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Reduced error-related activation in two anterior cingulate circuits is related to impaired performance in schizophrenia

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To perform well on any challenging task, it is necessary to evaluate your performance so that you can learn from errors. Recent theoretical and experimental work suggests that the neural sequellae of error commission in a dorsal anterior cingulate circuit index a type of contingency- or reinforcement-based learning, while activation in a rostral anterior cingulate circuit reflects appraisal of the affective or motivational significance of errors. Patients with schizophrenia show rigid, perseverative behaviour that is not optimally responsive to outcome. Findings of reduced anterior cingulate cortex (ACC) activity during error commission in schizophrenia suggest that difficulties in evaluating and modifying behaviour in response to errors may contribute to behavioural rigidity. Using event-related functional MRI and an antisaccade paradigm with concurrent monitoring of eye position, the present study examined error-related activation and its relation to task performance in the anatomic components of two ACC circuits that are theorized to make distinct contributions to error processing. Eighteen chronic-medicated schizophrenia patients and 15 healthy controls participated. Compared to controls, patients showed increased antisaccade error rates and decreased error-related activation in the reinforcement learning network—dorsal ACC, striatum and brainstem (possibly substantia nigra)—and also in the affective appraisal network—rostral ACC, insula and amygdala. These reductions remained when the effects of antipsychotic medication dose and error rate were statistically controlled. Activation in these networks was inversely related to error rate in both patient and control groups, but the slope of this relation was shallower in patients (i.e. across participants with schizophrenia, decrements in error rate were associated with smaller decrements in activation). This indicates that the blunted neural response to errors in schizophrenia was not simply a reflection of more frequent errors. Our findings demonstrate a blunted response to error commission that is associated with worse performance in two ACC circuits in schizophrenia. In the dACC circuit, the blunted response may reflect deficient modification of prepotent stimulus-response mappings in response to errors, and in the rACC network it may reflect diminished concern regarding behavioural outcomes. However, despite these deficits and in the absence of external feedback regarding errors, patients corrected their errors as frequently as controls suggesting intact error recognition and ability to institute corrective action. Impairments in evaluating and learning from errors in schizophrenia may contribute to behaviour that is rigid and perseverative rather than optimally guided by outcomes, and may compromise performance across a wide range of tasks.

Keywords: schizophrenia; anterior cingulate cortex; response monitoring; functional MRI; error processing

Abbreviations: ACC = anterior cingulate cortex; BPRS = Brief Psychiatric Rating Scale; CPZ = chlorpromazine; ERN = error-related negativity; ERP = event-related potentials; FIR = finite impulse response; HDR = haemodynamic responses; PANSS = Positive and Negative Syndrome Scale

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Introduction

Adaptive behaviour depends on the continuous monitoring and flexible adjustment of responses based on their outcome. Schizophrenia is characterized by behaviour that is rigid and perseverative, rather than guided by outcome. Findings of abnormal brain activity during error commission in schizophrenia suggest that difficulty in learning from errors may contribute to behavioural rigidity. Error processing, which encompasses error detection, evaluation and consequent behavioural adjustments, is thought to rely on the anterior cingulate cortex (ACC) on the basis of extensive evidence from functional neuroimaging, electrophysiological, lesion and intracranial recording studies (Taylor *et al.*, 2007). In schizophrenia, functional MRI (fMRI) studies provide evidence of a diminished ACC response to error commission (Carter *et al.*, 2001; Laurens *et al.*, 2003; Kerns *et al.*, 2005). Using event-related fMRI and an antisaccade paradigm, the present study extends this work by examining error-related activation in the anatomic components of two ACC circuits that are theorized to make distinct contributions to error processing and by examining the relation of error-related activation to task performance.

The ACC can be divided into a dorsal region (dACC) that connects with striatum to oversee motor and cognitive processes, and a rostral region (rACC) that interacts with other paralimbic and limbic regions, including the amygdala and insula, to mediate emotional processes (Devinsky *et al.*, 1995; Bush *et al.*, 1998; Whalen *et al.*, 1998; Bush *et al.*, 2000; Phillips *et al.*, 2003). Both dorsal and rostral ACC show increased activation in response to errors (Carter *et al.*, 1998; Kiehl *et al.*, 2000) and have been identified as potential generators of event-related potentials (ERPs) that follow errors (Dehaene *et al.*, 1994; van Veen and Carter, 2002; Luu *et al.*, 2003; Mathalon *et al.*, 2003; Miltner *et al.*, 2003). Consistent with their differences in cytoarchitecture, connectivity, and function, dorsal and rostral ACC are thought to make distinct contributions to error processing.

A recent theory proposes that following error commission, dACC implements error-based reinforcement learning using feedback from the striatum and the mesencephalic dopamine system (Holroyd and Coles, 2002). Specifically, using dopaminergic input, the dACC is thought to modify the strength of stimulus-response mappings in response to error feedback and thereby improve performance. In this theory, errors are followed by a phasic suppression of dopamine that increases dACC activity and elicits the error-related negativity (ERN: Falkenstein *et al.*, 1991; Gehring *et al.*, 1993), an event-related potential (ERP) occurring ~100 ms post-error. Thus both dACC activity following errors and ERN can be conceptualized as training signals that are used to implement reinforcement learning in response to error feedback (Holroyd and Coles, 2002; Brown and Braver, 2005).

Rostral ACC activity following errors has been proposed to reflect appraisal of the affective or motivational significance of errors (van Veen and Carter, 2002; Luu *et al.*, 2003; Taylor *et al.*, 2006). Such appraisal may also involve the insula and amygdala, both of which are densely interconnected with the rACC (van Hoesen *et al.*, 1993) and show increased activity with errors (Menon *et al.*, 2001; Brazdil *et al.*, 2002; Garavan *et al.*, 2002).

In schizophrenia, ERP and fMRI studies report reduced ERN amplitude and reduced activation in both rostral and dorsal ACC following errors (Kopp and Rist, 1999; Carter *et al.*, 2001; Alain *et al.*, 2002; Mathalon *et al.*, 2002; Bates *et al.*, 2002; Laurens *et al.*, 2003; Kerns *et al.*, 2005; Morris *et al.*, 2006). Even in the context of an abnormal ERN however, error positivity (Pe) (Falkenstein *et al.*, 1995), an ERP occurring ~200–500 ms following an error (van Veen and Carter, 2002), is intact suggesting that error-processing deficits in schizophrenia are selective (Alain *et al.*, 2002; Mathalon *et al.*, 2002; Morris *et al.*, 2006).

The present study employed an antisaccade paradigm to examine error-related activation of dorsal and rostral ACC circuitry in schizophrenia, and its relation to task performance. The paradigm consisted of a pseudorandom sequence of prosaccade and antisaccade trials. Prosaccade trials require the simple prepotent response of looking towards a suddenly appearing visual stimulus. Antisaccade trials require suppression of the prepotent prosaccade, and the substitution of the novel behaviour of looking in the opposite direction (Hallett, 1978). Schizophrenia patients consistently show an elevated antisaccade error rate (McDowell and Clementz, 1997; Hutton *et al.*, 1998; Curtis *et al.*, 2001; Manoach *et al.*, 2002; Radant *et al.*, 2007). Analyses of error-related activation were restricted to antisaccade trials since healthy and schizophrenia participants produce few prosaccade errors with this paradigm (Manoach *et al.*, 2002).

We expected patients to make more antisaccade errors and show reduced error-related activation in the dACC, consistent with previous reports, and also in striatum and substantia nigra—constituents of the network theorized to mediate error-based reinforcement learning. Since error-related dACC activation is reduced when errors are more frequent (Brown and Braver, 2005), we also expected dACC activation to be inversely related to error rate. This hypothesis is consistent with the theory that both dACC activity following errors and ERN are training signals that code discrepancies between actual and expected outcomes, and their strength directly reflects the degree to which errors are unexpected (Holroyd and Coles, 2002; Brown and Braver, 2005). More frequent errors are also more predictable and should therefore elicit a reduced dACC and ERN response. This is consistent with previous findings of an inverse relation of ERN amplitude with error rate (Gehring *et al.*, 1993; Hajcak *et al.*, 2003). We investigated whether the relation of error rate with dACC activation was altered in schizophrenia. If the slope of the relation

Table 1 Means,standard deviations and group comparisons of demographic data and rating scale scores.

Subject characteristics	Healthy controls ($n = 15$)	Schizophrenia patients ($n = 18$)	t	P
Age	37 ± 10	42 ± 11	-1.50	0.14
Sex	11M/4F	13M/5F	Phi = 0.01	0.99
Laterality score (Handedness)	92 ± 11	89 ± 13	0.59	0.56
Parental SES[a]	2.4 ± 0.3	2.5 ± 0.2	$z = -0.42$	0.66
Age of onset		25 ± 2		
Length of Illness (years)		17 ± 2		
BPRS		18 ± 2	Minimal level of severity	
PANSS positive		14 ± 1	Mild level of severity	
PANSS negative		17 ± 2	Mild level of severity	

[a]A lower score denotes higher status.
The Phi value is the result of a Fishers exact test. The z value is the result of a nonparametric Mann–Whitney U comparison.

were the same in patients and controls (i.e. patients have increased errors and correspondingly lower dACC activation), this would imply a normal network response to a higher error rate in schizophrenia and group differences in dACC activation should disappear when error rate is controlled. If, however, the relation were disrupted in schizophrenia (i.e. either no relation or a shallower slope in patients than controls), this would imply an abnormally reduced dACC response to errors. We also examined activation in rACC, amygdala and insula and its association with error rate. Reduced activation in this network in schizophrenia would be consistent with reduced affective appraisal of errors.

Methods

Participants

Schizophrenia outpatients were recruited from an urban mental health centre. They had been maintained on stable doses of atypical antipsychotic medications for at least 6 weeks, with the exception of one participant taking fluphenazine. Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV (First *et al.*, 1997). Clinical status was characterized with the Positive and Negative Syndrome Scale (PANSS, Kay *et al.*, 1987) and the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham, 1962). Healthy control participants, without a history of psychiatric illness, were recruited from the hospital and research communities by poster and website advertisements. All participants were screened to exclude substance abuse or dependence within the preceding 6 months and any independent conditions that might affect brain function. The data from two patients and one control participant could not be used due to eye tracker malfunction during scanning. Analyses were conducted on the remaining 18 schizophrenia patients and 15 control participants. Groups did not differ in age, gender, handedness as measured by the modified Edinburgh Handedness Inventory (Oldfield, 1971; White and Ashton, 1976), or parental socioeconomic status as determined by the Hollingshead Index (Hollingshead, 1965) (Table 1). The study was approved by the Partners Human Research Committee and the Central Office Research Review Committee of the Massachusetts Department of Mental Health. All participants gave written informed consent after the experimental procedures had been fully explained.

Saccadic paradigm

Prior to scanning, the task was explained and participants practiced in a mock scanner until their performance indicated that they understood the directions and were comfortable performing the task. Participants were encouraged to respond as quickly and accurately as possible. In addition to a base rate of pay, they received 5 cents for each correct response, an incentive intended to enhance attention and motivation. Each run of the task consisted of a pseudorandom sequence of prosaccade and antisaccade trials that were balanced for right and left movements. Figure 1 provides a graphic depiction of the task and a description of task parameters. Randomly interleaved with the saccadic trials were intervals of fixation lasting 2, 4 or 6 s. The fixation intervals provided a baseline and their variable length introduced 'temporal jitter', which optimizes the analysis of rapid presentation event-related fMRI designs (Buckner *et al.*, 1998; Burock and Dale, 2000; Miezin *et al.*, 2000). The schedule of events was determined using a technique to optimize the statistical efficiency of event-related designs (Dale, 1999). Participants performed six runs of the task, each lasting 5 min 22 s, with short rests between runs. The total experiment lasted about 40 min and generated a total of 211 prosaccade trials, 211 antisaccade trials and 80 fixation intervals.

Stimulus display and eye tracking

Displays of the eye movement task were generated using the Vision Shell programming platform (www.visionshell.com), and back-projected with a Sharp XG-2000 color LCD projector (Osaka, Japan) onto a screen at the rear of the bore that was viewed by the participant via a mirror on the head coil. Vision Shell triggered the scanner to begin acquiring data. The ISCAN fMRI Remote Eye Tracking Laboratory (ISCAN, Burlington, MA) recorded saccades during scanning. This system used a video camera mounted at the rear of the MRI bore. The camera imaged the eye of the supine participant via an optical combiner, a 45° cold transmissive mirror that reflects an infrared image of the eye, with the infrared illumination being provided by an LED mounted on the head coil. The system uses passive optical components with

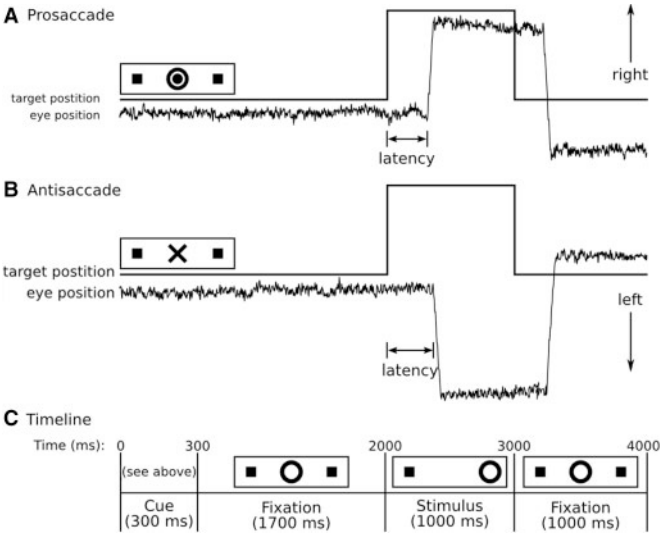

Fig. 1 Saccadic paradigm with idealized eye position traces. Saccadic trials lasted 4000 ms and began with an instructional cue at the center of the screen. For half of the participants, orange concentric rings were the cue for a prosaccade trial (**A**) and a blue X was the cue for an antisaccade trial (**B**). These cues were reversed for the rest of the participants. The cue was flanked horizontally by two small green squares of 0.2° width that marked the potential locations of targets, 10° left and right of center. These squares remained on the screen for the duration of each run. (**C**) At 300 ms, the instructional cue was replaced by a green fixation ring at the center of the screen, of 0.4° diameter and luminance of 20 cd/m^2. After 1700 ms, the ring shifted to one of the two target locations, right or left, with equal probability. This was the target to which the participant responded. The green ring remained in the peripheral location for 1000 ms and then returned to the center, where participants were also to return their gaze for 1000 ms before the start of the next trial. Fixation intervals were simply a continuation of the fixation display that constituted the final second of the previous saccadic trial.

no ferrous content within the bore in order to minimize artifacts in the MRI images. Eye position was sampled at a rate of 60 Hz. Eye images were processed by ISCAN's RK-726PCI high resolution Pupil/Corneal reflection tracker, located outside of the shielded MRI room. Stimuli presented by Vision Shell were digitally encoded and relayed to ISCAN as triggers that were inserted into the eye-movement recordings.

Scoring and analysis of eye movement data

Eye movement data were scored in MATLAB (Mathworks, Natick, MA) using a partially automated program that determined the directional accuracy of each saccade with respect to the required response and the latency from target onset. Saccades were identified as horizontal eye movements with velocities exceeding 47°/s. The onset of a saccade was defined as the point at which the velocity of the eye movement first exceeded 31°/s. Only trials with saccades in the desired direction and latencies over 130 ms were considered correct, and only correct saccades were included in the latency analyses. The cutoff of 130 ms excluded anticipatory saccades, which are executed too quickly to be a valid response to the appearance of the target (Fischer and Breitmeyer, 1987). We divided corrective saccades that followed antisaccade errors into short and long latency self-corrections (cf., Polli *et al.*, 2006): those for which the corrective saccade followed the initiation of the error by more than 130 ms, which suggests that the correction was a conscious (aware) response to visual feedback regarding an error, and those with latencies under 130 ms, which suggests that the correction represented a concurrently programmed correct saccade, and that the participant was unaware of having made an error (Mokler and Fischer, 1999; McPeek *et al.*, 2000). Error rate, latency of correct trials and self-correction rates for antisaccade errors, were compared by group.

Image acquisition

Images were acquired with a 3.0T Siemens Trio whole body high-speed imaging device equipped for echo planar imaging (EPI) (Siemens Medical Systems, Erlangen, Germany). Head stabilization was achieved with cushioning, and all participants wore earplugs (29 dB rating) to attenuate noise. Automated shimming procedures were performed and scout images were obtained. Two high-resolution structural images were acquired in the sagittal plane for slice prescription, spatial normalization (spherical and Talairach) and cortical surface reconstruction using a high resolution 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR), 2530 ms; echo spacing, 7.25 ms; echo time (TE), 3 ms; flip angle 7°) with an in-plane resolution of 1 mm and 1.3 mm slice thickness. T_1 and T_2-weighted structural images, with the same slice specifications as the Blood Oxygen Level Dependent (BOLD) scans, were obtained to assist in registering functional and structural images. Functional images were collected using a gradient echo T_2^*-weighted sequence (TR/TE/Flip = 2000 ms/30 ms/90°). Twenty contiguous horizontal slices parallel to the intercommissural plane (voxel size: $3.13 \times 3.13 \times 5\,mm^3$) were acquired interleaved. The functional sequences included prospective acquisition correction (PACE) for head motion (Thesen *et al.*, 2000). PACE adjusts slice position and orientation in real time during data acquisition. This reduces motion-induced effects on magnetization history.

Analysis of imaging data

All analyses were conducted using FreeSurfer (Fischl *et al.*, 1999*a*) and FreeSurfer Functional Analysis Stream (FS-FAST) software (Burock and Dale, 2000). In addition to on-line motion correction (PACE), functional scans were corrected retrospectively for motion using the AFNI algorithm (Cox and Jesmanowicz, 1999), intensity normalized, and smoothed using a 3D 8 mm FWHM Gaussian kernel. Functional images were aligned to the 3D structural image for each participant that was created by averaging the two MPRAGE scans after correcting for motion. For surface-based analyses, the averaged MPRAGE scans were used to construct inflated (2D) models of individual cortical surfaces using previously described segmentation, surface reconstruction and inflation algorithms (Dale *et al.*, 1999; Fischl *et al.*, 1999*a*). Finite impulse response (FIR) estimates (Burock and Dale, 2000; Miezin *et al.*, 2000) of the event-related haemodynamic responses (HDR) were calculated for each of the four trial types (correct prosaccades, error prosaccades, correct antisaccades and error antisaccades) for each participant. This involved using a linear model to provide unbiased estimates of the average signal intensity at each time point for each trial type without making *a priori* assumptions about the shape of the HDR. HDR estimates were

computed at 12 time points with an interval of 2 s (corresponding to the TR) ranging from 4 s prior to the start of a trial to 18 s after the start. Temporal correlations in the noise were accounted for by prewhitening using a global estimate of the residual error autocorrelation function truncated at 30 s (Burock and Dale, 2000).

Region-of-interest (ROI) analyses

Given our *a priori* hypotheses, we first examined group differences in activation in the regions that comprise the dACC and rACC circuits. We used a two-step approach to define these regions based on individual participant anatomy and regional activity. This approach avoids signal loss due to morphological and functional variability between participants (Brett *et al.*, 2002) and increases statistical power due to signal averaging within participants. This is particularly important for inter-group comparisons given the greater morphological variability (Park *et al.*, 2004) and greater heterogeneity in the location of peak fMRI activation (Manoach *et al.*, 2000; Manoach, 2003) in schizophrenia.

ROIs were defined in the unregistered images of individual participants. ACC and insula were defined using an automated parcellation for the cortical surface (Fischl *et al.*, 2004). The ACC ROI was divided into dorsal and rostral regions using a line drawn perpendicular to the intercommissural plane at the anterior boundary of the genu of the corpus callosum (Devinsky *et al.*, 1995). Caudate, putamen, brainstem and amygdala were defined using a volumetric segmentation procedure (Fischl *et al.*, 2002). Despite our specific interest in the substantia nigra, our ROI encompassed the entire brainstem since the segmentation procedure does not subdivide the brainstem. We quantified activation in each ROI by averaging across the voxels (or vertices on the cortical surface) showing positive activation in the error versus correct contrast at 6 and 8 s, since these time points showed peak error-related activation in a previous study (Polli *et al.*, 2005). Only the 6 s data is presented since only one ROI, the putamen, showed a significant group difference at 8 s.

Analysis of registered group data

We also examined activation on the cortical surface and in the volume for the registered group data to determine the localization of activation within *a priori* ROIs. To register data across participants, anatomical and functional scans were spatially normalized using a surface-based spherical coordinate system that employs a non-rigid alignment algorithm based on sulcal and gyral patterns (Dale *et al.*, 1999; Fischl *et al.*, 1999*a*, *b*) and smoothed with a 2D 4.6 mm FWHM Gaussian kernel. Cortical activation was localized using an automated surface-based parcellation system (Fischl *et al.*, 2004). To investigate subcortical activation, structural and functional volumes were registered to the Montreal Neurological Institute (MNI305) atlas (Collins *et al.*, 1994), and coordinates were transformed to standard Talairach space using an algorithm developed by Matthew Brett (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

We compared activation in error versus correct antisaccades both within and between groups using a random effects model at 6 and 8 s. To correct for multiple comparisons on the cortical surface, 10 000 Monte Carlo simulations of synthesized white Gaussian noise were run using the smoothing, resampling, and averaging parameters of the functional analyses. This determines the likelihood that a cluster of a certain size would be found by chance for a given threshold. For the between-group comparison the threshold was set to $P \leqslant 0.05$ to be sensitive to group differences, and for the within-group analyses it was set to $P \leqslant 0.001$. The difference in thresholds reflects the expectation that the between-group differences (group by condition interaction) would be smaller than the main effect of condition (i.e. the greater activity for error than correct trials within each group). For both between and within group analyses the cluster-wise threshold (CWP) derived from the simulations was $P \leqslant 0.05$ corrected for multiple comparisons on the surface. For the subcortical analyses, a false discovery rate was used to set the overall P-level to 0.05. This method of correction for multiple comparisons accounts for the smaller volume of subcortical structures (Filipek *et al.*, 1994).

Regressions of error-related activation on error rate

To examine the relations between error-related activation and error rate, activation in the error versus correct contrast at 6 s was regressed on error rate for each ROI. An interaction term (error rate by group) was included in the model to test whether the slope of the relation differed by group. We also conducted these regressions in the registered group data for each vertex on the cortical surface and for each voxel in the volume. Correction for multiple comparisons on the cortical surface was based on Monte Carlo simulations (described above) restricted to *a priori* regions. For the volume we used false discovery rate. These methods set the corrected overall probability level to 0.05.

Relations of error-related activation to symptoms

On an exploratory basis, we examined the relations of error-related activation in each ROI to positive and negative symptom scores on the PANSS.

Control analyses

Motion

To characterize average motion for each participant, the total motion in millimetres for all six directions (x, y, z and three rotational directions), as determined by the AFNI motion correction algorithm, was averaged across the six runs of the task and compared between groups.

Effect of antipsychotic medications

To estimate the effect of medication on BOLD signal and to determine whether group differences in activation remained significant when this effect was statistically controlled, we regressed activation in the error versus correct contrast at 6 s on antipsychotic medication dose as measured by chlorpromazine (CPZ) equivalent (Woods, 2003) for each ROI. We adjusted the estimates of activation by subtracting the product of the slope of the regression and CPZ equivalent from activation for each ROI in each participant with schizophrenia. These adjusted ROI activation estimates in patients were compared with the original estimates in controls using t-tests.

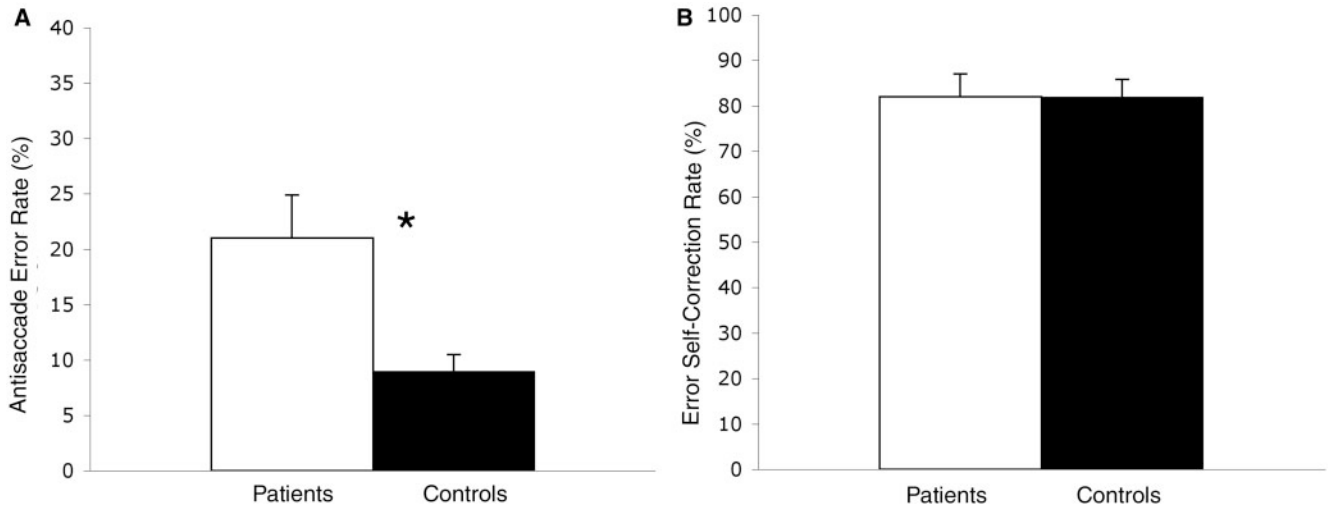

Fig. 2 Bar graphs of performance for each group as measured by (**A**) antisaccade error rate and (**B**) percentage of antisaccade error self-corrections with standard error bars. The filled bars represent the controls.

Effect of error rate

We used a similar procedure to determine whether group differences in activation remained after error rate was controlled. Regressions of error-related activation on error rate were performed in each group separately for each ROI. Estimates of activation were adjusted by subtracting the product of the slope of the regression and error rate for each ROI in each participant. These adjusted ROI activation estimates were compared between groups using *t*-tests.

Effect of age

Although the groups did not differ significantly in age, on average patients were 5 years older than controls. To determine whether group differences in activation remained significant when the effect of age was controlled, regressions of error-related activation on age were performed in each group separately for each ROI. Estimates of activation were adjusted by subtracting the product of the slope of the regression and age for each ROI in each participant. These adjusted ROI activation estimates were compared across groups.

Results

Saccadic performance

Schizophrenia patients made more errors than healthy controls [$F(1,31) = 8.19$, $P = 0.007$] and there was a group by task interaction [$F(1,31) = 4.45$, $P = 0.04$] reflecting that patients made significantly more antisaccade errors than controls [Fig. 2; $21 \pm 17\%$ versus $9 \pm 6\%$; $t(31) = 3.55$, $P = 0.001$], but did not differ in prosaccade errors [$3 \pm 2\%$ versus $6 \pm 7\%$; $t(31) = 0.84$, $P = 0.41$]. Patients also showed a trend toward longer latencies for correct responses [$F(1,29) = 2.87$, $P = 0.10$; antisaccades: 326 ± 64 ms versus 293 ± 41 ms, $t(29) = 1.72$, $P = 0.08$; prosaccades: 268 ± 99 ms versus 240 ± 68 ms, $t(29) = 1.65$, $P = 0.10$] that did not differ by task [$F(1,29) = 0.17$, $P = 0.68$]. Total rate of antisaccade error self-correction did not differ by group [Fig. 2; controls: $82 \pm 15\%$; patients: $78 \pm 21\%$; $F(1,31) < 1$, $P = 0.50$], nor did the rates of either long [controls: $53 \pm 26\%$; patients: $54 \pm 20\%$; $t(31) = 0.14$, $P = 0.89$] or short latency self-corrections [controls: $30 \pm 30\%$; patients: $24 \pm 23\%$; $t(31) = 0.63$, $P = 0.54$]. There was a trend to post-error slowing [$F(1,29) = 3.58$, $P = 0.07$] that did not differ by group [$F(1,29) = 0.87$, $P = 0.36$].

Group comparisons of activation in the error versus correct antisaccade contrast at 6 s

Patients and controls did not differ in mean motion detected by the AFNI motion correction algorithm [controls: 1.86 ± 0.78 mm, patients: 1.71 ± 0.64 mm, $t(31) = 0.79$, $P = 0.43$].

Dorsal ACC Circuit

In the ROI analyses patients showed significantly reduced error-related activation in bilateral dACC and putamen relative to controls (Table 2). There was a trend to reduced activation in the brainstem. In the registered group data, both groups showed significant error-related activation in bilateral dACC and brainstem (maxima in left red nucleus with activation extending into substantia nigra), and patients showed significantly reduced error-related activation in left dACC (right dACC trend) and left brainstem (maximum in substantia nigra) (Tables 3 and 4; Figs 3 and 4).

Rostral ACC circuit

In the ROI analyses patients showed significantly reduced error-related activation in right rACC (left rACC trend), bilateral insula and bilateral amygdala (Table 2). In the registered group data, both groups showed greater error-related activation in right rACC and bilateral insula

Table 2 Group comparisons of ROI activation during error vs. correct antisaccade trials at 6 s

ROI	Hemi	Indices of activation		Adjusted for CPZ equivalent		Adjusted for error rate		Adjusted for age	
		t	*P*	*t*	*P*	*t*	*P*	*t*	*P*
dACC circuit									
dACC	LH	3.56	0.003*	3.40	0.004*	6.48	<0.001*	10.33	<0.001*
	RH	3.46	0.003*	3.26	0.005*	5.33	<0.001*	7.93	<0.001*
Caudate	LH	1.17	0.25	1.15	0.26	1.12	0.28	4.71	<0.001*
	RH	1.19	0.25	1.06	0.30	2.19	0.04*	5.74	<0.001*
Putamen	LH	2.42	0.02*	2.58	0.02*	2.81	0.01*	9.58	<0.001*
	RH	2.19	0.04*	1.53	0.14	4.24	<0.001*	7.65	<0.001*
Brainstem		1.95	0.07†	1.71	0.10†	4.10	<0.001*	5.63	<0.001*
rACC circuit									
rACC	LH	1.77	0.09†	1.55	0.13	3.29	0.003*	3.21	0.003*
	RH	2.80	0.01*	2.31	0.03*	6.18	<0.001*	6.43	<0.001*
Insula	LH	3.69	0.002*	3.31	0.004*	5.03	<0.001*	11.35	<0.001*
	RH	3.05	0.007*	2.83	0.01*	4.01	0.001*	7.75	<0.001*
Amygdala	LH	3.03	0.006*	2.94	0.008*	1.86	0.08†	.57	0.57
	RH	3.78	0.002*	3.55	0.003*	5.78	<0.001*	7.41	<0.001*

*Significant.
†Trend.
Patients showed reduced activation that remained after adjusting activation indices for error rate and age in both groups, and for CPZ equivalents in patients.

(trend in left insula in patients) and, compared to controls, patients showed a trend to reduced right rACC activation and significantly reduced left insula activation (right insula trend) (Table 3; Fig. 3).

In both circuits, reduced error-related activation in schizophrenia reflected lower activation for errors rather than greater activity for correct trials. Adjusting activation indices for error rate and for age in both groups, and for CPZ equivalents in patients, did not substantially alter the findings (Table 2). Moreover, in patients, CPZ equivalent was not significantly related to activation in any ROI. In the registered group data there were no brain regions in which patients showed significantly greater error-related activation than controls. Table 3 provides a complete list of regions showing significant error-related activation at 6s.

Relations between error-related activation and error rate

Dorsal ACC Circuit

ROI-based regression analyses (Table 5) showed significant inverse relations between error rate and activation in bilateral dACC, brainstem, right caudate and right putamen (left caudate and putamen trend). Significant group differences in the relation between error rate and activation were observed in left dACC (right dACC trend), right putamen and brainstem. These interactions reflected a shallower negative slope in patients than controls (i.e. a unit decrease in error rate predicted a smaller increase in activation for patients than controls; see plots in Figs 5 and 6). Since peak brainstem activation in patients occurred at 8 s rather than 6 s (see HDR graph in Fig. 4), we confirmed that this interaction remained significant when brainstem activation at 8 s was used for patients in the analysis.

In the registered group data, group differences in the relation between error rate and activation were significant in bilateral dACC (LH maximum: −6, 24, 20, cluster size = 263 mm^2, CWP = 0.0002; RH maximum: 7, 17, 25, cluster size = 238 mm^2, CWP = 0.0002) and in a brainstem cluster spanning red nucleus and left substantia nigra (maximum in red nucleus: 0, −16, −13, $P = 3E-6$; substantia nigra maximum: −4, −16, −13, $P = 0.0001$; Figs 5 and 6), reflecting a shallower negative slope in patients.

Rostral ACC circuit

ROI-based regression analyses (Table 5) showed significant inverse relations between error rate and activation in bilateral rACC, bilateral insula and right amygdala. A significant group difference in the relation between error rate and activation was seen in right rACC (trend in left rACC) and there was a trend in right amygdala, indicating a shallower slope of the relation in patients.

In the registered group data, only the left insula showed a group by error rate interaction (maximum: −30.6, 23.1, −2.2, cluster size = 230 mm^2, CWP = 0.0002) reflecting a shallower inverse relation in patients than controls. The right hemisphere rACC cluster displayed in Fig. 5 did not meet correction for multiple comparisons (maximum: 6, 36, −2, cluster size = 73 mm^2, CWP = 0.27).

Table 3 Cortical areas with significant activation during error vs. correct antisaccade trials at 6 s in healthy controls, schizophrenia patients, and in the group comparison

Region	Maximum *P*-value	Approximate Talairach coordinates[a]			Cluster size (mm^2)	Cluster *P*-value
		x	*y*	*z*		
Healthy controls						
LH dACC	2.79*E*−07	−11	22	27	715	2.50*E*−03
LH Insula	4.34*E*−07	−27	24	−6	844	1.30*E*−03
LH Inferior frontal gyrus	9.91*E*−07	−49	20	8	375	5.00*E*−03
LH Calcarine sulcus	2.16*E*−06	−22	−43	−18	1875	2.00*E*−04
LH Calcarine sulcus	3.09*E*−05	−10	−83	4	225	2.62*E*−02
LH Superior frontal gyrus[b]	2.25*E*−04	−7	33	40	161	7.76*E*−02
RH Calcarine sulcus	1.21*E*−05	26	−50	4	2218	1.00*E*−04
RH Insula	1.59*E*−05	31	21	−4	817	1.60*E*−03
RH dACC	2.08*E*−05	4	10	25	522	2.40*E*−03
RH rACC	6.78*E*−05	8	29	22	522	2.40*E*−03
RH Superior frontal gyrus	1.95*E*−04	12	16	57	224	3.13*E*−02
Schizophrenia patients						
LH dACC	3.19*E*−07	−12	14	28	341	3.00*E*−03
LH Lateral fissure	1.48*E*−06	−44	21	8	621	1.00*E*−03
LH Calcarine sulcus	2.70*E*−06	−14	−65	6	1031	1.00*E*−04
LH Occipitotemporal gyrus	1.39*E*−05	−16	−42	−5	184	3.18*E*−02
LH Insula[b]	1.70*E*−05	−31	24	−1	142	7.35*E*−02
LH Superior frontal gyrus	4.93*E*−05	−9	23	53	474	1.40*E*−03
LH Occipitotemporal gyrus	7.33*E*−05	−17	−70	−6	167	4.39*E*−02
RH Inferior frontal gyrus	4.66*E*−07	53	23	12	584	2.10*E*−03
RH Superior frontal gyrus	5.61*E*−07	10	21	56	1383	1.00*E*−04
RH dACC	1.36*E*−05	5	23	23	248	9.10*E*−03
RH Insula	2.31*E*−05	35	31	−2	157	5.26*E*−02
RH Calcarine sulcus	3.55*E*−05	16	−76	12	739	1.50*E*−03
RH Middle frontal gyrus	9.14*E*−05	38	17	43	210	1.66*E*−02
RH rACC	2.31*E*−04	12	32	26	1383	1.00*E*−04
Healthy controls versus Schizophrenia patients						
LH dACC	2.57*E*−05	−13	17	26	1216	2.89*E*−02
LH Superior temporal gyrus	3.51*E*−05	−48	18	−13	1270	2.18*E*−02
LH Insula	8.93*E*−05	−41	27	−19	1270	2.18*E*−02
LH Calcarine sulcus	1.73*E*−04	−23	−45	−19	2248	1.00*E*−04
RH Insula[b]	1.15*E*−04	32	20	−4	985	1.03*E*−01
RH Calcarine sulcus	1.72*E*−04	22	−50	1	3299	1.00*E*−04
RH dACC[b]	5.89*E*−04	8	13	25	1065	7.62*E*−02
RH rACC[b]	2.08*E*−03	8	29	21	1065	7.62*E*−02

There were no regions that patients activated more than controls. Regions ordered by hemisphere and then by ascending *P*-value of maximum. Probability values are listed in scientific (exponent) notation. dACC: dorsal anterior cingulate cortex; rACC: rostral anterior cingulate cortex.

[a]Approximate Talairach coordinates were derived by mapping surface-based coordinates of peak activations back to the original structural volumes for each participant, registering these volumes to the Montreal Neurological Institute (MNI305) atlas (Collins *et al*., 1994), and transforming the resulting coordinates to standard Talairach space using an algorithm developed by Matthew Brett (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). The average Talairach coordinates across participants for each activation peak is reported. Because localization is based on cortical surface analyses, the surface localizations are accurate and may not correspond to the approximate Talairach localizations which are provided for comparison across studies. [b]denotes a trend as determined by *P*-value from multiple comparisons correction using cluster thresholding.

Relations of error-related activation to symptoms

Exploratory analyses of the relation of error-related activation to symptoms in the ROIs that comprise the dACC and rACC circuits revealed that activation in the left amygdala was inversely related to the severity of both positive ($r = -0.46$, $P = 0.05$) and negative symptoms (trend: $r = -0.42$, $P = 0.08$) on the PANSS. These relations did not survive correction for multiple comparisons.

Discussion

Impairments in evaluating and learning from errors in schizophrenia may contribute to behaviour that is rigid and

Table 4 Subcortical areas showing significant activation during error vs. correct antisaccade trials

Region	*P*	Talairach coordinates			Cluster size (mm^3)
		x	*y*	*z*	
Healthy controls					
LH Brainstem (red nucleus)	4.84*E*−06	−4	−24	−16	1216
RH Hippocampus	1.35*E*−05	28	−31	−5	128
LH Thalamus	3.42*E*−05	−4	−23	5	64
LH Thalamus	6.23*E*−05	−20	−31	2	64
RH Thalamus	1.11*E*−04	8	−15	5	64
RH Globus pallidus	1.78*E*−04	12	−4	0	64
Schizophrenia patients					
LH Brainstem (red nucleus)	1.11*E*−05	−4	−24	−9	64
RH Thalamus	4.03*E*−05	4	−4	8	64
Healthy controls versus Schizophrenia patients					
LH Brainstem (substantia nigra)	3.70*E*−05	−4	−16	−13	128

Probability values are listed in scientific (exponent) notation. Regions are ordered by ascending *P*-value of maximum.

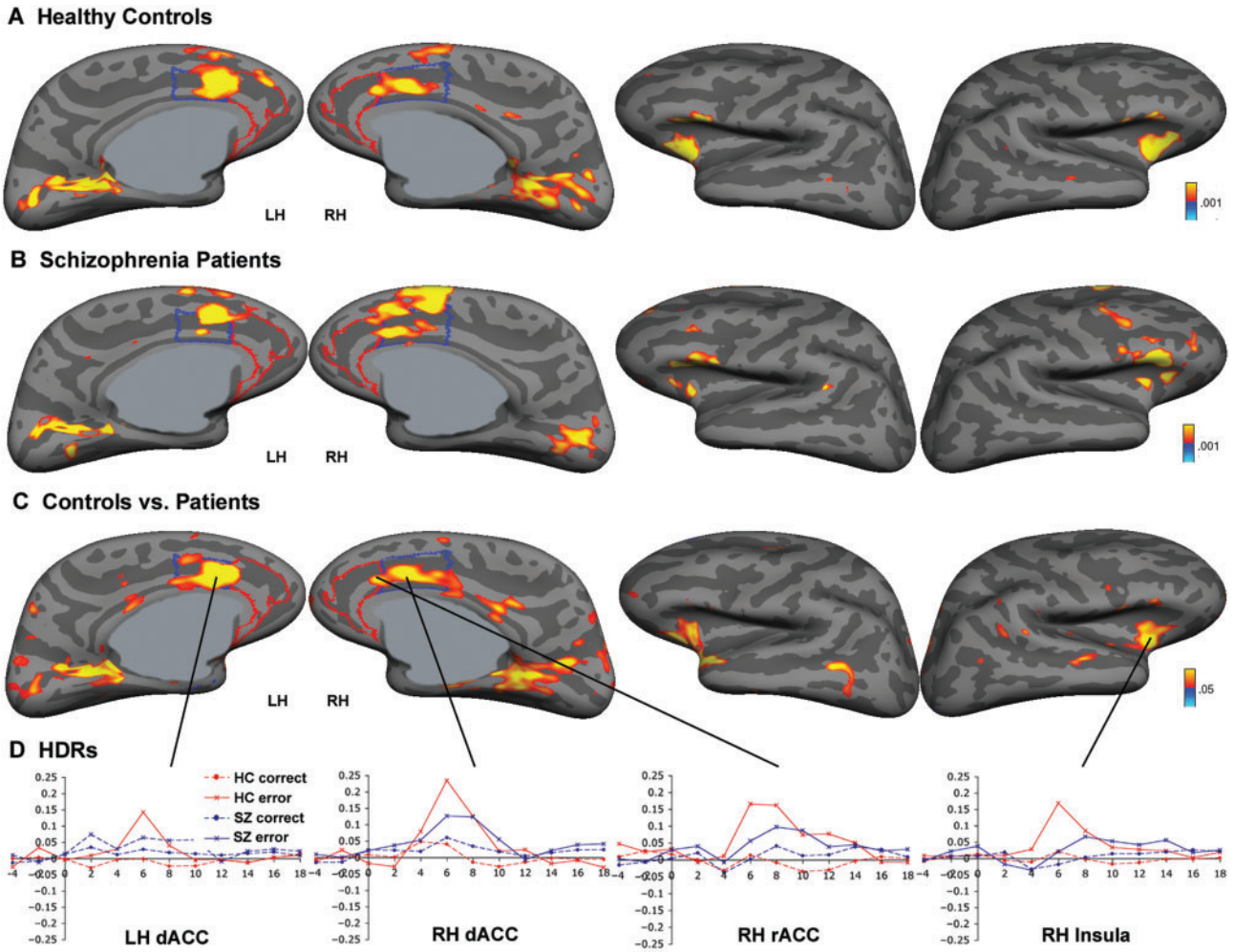

Fig. 3 Cortical activation for the contrast of error versus correct antisaccade at 6 s in (**A**) healthy controls, (**B**) schizophrenia patients and (**C**) the group comparison displayed on the lateral and medial views of the inflated cortical surface. rACC is outlined in red and dACC in blue. The grey masks cover non-surface regions in which activity is displaced. (**D**) The HDR time course graphs are displayed for vertices with peak activation in selected regions for each group and each condition. Time in seconds is on the *x*-axis and percent signal change relative to the fixation baseline is on the *y*-axis. Surface localizations and approximate Talairach coordinates for clusters that met the cluster thresholding criterion to correct for multiple comparisons are given in Table 2.

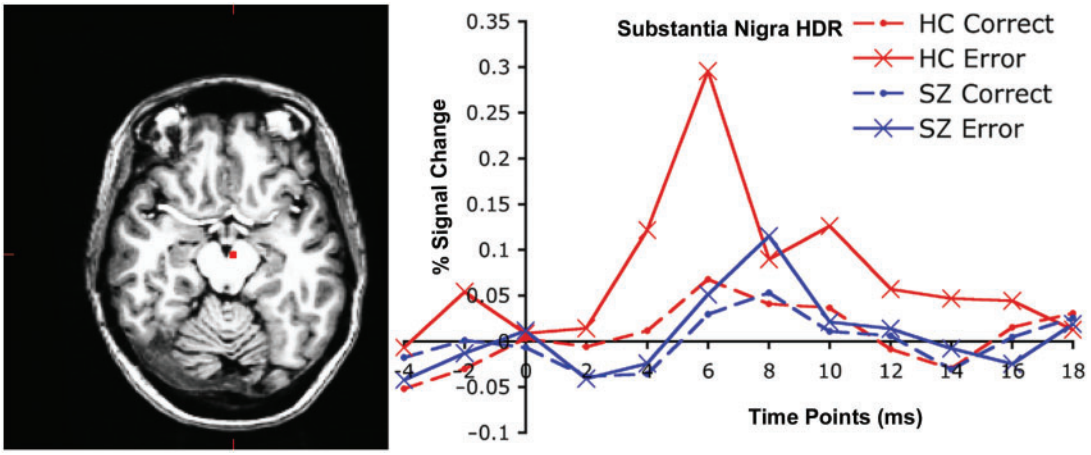

Fig. 4 FDR-corrected statistical map showing greater activation in controls than patients in the substantia nigra for error versus correct antisaccade contrast at 6 s displayed on the high resolution structural scan of an individual participant that was registered to the Montreal Neurological Institute (MNI305) atlas (Collins *et al*., 1994). The HDR time courses are displayed for the voxel with peak activation. Time in seconds is on the *x*-axis and percent signal change relative to the fixation baseline is on the *y*-axis.

Table 5 Regression analyses of activation on error rate, between group comparisons, and within-group regressions

ROI	Hemisphere	Error rate		Error rate by group		Within group			
						Controls		Patients	
		t	*P*	*t*	*P*	*t*	*P*	*t*	*P*
dACC	LH	−3.15	0.004*	−2.53	0.02*	−2.14	0.05*	−2.01	0.06*
	RH	−2.66	0.01*	−1.86	0.07†	−1.71	0.11	−2.61	0.02*
Caudate	LH	−1.85	0.07†	0.49	0.51	−1.04	0.32	−2.63	0.02*
	RH	−2.71	0.01*	−1.53	0.14	−1.70	0.11	−2.85	0.01*
Putamen	LH	−1.83	0.08†	−0.84	0.41	−1.16	0.27	−1.91	0.07†
	RH	−2.67	0.01*	−2.03	0.05*	−1.85	0.09†	−1.67	0.11
Brainstem		−2.67	0.01*	−2.08	0.05*	−1.92	0.08†	−1.40	0.18
rACC	LH	−3.08	0.005*	−1.84	0.08†	−2.57	0.02*	−1.91	0.07†
	RH	−3.70	<0.001*	−2.94	0.006*	−2.68	0.02*	−1.81	0.09†
Insula	LH	−2.99	0.006*	−1.62	0.12	−1.78	0.10†	−4.00	0.001*
	RH	−2.20	0.03*	−1.29	0.21	−1.34	0.20	−3.66	0.002*
Amygdala	LH	0.34	0.69	0.37	0.62	0.04	0.97	−2.07	0.06†
	RH	−2.82	0.009*	−1.95	0.06†	−1.75	0.10†	−3.81	0.002*

*Significant.
†Trend.

perseverative rather than optimally guided by outcomes. Our findings demonstrate that the anatomical components of two ACC circuits that are theorized to play distinct roles in error processing show a blunted response to error commission in schizophrenia. Relative to controls, patients showed reduced error-related activation in dACC circuitry hypothesized to mediate reinforcement learning (Holroyd and Coles, 2002) and in rACC circuitry hypothesized to appraise the affective and motivational salience of errors. Reduced activation in these circuits was related to increased error rate. While these relations were seen across participants in each group, their slope was shallower in the patient group (i.e. across participants with schizophrenia, decrements in error rate were associated with smaller decrements in activation—see Fig. 5). We interpret our findings of a blunted neural response to errors in the dACC circuit in schizophrenia to reflect deficient reinforcement learning, while in the rACC circuit it may reflect an affective insensitivity to behavioural outcomes.

The diminished neural response to errors occurred in the context of normal rates of error self-correction in the absence of external feedback regarding errors. This suggests that error-processing deficits in schizophrenia are selective. Intact self-correction is consistent with previous

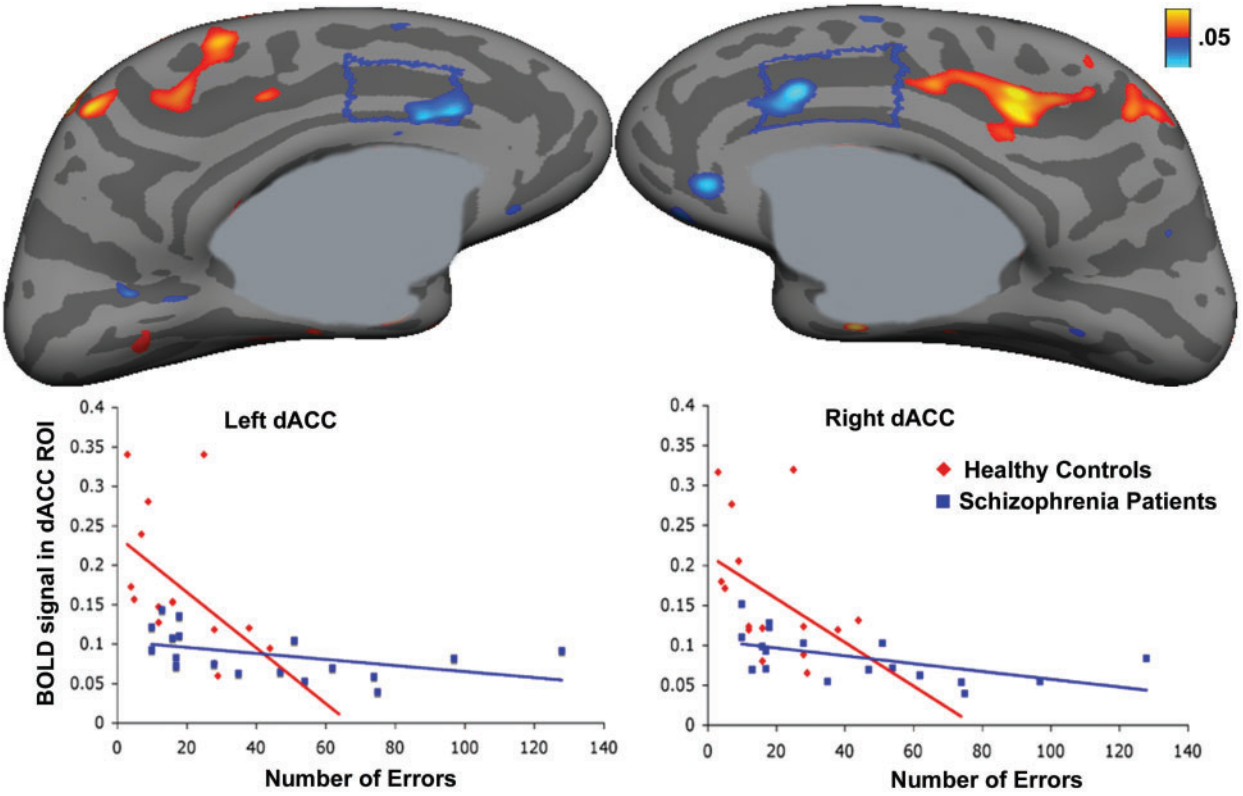

Fig. 5 Statistical map for regression of raw BOLD signal in error versus correct contrast at 6 s on error rate by group on the cortical surface. rACC is outlined in red and dACC in blue. Coloured regions indicate regions where controls showed a steeper slope than patients. Blue regions indicate a shallower negative relationship in patients and red regions indicate a shallower positive relationship in patients. None of the regions displayed showed a steeper slope in patients. Scatter plots show the error rate on the *x*-axis plotted against percent signal change from the dACC ROI for each hemisphere on the *y*-axis by group.

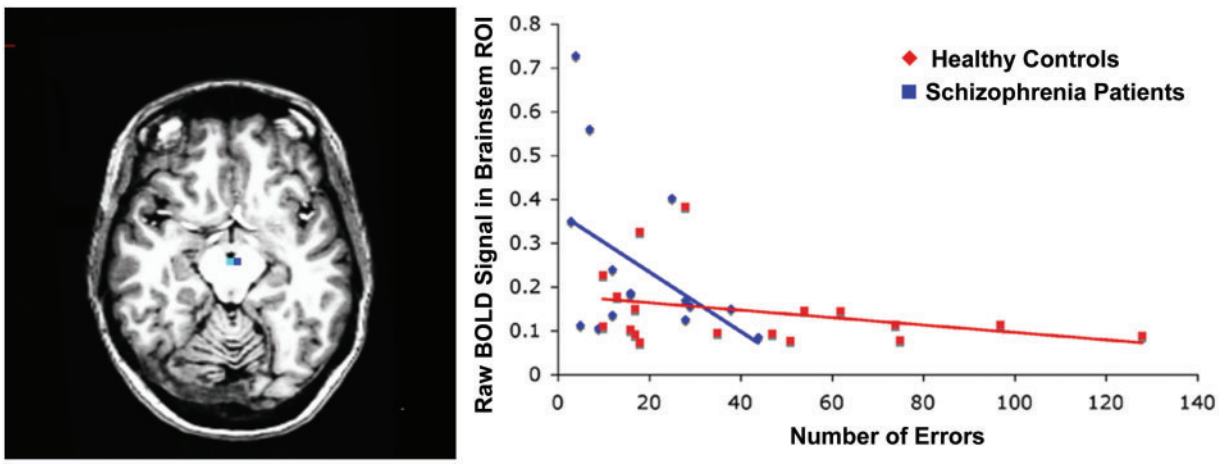

Fig. 6 FDR-corrected statistical map of the group interaction in the regression of raw BOLD signal (error versus correct contrast at 6 s) on error rate displayed on the high resolution structural scan of an individual participant that was registered to the Montreal Neurological Institute (MNI305) atlas (Collins *et al*., 1994). The brainstem cluster spans the red nucleus and substantia nigra. The inverse relation of BOLD signal with error rate was shallower in patients than controls. The scatter plot shows the error rate on the *x*-axis plotted against percent signal change from the brainstem ROI on the *y*-axis by group.

behavioural findings in schizophrenia (Kopp and Rist, 1994; Kopp and Rist, 1999), including on an antisaccade task (Polli *et al*., 2006). Patients showed normal rates of both long and short latency error self-corrections, as was also the case in our previous behavioural study (Polli *et al*., 2006). Long latency error self-corrections are more likely to be conscious responses to visual feedback regarding an error than short latency corrections, which may be concurrently

programmed correct responses (Mokler and Fischer, 1999; McPeek *et al.*, 2000). Thus a comparable rate of long latency self-corrections suggests intact error awareness in patients. We also observed a trend to post-error slowing that did not differ by group. This could be consistent with previous reports of intact post-error slowing in schizophrenia (Alain *et al.*, 2002; Mathalon *et al.*, 2002; Laurens *et al.*, 2003; Morris *et al.*, 2006) although some studies find reduced post-error slowing (Carter *et al.*, 2001; Kerns *et al.*, 2005) [The weak post-error slowing of the present study may reflect that the design consisted of interleaved pro- and antisaccades rather than only antisaccades. In our prior study using only antisaccades we found normal post-error slowing in schizophrenia (Polli *et al.*, 2006). In mixed task designs, task-switching and carry-over effects of previous antisaccades interact to affect response latency (Barton *et al.*, 2006; Cherkasova *et al.*, 2002; Fecteau *et al.*, 2004; Manoach *et al.*, 2007) and may partially obscure the effects of a prior error on latency. Post-error slowing has been linked to Pe, which was associated with subjective awareness of errors on an antisaacade task in healthy individuals (Nieuwenhuis *et al.*, 2001)]. The present findings of intact error self-correction and no group differences in post-error slowing in conjunction with previous reports of normal post-error slowing and Pe (Alain *et al.*, 2002; Mathalon *et al.*, 2002; Morris *et al.*, 2006) suggest that the systems that recognize errors, immediately institute corrective action, and slow responses in the subsequent trial, are intact in schizophrenia.

Our findings of decreased error-related activation in dACC and putamen are consistent with previous reports (Carter *et al.*, 2001; Kerns *et al.*, 2005). This study extends previous work by finding decreased error-related activation in the brainstem (trend in ROI analysis, significant in registered group data), which may be attributable to the substantia nigra (see discussion below), another key node in the reinforcement learning network (Holroyd and Coles, 2002), and by linking reduced activation to impaired task performance in schizophrenia. We interpret the blunted response to errors in dACC circuitry in schizophrenia to reflect deficient error-based reinforcement learning. While we did not use a classic reinforcement learning paradigm, nor did we examine behavioural indices of learning, recent theoretical and experimental work suggests that the neural sequellae of error commission index a type of contingency- or reinforcement-based learning (Holroyd and Coles, 2002; Schultz, 2002). Holroyd and Coles (2002) theorized that with errors, the striatum detects a mismatch between the intended (correct) versus actual (error) outcome. This mismatch or 'prediction error' results in a phasic decrease in mesencephalic dopamine release that disinhibits dACC neurons and elicits the ERN. According to this theory, both increased dACC activation and the ERN reflect the use of prediction error signals to modify the associative strength of stimulus-response mappings in the service of optimizing behavioural outcomes (Holroyd *et al.*, 2003; Holroyd *et al.*, 2004). In the present study, error-related activation in dACC, substantia nigra, caudate and putamen was inversely related to error rate. This is consistent with previous reports of greater dACC activation for less predictable errors (Brown and Braver, 2005) and an inverse relation of ERN amplitude with error rate (Gehring *et al.*, 1993; Hajcak *et al.*, 2003). These findings suggest that ERN and dACC activation, as indices of prediction error, become smaller as errors become more frequent and therefore more predictable. If this were the case, reduced activation in dACC circuitry in schizophrenia may simply reflect their more frequent errors. Our findings suggest, however, that increased errors do not fully account for the reduced response in dACC circuitry. First, activation reductions remained significant when the effect of error rate was statistically controlled. Second, the slopes of the relations between error rate and activation in dACC, substantia nigra and putamen were significantly shallower in patients. This suggests that the reinforcement learning network has an abnormally restricted response to error commission in schizophrenia. Dysfunction of this network, by impairing the modification of contextually inappropriate stimulus-response mappings, could lead to the inefficient substitution of erroneous prepotent responses with correct effortful ones. This provides a plausible account of the persistence of antisaccade deficits in schizophrenia in spite of intact error self-correction (Calkins *et al.*, 2003; Gooding *et al.*, 2004). More generally, impaired error-based reinforcement learning in schizophrenia may contribute to impairments in the use feedback to ameliorate performance (Waltz *et al.*, 2007) and to perseveration—the persistence of contextually inappropriate and unreinforced responses.

Consistent with a previous report of decreased error-related activation of the rACC in schizophrenia (Laurens *et al.*, 2003), we observed decreased activation in the rACC, insula and amygdala in schizophrenia. Insula and amygdala are interconnected with rACC (van Hoesen *et al.*, 1993), show increased activity in response to errors (Menon *et al.*, 2001; Brazdil *et al.*, 2002; Garavan *et al.*, 2002), and are functionally and structurally abnormal in schizophrenia (Aleman and Kahn, 2005; Makris *et al.*, 2006). The insula is thought to contribute to emotional experience by representing awareness of bodily states based on visceral and autonomic information (Critchley *et al.*, 2000a, b, 2001). The amygdala is involved in the appraisal of salient and/or aversive events or stimuli (Phelps and LeDoux, 2005). Thus, we interpret reduced error-related activity in this network to indicate affective and interoceptive insensitivity to errors. Activation in the rACC, insula and right amygdala was inversely related to error rate, and the slope of this relation was significantly shallower for patients in right rACC consistent with the notion of a diminished neural response to errors in schizophrenia. In humans, the rACC and amygdala, particularly in the right hemisphere, have been shown to activate in response to aversive outcomes, and the amygdala response has been correlated with an autonomic

index of conditioned fear (LaBar *et al.*, 1998). These findings, along with extensive evidence from both rat and human studies, suggest that these structures mediate emotional learning (for review see: Phelps and LeDoux, 2005). Errors can be considered aversive outcomes that should prompt avoidance learning. The blunted response to errors in rACC circuitry in schizophrenia may reflect that errors are less aversive to patients than controls and/or that they fail to motivate the same level of learning.

Exploratory analyses revealed that activation of the left amygdala in patients was inversely related to increased severity of both positive and negative (trend) symptoms. These relations should be interpreted with caution as they did not meet correction for multiple comparisons. It is noteworthy, however, that activation in left amygdala has been previously correlated with positive symptoms (Taylor *et al.*, 2002) and amygdala abnormalities have been theoretically linked to the expression of both positive and negative symptoms (Aleman and Kahn, 2005) in schizophrenia.

Several study limitations and alternative interpretations of our findings merit consideration. First, while our hypothesis that decreased error-related dACC activation in schizophrenia reflects deficient reinforcement learning is consistent with prior literature, it lacks direct empirical support in the present study. In future work it will be important to examine the relation between error-related dACC activation and learning in schizophrenia to more directly test this theory. Second, we attribute increased brainstem activation to error-related activity in the substantia nigra. In the registered group data, the brainstem maximum in the between group comparison was in substantia nigra, but in the regression analysis, it was in the red nucleus and activation extended to the substantia nigra. The substantia nigra is a small structure, and accurate localization strains the limits of spatial resolution in this study. However, given the extensive animal literature implicating the substantia nigra in reinforcement learning (e.g. Schultz, 2002), of which error processing is a special case (Holroyd and Coles, 2002), we tentatively attribute the activation to substantia nigra. Assuming that the activation does stem from the substantia nigra, it might reflect the generation of corrective saccades rather than error processing since some substantia nigra neurons contribute to ocular motor behaviour (e.g. Hikosaka and Wurtz, 1983). This seems unlikely given the time course of the brainstem activation (Fig. 4), which is inconsistent with a role in the generation of the initial correct or erroneous antisaccade in both its later onset and peak than regions involved in saccade generation, but is consistent with regions that respond to errors (Polli *et al.*, 2005). Another issue concerns reconciling our finding of *increased* brainstem activation with errors with single-unit recording studies that show a phasic *decrease* in substantia nigra neuronal activity following reward omission (Schultz and Dickinson, 2000) and the hypothetical decrease following errors in error-based reinforcement learning theory (Holroyd *et al.*, 2002). BOLD activation correlates with local field potentials that reflect both excitatory and inhibitory input to a region, interneuron activity, and neuronal spiking (Logothetis *et al.*, 2001; Lauritzen, 2005; Mukamel *et al.*, 2005). Thus, a plausible interpretation of the increased BOLD activation in the brainstem is that it reflects inhibitory input from the striatum that results in a phasic decrease in mesencephalic dopamine release with reward omission, as seen in animal studies (Nakahara *et al.*, 2004). Clearly, other interpretations are possible, and a more definitive localization and explanation of the neuronal basis of the finding of increased BOLD activity in the brainstem in response to errors will require a convergence of information from other techniques.

Is it possible that the findings of reduced activation in schizophrenia reflect a diminished response to reward omission, rather than to errors? Despite dopamine dysregulation in schizophrenia, the reward system itself has not been a topic of active research, but has been hypothesized to play a role in amotivation and learning deficits (Schultz, 2001) and patients have been shown to be relatively insensitive to positive feedback (Waltz *et al.*, 2007). Although no trial-by-trial feedback was provided, in addition to a base payment, participants received a monetary bonus for each correct response following study completion. The ACC is known to be sensitive to reward (e.g. Bush *et al.*, 2002), and reward amount and motivation are related to the amplitude of the ERN (Hewig *et al.*, 2007). The bonus was intended to ameliorate motivational deficits that are a prominent feature of schizophrenia and a possible confound in cognitive studies (Schmand *et al.*, 1994). In practice, the effects of errors and loss of an anticipated reward may be difficult to disentangle since correct performance is inherently reinforcing and errors represent a loss of this reinforcement. Moreover, theoretically, the effects of both errors and reward rely on the same dopamine-dependent reinforcement learning network, which has been modeled primarily on the basis of studies of rewarded behaviour in animals (e.g. Schultz and Dickinson, 2000). Our findings of a diminished neural response to errors are consistent with the previous literature on unrewarded performance in schizophrenia, and demonstrate that, even when provided with an extrinsic reward, patients show a diminished response to errors.

Related to this, all of the patients in this study were taking antipsychotic medications that affect the dopamine system. Although statistical controls for antipsychotic dosage did not alter the findings and there were no relations between dosage and activation, this study cannot determine whether the abnormalities observed are due to schizophrenia or its treatment. In addition, our sample was restricted to chronically ill patients and it is unclear whether the abnormalities observed are present at the onset of illness or whether they represent the effects of disease progression and/or a secondary effect of long-term illness.

Studying antipsychotic-naïve patients early in the course of illness could resolve these questions. Even if the abnormalities are due to medication, progression or other epiphenomena of long-term illness, they are clinically relevant since the vast majority of patients with schizophrenia are chronically ill and medicated. Deficient error processing may represent a previously unrecognized and disabling effect or medication and/or chronicity.

In summary, these findings demonstrate blunted error-related responses in dorsal and rostral ACC circuitry that are related to impaired cognitive performance in chronic, medicated schizophrenia. Deficits in dACC-mediated error-based reinforcement learning may contribute to perseverative behaviour, and a blunted rACC-mediated affective/motivational response to errors may be manifested in a lack of concern regarding behavioural outcomes. However, despite these deficits, patients correct their errors as frequently as controls in the absence of external feedback. This suggests intact error recognition and ability to institute corrective action, capacities that can be exploited for rehabilitation.

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