative underactivity in patients with schizophrenia compared with healthy participants in the hippocampus and posterior cingulate cortex during EoC. The cingulate and hippocampal gyri constitute part of the limbic lobe that regulates affective and motivational functions. Relative underactivity in patients in extended limbic cortex thus provides support for the hypothesis that the error-related abnormality in rostral ACC function is associated with a disturbed emotional or motivational reaction to errors in schizophrenia. While the hippocampal and

rostral ACC underactivity in schizophrenia were associated specifically with EoC, the posterior cingulate underactivity was also observed during correct response behaviour (i.e., on correctly-rejected NoGo events). Vogt et al. (1992) proposed a functional dichotomy between the anterior and posterior cingulate cortices, whereby the former is involved with executive functions and the emotional regulation of behaviour and the latter subserves evaluative events such as monitoring sensory events and the organism's own behaviour. Thus, the reported underactivity in posterior cingulate cortex in schizophrenia might reflect a generalised impairment in the ability to evaluate rare but behaviourally-relevant stimuli that occur against a background of more common events signalling an alternative behavioural response. Such a breakdown in posterior evaluative functions might be expected to increase the likelihood of error responses. While the limbic lobe activations reported outside the rostral ACC did not satisfy multiple correction criteria across the whole-brain and must be interpreted with caution, they are suggestive of widespread dysfunction within the limbic system in schizophrenia.

In addition to observing areas of relative underactivity in patients with schizophrenia, a number of brain areas showed greater activity in patients than in the healthy participants. On NoGo trials, regardless of the accuracy of their subsequent response, patients with schizophrenia showed a relative increase in activity bilaterally around the interparietal sulcus. Several fMRI studies employing event-related Go/NoGo paradigms in healthy adults have reported activation of the interparietal sulcus during response inhibition on NoGo trials that occurred in the context of prepotent responding to Go stimuli (Garavan et al., 1999; Braver et al., 2001; Liddle et al., 2001; Menon et al., 2001). The interparietal sulcus region is also activated across multiple sensory modalities during the detection of salient stimuli (Downar et al., 2000; 2001; 2002) and during the detection of rare, behaviourally-relevant target stimuli (Kiehl et al., 2001a; 2001b). Together, these results suggest that the interparietal

sulcus area plays an important role in assessing the relevance of incoming stimuli for the purposes of deciding whether or not a behavioural response to the stimuli is required. The relative hyperactivity of this region in patients with schizophrenia may imply that this process is more difficult for patients than healthy individuals, and hence requires relatively greater engagement of resources to perform the task.

The other clusters of increased activity in patients with schizophrenia relative to healthy participants during correctly-rejected NoGo trials occurred in right premotor cortex and left unimodal visual association cortex. Premotor cortex is involved in the planning and production of movements, particularly movements guided by external stimuli. The activated region was ipsilateral to the responding hand and the activation occurred during a trial that involved suppression, rather than commission, of a prepotent motor act. In acts of simple motor responding, patients with schizophrenia are characterised by reduced lateralisation of premotor activation compared to healthy participants (Mattay et al., 1997). Our results suggest that patients with schizophrenia also show a loss of hemispheric specialisation during regulation of motor activity. The explanation for the greater activation in visual association cortex is also uncertain. However, previous neuroimaging research has described an increase in the relative magnitude of signal intensity (Renshaw et al., 1994) and extent of activation (Taylor et al., 1997) in patients with schizophrenia relative to healthy participants in striate cortex during photic stimulation. Our results suggest that abnormalities in visual cortex function may extend beyond the initial processing of sensory stimuli in the context of minimal task requirements (i.e., maintaining fixation on visual stimuli) to disturbed function in areas concerned with evaluating the identity of visual stimuli.

The reported underactivity in rostral ACC and extended limbic-paralimbic cortex during EoC in patients with schizophrenia relative to healthy participants was observed in spite of the low levels of symptomology reported by the patients, who were outpatients living and

functioning in the community. Reality distortion symptoms (i.e., delusions and hallucinations) were the most common symptoms reported, with a variable, though relatively low occurrence of disorganised or negative symptoms reported across the patient group. Further research in a larger patient group is needed to clarify the relationship between affective and motivational disturbance (as well as other symptomology) and the relative reduction in rostral ACC activity during error commission in schizophrenia.

This paper examines the cortical response to the commission of errors in a medicated patient population, which raises the possibility that some of the observed differences between groups may be attributable to the effects of antipsychotic medication. Previous neuroimaging studies that have examined frontal function in unmedicated patients with schizophrenia have demonstrated both hypofrontality (Andreasen et al., 1992) and hyperfrontality (e.g., Ebmeier et al., 1993) of function, with patient symptomology contributing to variability in the extent of dysfunction. ACC function may be differentially affected by type of antipsychotic medication, as Braus et al. (2001, 2002) report higher levels of neuronal function markers in patients receiving atypical antipsychotics than in those receiving typical antipsychotics. The present study indicates that rostral ACC activity is reduced compared to healthy participants even in a sample of patients who were receiving atypical antipsychotic medication. Further research examining error-related activity in unmedicated patients pre- and post-treatment is required to determine the effect of antipsychotic medication on error processing and internal monitoring in schizophrenia.

In the present study, we have demonstrated that schizophrenia is associated with relative underactivity of the rostral ACC and associated limbic-paralimbic structures during the commission of errors in a simple Go/NoGo task variant. We additionally identified several brain regions, particularly bilateral parietal cortex, in which patients were characterised by abnormal overactivity compared with healthy participants during NoGo trial processing,

suggesting a disturbance in response inhibition or stimulus evaluation processes in schizophrenia. Our results indicate that during performance of the simple Go/NoGo task employed in this study, the error monitoring system of patients with schizophrenia functions sufficiently well to detect errors. However, the pattern of activation and corresponding behavioural data indicate that the affective evaluation or motivational response to error commission is impaired. Future research might test this hypothesis by examining whether the rostral ACC activity associated with EoC normalises in patients with schizophrenia when the salience of response accuracy is increased (e.g., by rewarding correct responses and/or penalising erroneous responses).

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Acknowledgements

The authors wish to thank Tara Cairo and Cameron Anderson for assistance with participant recruitment and data collection, MR technicians Jennifer McCord, Sylvia Renneberg, and Trudy Shaw, and Drs. Alex MacKay, Ken Whittall, and Bruce Forster. This research was supported in part by grants from the Dr. Norma Calder Foundation for Schizophrenia Research and the Medical Research Council of Canada. KRL was supported by the Gertrude Langridge Graduate Scholarship in Medical Sciences and a University of British Columbia Graduate Fellowship. ATB was supported by a scholarship from the Natural Science and Engineering Research Council of Canada.

Table 1. Demographic data for patients with schizophrenia and matched healthy control participants.

Variable	Healthy		Schizophrenic	
	Participants		Patients	
	Mean	SD	Mean	SD
Age	32.3	10.6	32.9	12.9
Parental socioeconomic status (Hollingshead)	3.7	1.2	3.5	1.0
Premorbid intellectual functioning (NART)	116	6.1	116	7.3
Current intellectual functioning (Quick Test) ^a	107	9.7	101	8.2

Note: ^a Data from one healthy participant was not available.

Table 2. Significance of post-hoc Scheffé tests on reaction time means for the main effect of Condition.

	Reaction Time Condition			
	Go-Go (Mean: 366 ms)	EoC-Go (Mean: 365 ms)	CR-Go (Mean: 329 ms)	EoC (Mean: 327 ms)
Go-Go		.9993	.0124*	.0082*
EoC-Go			.0178*	.0120*
CR-Go				.9991

Note: Condition Go-Go = Correct-hits to Go trials following another correctly-hit Go trial; EoC-Go = Correct-hits to Go trials following an error of commission to a NoGo trial; CR-Go = Correct-hits to Go trials following a correctly-rejected NoGo trial; EoC = Errors of commission on NoGo trials

Table 3. Clusters showing significantly greater activation in patients with schizophrenia compared with healthy participants for errors of commission to NoGo stimuli and correctly-rejected NoGo stimuli. Random effects cluster-level statistics ($p \leq 0.01$ height threshold for inclusion in the cluster) are reported along with voxel-level statistics from several representative maxima of activation within the cluster.

Cluster-level statistics			Voxel-level statistics				Talairach co-ordinates			Anatomical Label (Brodmann Area ^a)
$p_{\text{corrected}}$	k_E	$p_{\text{uncorrected}}$	$p_{\text{corrected}}$	T	(Z_e)	$p_{\text{uncorrected}}$	x	y	z	

Errors of Commission

0.001	165	0.000	0.888	4.42	(3.74)	0.000	-24	-72	44	Left superior and inferior parietal
			0.999	3.75	(3.29)	0.000	-36	-44	40	lobules, precuneus, and postcentral
			1.000	3.17	(2.87)	0.002	-28	-44	64	gyrus (7/40/2/3)
0.001	157	0.000	0.816	4.45	(3.83)	0.000	20	-64	52	Right precuneus and superior parietal
			1.000	3.64	(3.22)	0.001	28	-80	32	lobule (7/19)
			1.000	3.64	(3.21)	0.001	16	-72	60	

Correct-Rejects

0.003	134	0.000	0.882	4.44	(3.75)	0.000	24	-12	60	Right middle frontal gyrus (6/9)
			1.000	3.65	(3.22)	0.001	28	-4	48	
			1.000	3.20	(2.89)	0.002	40	8	40	
0.007	115	0.000	0.936	4.30	(3.67)	0.000	40	-36	44	Right inferior parietal lobule, precuneus, and postcentral gyrus (40/7/2)
			0.999	3.80	(3.33)	0.000	32	-40	52	
			1.000	3.57	(3.16)	0.001	20	-60	56	
0.031	86	0.001	0.999	3.82	(3.35)	0.000	-28	-56	48	Left inferior parietal lobule, and precuneus (7/19)
			1.000	3.70	(3.26)	0.001	-20	-76	48	
			1.000	3.03	(2.76)	0.003	-24	-76	32	
0.039	82	0.001	0.810	4.57	(3.84)	0.000	-44	-80	0	Left middle occipital gyrus, cuneus, and lingual gyrus (19/17/18)
			0.997	3.90	(3.40)	0.000	-16	-84	4	

1.000 3.18 (2.88) 0.002 -20 -80 -4

Note: ^a Brodmann areas correspond to those provided in the atlas of Talairach and Tournoux (1988).

Figure 1. Mean magnitude of the fitted response (± 2 standard errors of the mean) at the voxel of peak activation (x y z co-ordinates = -8 52 16) located within the rostral anterior cingulate cortex/medial frontal gyrus region-of-interest identified in the comparison of errors of commission on NoGo trials relative to a baseline of responding to Go trials. The magnitude of the fitted response is provided for errors of commission to NoGo trials (EoC; solid lines) and correctly-rejected NoGo trials (CR; hashed lines) relative to baseline in patients with schizophrenia (right) and healthy control participants (left).

Figure 2 Illustration of limbic and paralimbic clusters in which greater haemodynamic activity was observed in healthy participants than in patients with schizophrenia during errors of commission to NoGo stimuli (EoC; top row) and correctly-rejected NoGo stimuli (CR; bottom row) relative to a baseline of responding to Go stimuli. Data is presented in the modified Talairach space used in SPM99 and is rendered onto a standard reference brain. The sagittal slices illustrating clusters in the anterior and posterior cingulate cortex are located at $x = -4$; the transverse slice illustrating the cluster in the hippocampal gyrus is located at $z = -16$. The view is in neurological convention, with the left hemisphere indicated by 'L' and the right hemisphere indicated by 'R'. The image is thresholded at a height of $t(24) = 2.49$, which corresponds to a significance level of $p \leq 0.01$ uncorrected for multiple comparisons. None of the illustrated differences in cerebral activation were statistically significant after correcting for multiple comparisons across the whole brain.

Figure 3 Illustration of the significant clusters in which greater haemodynamic activity was observed in patients with schizophrenia than in healthy participants during errors of commission to NoGo stimuli (EoC; top row) and correctly-rejected NoGo stimuli (CR; bottom row) relative to a baseline of responding to Go stimuli. Data is presented in the modified Talairach space used in SPM99 and is rendered onto a standard reference brain. For EoC, the sagittal slices are located at (from left) $x = -32, -24,$ and $+ 24$; the sagittal slices for CR are located at (from left) $x = -32, -24, +40$ and -44 . The view is in neurological convention, with the left hemisphere indicated by 'L' and the right hemisphere indicated by 'R'. The image is thresholded at a height of $t(24) = 2.49$, which corresponds to a significance level of $p \leq 0.01$ uncorrected for multiple correction criteria across the whole brain. All clusters are significant at $p \leq 0.05$ corrected for multiple comparisons.

Figure 1.

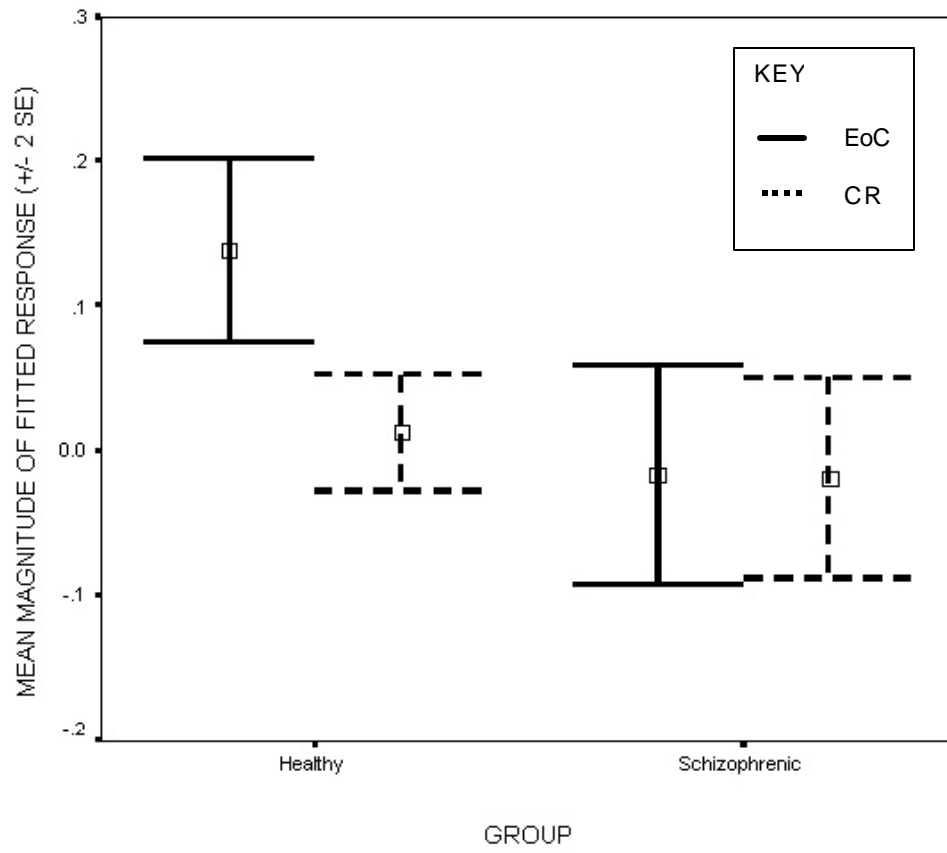


Figure 2.

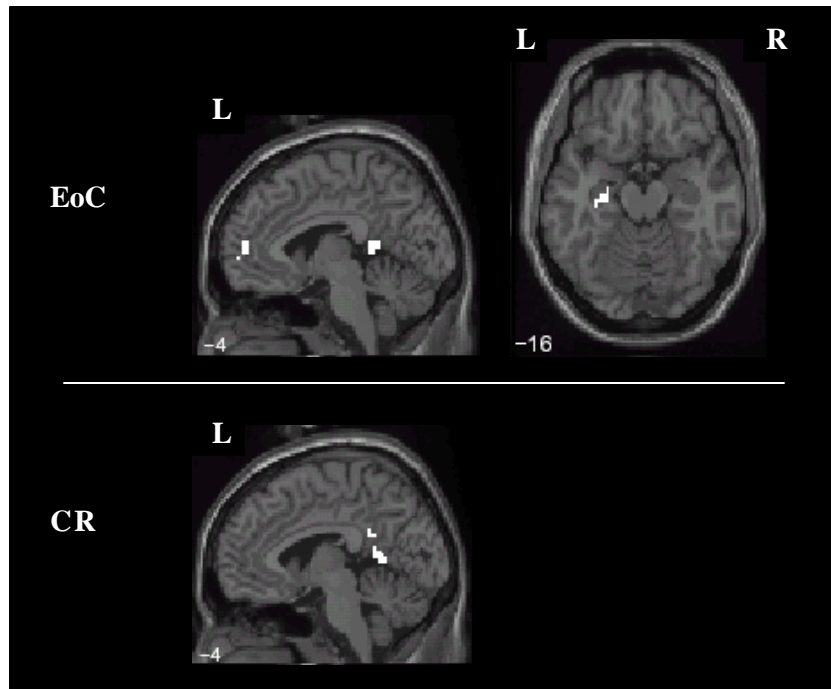


Figure 3.

