

Response monitoring, repetitive behaviour and anterior cingulate abnormalities in autism spectrum disorders (ASD)

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Autism spectrum disorders (ASD) are characterized by inflexible and repetitive behaviour. Response monitoring involves evaluating the consequences of behaviour and making adjustments to optimize outcomes. Deficiencies in this function, and abnormalities in the anterior cingulate cortex (ACC) on which it relies, have been reported as contributing factors to autistic disorders. We investigated whether ACC structure and function during response monitoring were associated with repetitive behaviour in ASD. We compared ACC activation to correct and erroneous antisaccades using rapid presentation event-related functional MRI in 14 control and ten ASD participants. Because response monitoring is the product of coordinated activity in ACC networks, we also examined the microstructural integrity of the white matter (WM) underlying this brain region using diffusion tensor imaging (DTI) measures of fractional anisotropy (FA) in 12 control and 12 adult ASD participants. ACC activation and FA were examined in relation to Autism Diagnostic Interview-Revised ratings of restricted and repetitive behaviour. Relative to controls, ASD participants: (i) made more antisaccade errors and responded more quickly on correct trials; (ii) showed reduced discrimination between error and correct responses in rostral ACC (rACC), which was primarily due to (iii) abnormally increased activation on correct trials and (iv) showed reduced FA in WM underlying ACC. Finally, in ASD (v) increased activation on correct trials and reduced FA in rACC WM were related to higher ratings of repetitive behaviour. These findings demonstrate functional and structural abnormalities of the ACC in ASD that may contribute to repetitive behaviour. rACC activity following errors is thought to reflect affective appraisal of the error. Thus, the hyperactive rACC response to correct trials can be interpreted as a misleading affective signal that something is awry, which may trigger repetitive attempts at correction. Another possible consequence of reduced affective discrimination between error and correct responses is that it might interfere with the reinforcement of responses that optimize outcomes. Furthermore, dysconnection of the ACC, as suggested by reduced FA, to regions involved in behavioural control might impair on-line modulations of response speed to optimize performance (i.e. speed-accuracy trade-off) and increase error likelihood. These findings suggest that in ASD, structural and functional abnormalities of the ACC compromise response monitoring and thereby contribute to behaviour that is rigid and repetitive rather than flexible and responsive to contingencies. Illuminating the mechanisms and clinical significance of abnormal response monitoring in ASD represents a fruitful avenue for further research.

Keywords: autism; anterior cingulate cortex; response monitoring; functional MRI; diffusion tensor imaging

Abbreviations: ACC = anterior cingulate cortex; ADI-R = autism diagnostic interview-revised; ASD = autism spectrum disorders; BOLD = blood oxygen level dependent; CWP = cluster-wise probability; dACC = dorsal ACC; DTI = diffusion tensor imaging; ERN = error-related negativity; HC = healthy control; IQ = intelligence quotient; MPRAGE = magnetization prepared rapid gradient echo; OCD = obsessive-compulsive disorder; rACC = rostral ACC; TE = echo time; TR = repetition time; WM = white matter

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Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by the early onset of marked impairments in socialization and communication along with restricted and repetitive interests and activities. There is growing evidence that executive function deficits contribute to these core symptoms (Hill, 2004; Lopez *et al.*, 2005; South *et al.*, 2007). Executive function refers to diverse cognitive abilities involved in behavioural control including response monitoring—evaluating whether the consequences of behaviour are consistent with its intent, and instituting adjustments to optimize outcomes. Response monitoring is thought to rely on anterior cingulate cortex (ACC) on the basis of extensive evidence from functional neuroimaging, electrophysiological, lesion and intracranial recording studies (see Taylor *et al.*, 2007 for a recent review). There is evidence of abnormal response monitoring in autism including increased latency (and amplitude in a subset) of the error-related negativity (ERN) (Henderson *et al.*, 2006), an event-related potential that follows errors and is thought to be generated by the ACC (Gehring *et al.*, 1993; Dehaene *et al.*, 1994; van Veen and Carter, 2002); reduced error self-correction (Russell and Jarrold, 1998) and reduced post-error slowing, a compensatory mechanism to improve performance on the subsequent trial (Bogte *et al.*, 2007). Since the evaluation of behaviour and its consequences is necessary to determine whether or not current strategies should be maintained, abnormal response monitoring may contribute to behavioural rigidity in ASD. The aims of the present study were: (i) to examine ACC function during response monitoring using functional MRI (fMRI); (ii) to assess the microstructural integrity of the white matter (WM) underlying the ACC using diffusion tensor imaging (DTI) and (iii) to investigate the relations of ACC function and WM microstructure to restricted, repetitive behaviour in ASD.

There is growing evidence of both functional and structural abnormalities of the ACC in ASD. Abnormal ACC activation has been observed during a range of cognitive tasks (Haznedar *et al.*, 1997, 2000; Hall *et al.*, 2003; Gomot *et al.*, 2006; Kana *et al.*, 2007; Kennedy *et al.*, 2006; Silk *et al.*, 2006; Ashwin *et al.*, 2007; Dichter and Belger, 2007). There is also evidence of altered metabolism (Levitt *et al.*, 2003), reduced 5-HT_{2A} receptor binding (Murphy *et al.*, 2006) and reduced volume of the ACC (Haznedar *et al.*, 1997, 2000). A DTI study found reduced fractional anisotropy (FA—an index of WM microstructure: Beaulieu, 2002) of the WM adjacent to ACC (Barnea-Goraly *et al.*, 2004). Aberrant connectivity is also suggested by findings of decreased functional connectivity (synchronization of activation) between the ACC and other structures during a task requiring response inhibition (Kana *et al.*, 2007). These findings are consistent with the theory of abnormal inter-regional coordination in ASD (Courchesne and Pierce, 2005).

Abnormal ACC connectivity and function may contribute to the defining symptoms of autism. ACC dysfunction has been linked to indices of social impairment (Haznedar *et al.*, 2000; Ohnishi *et al.*, 2000; Kennedy *et al.*, 2006), but we are aware of only one study linking it to restricted and repetitive behaviours in ASD (Shafritz *et al.*, 2007). In this study restricted, repetitive behaviours were negatively correlated with fMRI activation in ACC during trials that required a switch in response. Such a link has face validity since the ACC contributes to evaluating and modifying behaviour based on its consequences and flexible behaviour depends on these functions. A link between abnormal ACC function and repetitive thoughts and behaviours has been more extensively documented in obsessive-compulsive disorder (OCD), which is often comorbid with ASD (Leyfer *et al.*, 2006). Relative to controls, individuals with OCD show increased fMRI activation of the ACC and increased ERN amplitude not only to error trials (Gehring *et al.*, 2000; Johannes *et al.*, 2001; Fitzgerald *et al.*, 2005; but see Nieuwenhuis *et al.*, 2005 for a negative finding), but also to correct trials with high response-conflict (i.e. those that require suppression of a competing response) in some (Ursu *et al.*, 2003; Maltby *et al.*, 2005), but not all studies (Gehring *et al.*, 2000; Fitzgerald *et al.*, 2005). These exaggerated responses suggest hyperactive monitoring of responses. Moreover, both increased ERN to errors (Gehring *et al.*, 2000) and increased ACC activation to error (Fitzgerald *et al.*, 2005) and correct trials (Ursu *et al.*, 2003) have been associated with the severity of obsessions and compulsions in OCD. These relations have been interpreted to reflect excessive or inappropriate error signalling that triggers a compulsion to repeat behaviours, even if they have already been successfully executed (Maltby *et al.*, 2005). The findings that in OCD the ACC and associated regions show increased activation during symptom provocation (Breiter *et al.*, 1996), and that cingulotomy relieves obsessions and compulsions (Dougherty *et al.*, 2002) further support the link between ACC function and rigid, repetitive behaviours. Measurements of obsessive-compulsive behaviour have also been related to response monitoring in non-clinical samples. Obsessive characteristics are related to the amplitudes of ERN and error positivity (another event-related potential that follows errors and is thought to be generated by the ACC, Falkenstein *et al.*, 1995; van Veen and Carter, 2002) in children (Santesso *et al.*, 2006) and to the amplitude of ERN in college undergraduates (Hajcak and Simons, 2002). These findings suggest that abnormally increased activity of the ACC following response execution contributes to rigid, repetitive behaviour. Based on this literature, we expected to find increased ACC activation on both error and correct trials that is correlated with repetitive behaviour in ASD.

We investigated the role of the ACC in response monitoring using an antisaccade paradigm. Antisaccades require suppression of the prepotent response of looking towards a suddenly appearing visual stimulus and substitution of the

novel behaviour of looking in the opposite direction (Hallett, 1978). Antisaccades are well-suited for examining response monitoring because they have a relatively well-delineated neuroanatomy and neurophysiology (for review see: Munoz and Everling, 2004), generate robust electrophysiological error markers, ERN, error positivity (Nieuwenhuis *et al.*, 2001) and ACC hemodynamic responses (Polli *et al.*, 2005) and involve a high degree of response conflict. Moreover, individuals with developmental disorders affecting social processing, including ASD, consistently show an increased rate of antisaccade errors (i.e. a failure to suppress the prepotent prosaccade) (Manoach *et al.*, 1997, 2004; Minshew *et al.*, 1999; Goldberg *et al.*, 2002; Luna *et al.*, 2007), which may reflect, in part, aberrant evaluation of performance and modification of prepotent stimulus-response mappings.

We examined group differences in ACC activation during correct and erroneous antisaccade trials using rapid presentation event-related fMRI. Comparisons were restricted to antisaccade trials since healthy and ASD participants produce too few prosaccade errors with this paradigm (Manoach *et al.*, 2004). We examined activity in rostral and dorsal ACC (rACC, dACC) separately, given their differences in cytoarchitecture, function and connectivity (Devinsky *et al.*, 1995; Bush *et al.*, 1998; Whalen *et al.*, 1998) and distinct patterns of haemodynamic activity during antisaccade error commission (Polli *et al.*, 2005). Since response monitoring is the product of coordinated activity between the ACC and functionally related regions (Holroyd and Coles, 2002), and the ACC shows evidence of decreased structural and functional connectivity in autism (Barnea-Goraly *et al.*, 2004; Kana *et al.*, 2007), we also examined the microstructural integrity of the WM underlying the ACC using DTI. We expected ASD participants to show: (i) an increased antisaccade error rate; (ii) increased ACC activity during both correct and erroneous antisaccade trials and (iii) reduced FA in the WM underlying ACC. Finally, we hypothesized that (iv) structural and functional ACC abnormalities would be associated with rigid, repetitive behaviour in ASD.

Methods

Participants

Twelve adults with ASD and 14 healthy control (HC) participants were recruited by poster and website advertisements (see Table 1 for demographic data). Participants with ASD were diagnosed with autism ($n=8$), Asperger's disorder ($n=2$) or pervasive developmental disorder, not otherwise specified ($n=2$) by an experienced clinician (R.M.J.) on the basis of current presentation and developmental history as determined by medical record review and clinical interview. Potential participants meeting DSM-IV criteria for co-morbid psychiatric conditions or substance abuse were excluded. ASD diagnoses were confirmed using the Autism Diagnostic Interview-Revised (ADI-R; Rutter *et al.*, 2003) and the Autism Diagnostic Observation Schedule Module 4 (Lord *et al.*, 1999) administered by research reliable personnel.

Table 1 Means, standard deviations and group comparisons of demographic data

Subject characteristics	HC (n = 14)	ASD (n = 12)	T	P
Age	27 ± 8	30 ± 11	-0.69	0.50
Sex	8M/6F	10M/2F	$\phi = 0.28$	0.22
Laterality score (Handedness)	75 ± 45	61 ± 38	0.86	0.40
Parental SES ^a	1.31 ± 0.48	1.17 ± 0.39	$z = -0.60$	0.42
Years of education	16 ± 2	16 ± 3	-0.51	0.62
Estimated verbal IQ ^b	114 ± 9	116 ± 8	-0.62	0.54

^aA lower score denotes higher status. The Phi value is the result of a Fisher's exact test. The z-value is the result of a non-parametric Mann-Whitney U comparison. ^bBased on the American National Adult Reading Test.

Individuals with known autism-related medical conditions (e.g. Fragile-X syndrome, tuberous sclerosis) were not included. Four of the 12 ASD participants were taking the following medications: fluoxetine and lithium; bupropion and clonazepam; citalopram and sertraline and methylphenidate.

HC participants were screened to exclude a history of autism or any other neurological or psychiatric condition. All participants were screened to exclude substance abuse or dependence within the preceding 6 months, and any independent condition that might affect brain function. ASD and control groups were matched for age, sex, handedness as measured by a laterality score on the modified Edinburgh Handedness Inventory (scores of -100 and +100 denote exclusive use of left or right hands, respectively) (Oldfield, 1971; White and Ashton, 1976), parental socioeconomic status on the Hollingshead Index (Hollingshead, 1965), years of education and estimated verbal intelligence quotient (IQ) based on a test of single word reading (American National Adult Reading Test: Blair and Spreen, 1989). All ASD participants had average or above estimates of verbal (124 ± 12, range: 106–141) and non-verbal (120 ± 10, range: 100–138) IQ as measured by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). The study was approved by the Partners Human Research Committee. All participants gave written informed consent after the experimental procedures had been fully explained.

fMRI data were unusable for one ASD participant due to eye tracking malfunction. For a second ASD participant, data were not acquired because scanner-safe glasses of the correct prescription were not available. fMRI analyses were conducted on the remaining 10 ASD and 14 control participants. Saccadic latency data for one control participant was omitted from analysis due to an acquisition problem. DTI data were acquired on all 12 ASD participants and 12 of the 14 controls.

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 with the task. Participants were instructed to respond as quickly and accurately as possible and told that they would receive a bonus of 5 cents for each correct response in addition to a base rate of pay. 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 and 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, Watertown, MA, USA), 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. 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 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 used passive optical components with no ferrous content within the bore to minimize artefacts 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 programme 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

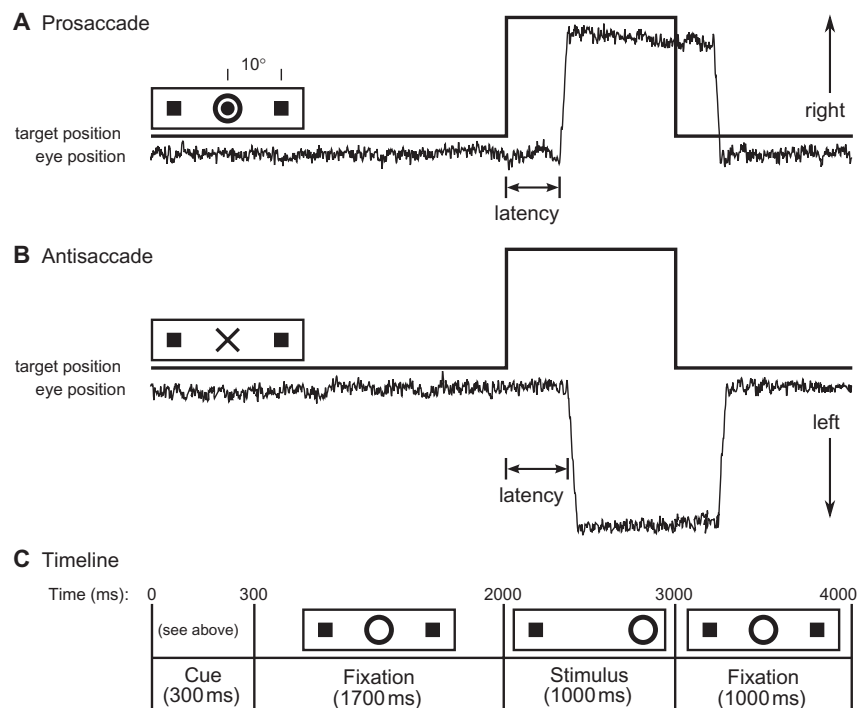


Fig. 1 Saccadic paradigm with idealized eye position traces. Saccadic trials lasted 4000 ms and began with an instructional cue at the centre of the screen. For half of the participants, orange concentric rings were the cue for a prosaccade trial (**A**) and a blue cross was the cue for an antisaccade 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 stimulus appearance, 10° left and right of centre. 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 centre of the screen, of 0.4° diameter and luminance of 20 cd/m². After 1700 ms, the ring shifted to one of the two target locations, right or left, with equal probability. This was the stimulus to which the participant responded by either making a saccade to it (prosaccade) or to the square on the opposite side (antisaccade). The green ring remained in the peripheral location for 1000 ms and then returned to the centre, 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.

the appearance of the target (Fischer and Breitmeyer, 1987). We classified corrective saccades that followed antisaccade errors into short and long latency self-corrections (c.f. Polli *et al.*, 2006): those with latencies (from error initiation) >130 ms suggesting that the correction was a conscious (aware) response to visual feedback regarding an error, and those with latencies <130 ms suggesting that the correction represented a concurrently programmed correct saccade and that the participant was unaware of having made an error (Mokler and Fischer, 1999; McPeck *et al.*, 2000). Post-error slowing was calculated for each participant as the difference in latency between correct trials preceded by an error and correct trials preceded by a correct response. Error rate and latency of correct trials were analysed using randomized block ANOVAs with Group (ASD versus controls) as the between-subjects factor, Task (antisaccade versus prosaccade) as the within-subjects factor and subjects nested within group as the random factor. Post-error slowing and self-correction rates for antisaccades were compared by group using *t*-tests.

Image acquisition

Images were acquired with a 3.0T Siemens Trio whole body high-speed imaging device equipped for echo planar imaging (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 and 1.3 mm slice thickness. T1- and T2-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.

fMRI

Functional images were collected using a gradient echo T2* weighted sequence (TR/TE/Flip = 2000 ms/30 ms/90°). Twenty contiguous horizontal slices parallel to the intercommissural plane (voxel size: 3.13 × 3.13 × 5 mm) were acquired interleaved. The functional sequences included prospective acquisition correction for head motion (Thesen *et al.*, 2000). Prospective acquisition correction adjusts slice position and orientation in real time during data acquisition. This reduces motion-induced effects on magnetization history.

DTI

Single-shot echo planar imaging DTI was acquired using a twice refocused spin echo sequence (Reese *et al.*, 2003) with the following sequence parameters: TR/TE = 8400/82 ms; $b = 700$ s/mm²; NEX = 1; 10 T2 images acquired with $b = 0$; 72 diffusion directions; 128 × 128 matrix; 2 × 2 mm in-plane resolution; 64 axial oblique (AC-PC) slices; 2 mm (0 mm gap) slice thickness; scan duration 12'44". The $n = 72$ diffusion directions were obtained using the electrostatic shell algorithm (Jones, 2004).

Surface-based analyses for fMRI and DTI

Functional and FA volumes were aligned to the 3D structural image for each participant that was created by averaging the two MPRAGE scans after correcting for motion. 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.*, 1999a). To register data across participants, anatomical, functional and DTI scans were spatially normalized using a surface-based spherical coordinate system that employs a non-rigid alignment algorithm that explicitly aligns cortical folding patterns and is relatively robust to inter-individual differences in the gyral and sulcal anatomy of cingulate cortex (Dale *et al.*, 1999; Fischl *et al.*, 1999a, b). For both fMRI and DTI, the ACC was localized using an automated surface-based parcellation system that includes a label for the ACC (Fischl *et al.*, 2004). The ACC label was divided into dorsal and rostral segments by drawing a line perpendicular to the intercommissural plane at the anterior boundary of the genu of the corpus callosum (Devinsky *et al.*, 1995).

fMRI and DTI results were displayed on a template brain consisting of the averaged cortical surface of an independent sample of 40 adults from the Buckner laboratory at Washington University. To correct for multiple comparisons we ran 10 000 Monte Carlo simulations of synthesized white Gaussian noise using a *P*-value of ≤ 0.05 and 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. To test our *a priori* hypotheses concerning ACC function and structure, we restricted the simulations to our ACC ROIs. To determine whether other regions also showed significant group differences we also ran simulations to correct for multiple comparisons on the entire cortical surface. To facilitate comparison with other studies, approximate Talairach coordinates were derived by mapping the surface-based coordinates of activation and FA maxima back to the original structural volume for each participant, registering the volumes to the Montreal Neurological Institute (MNI305) atlas (Collins *et al.*, 1994) and averaging the MNI305 coordinates that corresponded to the surface maxima across participants. The resulting coordinates were transformed to standard Talairach space using an algorithm developed by Matthew Brett (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>).

fMRI data analyses

Analyses were conducted using FreeSurfer (Fischl *et al.*, 1999a) and FreeSurfer Functional Analysis Stream (FS-FAST) software (Burock and Dale, 2000). In addition to on-line motion correction (prospective acquisition correction), functional scans were corrected retrospectively for motion using the AFNI algorithm (Cox and Jesmanowicz, 1999). To characterize average motion for each participant, total motion in millimetres for all six directions (x , y , z and three rotational directions) as determined by AFNI, was averaged across the six runs of the task and compared between groups. Following motion correction, scans were intensity normalized, and smoothed using a 3D 8 mm FWHM Gaussian kernel. Finite impulse response estimates (Burock and Dale, 2000; Miezin *et al.*, 2000) of the event-related haemodynamic responses 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 haemodynamic response. Haemodynamic response 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 pre-whitening using a global estimate of the residual error autocorrelation function truncated at 30 s (Burock and Dale, 2000).

Registered group data were smoothed with a 2D 4.6 mm FWHM Gaussian kernel. We compared activation in error versus correct antisaccades, and in both correct and error antisaccades versus fixation, both within and between groups using a random effects model. We examined the 6 and 8 s time points that showed peak error-related activation in previous studies (Polli *et al.*, 2005, 2008).

DTI analysis

The objective of the DTI analysis was to measure FA in the WM underlying specific regions using a vertex-wise analysis of the registered group data. FA was measured in the undeformed WM 2 mm below the WM/gray matter boundary. This strategy minimizes partial volume contributions from cortical gray matter and preserves regional specificity (the rationale for the surface-based approach is elaborated in Manoach *et al.*, 2007a). DTI data were analysed using the following multi-step procedure:

- (1) Motion/eddy current distortion correction: Raw diffusion data were corrected for head motion and residual eddy current distortion by registering all images to the first T2 image, which was acquired with $b=0$. The registration was performed using the FLIRT tool (Jenkinson and Smith, 2001) from the FSL software library (<http://www.fmrib.ox.ac.uk/fsl>). The registration used a global affine (12 df) transformation, a mutual information cost function and sinc resampling.
- (2) Tensor reconstruction: The diffusion tensor and FA volumes were reconstructed using the standard least-squares fit to the log diffusion signal (Basser *et al.*, 1994).
- (3) Registration of FA and T1 volumes: FA volumes were registered to the high-resolution structural (T1) volumes for each participant using the T2 volume as an intermediary. This avoids the potential bias that might arise from using the FA volume in the registration, since FA is the variable of interest. In addition, the gray/white boundary in the T1 volume has better correspondence with the T2 volume than the FA volume, allowing for a more accurate registration. The T2 volume was taken from the $b=0$ image in the DTI acquisition and was, therefore, in register with the FA volume. Each participant's averaged T2 volume was manually registered to the T1 volume with `Tkregister2` (<http://surfer.nmr.mgh.harvard.edu>) using 9 df including translation, rotation and scaling. Manual registration was used to maximize anatomic agreement along the medial wall and because echo planar imaging susceptibility distortions in DTI can confound global registration procedures. The resulting spatial transformation was applied to the FA volume, thus bringing the FA and T1 volumes into register.
- (4) Projection of subcortical FA values onto the WM/gray matter interface: For each participant, a surface representation of the WM/gray matter boundary was derived from the T1 volume

using the previously described segmentation, surface reconstruction and inflation algorithm (Dale *et al.*, 1999; Fischl *et al.*, 1999a). FA was sampled in the WM 2 mm below the WM/gray matter boundary for each vertex on the surface and then projected onto the WM/gray interface. FA values were smoothed using $n=50$ iterations of replacement by nearest neighbours. This corresponds to smoothing by ~ 10 mm FWHM on the surface.

- (5) Registration of surface FA maps across participants: This was achieved by applying the surface transformations from the spatial normalization of the T1 maps to the FA maps, which were in register with T1 maps (step 3).
- (6) To test for significant group differences in FA in the registered group data, a *t*-test was performed in the WM underlying each vertex.

Relations of ACC function and structure to restricted, repetitive behaviour in ASD

fMRI activation in each contrast at 6 and 8 s and FA values were regressed onto ADI-R diagnostic algorithm scores of restricted and repetitive behaviours for every vertex on the cortical surface. In the regression of FA values on ADI-R scores, age was used as a covariate given the documented relation of increasing age with decreasing FA (Pfefferbaum *et al.*, 2000).

Results

Saccadic performance

ASD participants made significantly more errors than HC [$F(1,22)=7.82$, $P=0.008$]. Although the group by task interaction was not significant [$F(1,22)=0.99$, $P=0.32$], ASD participants had a significantly higher antisaccade error rate than controls [Fig. 2A, $t(22)=2.68$, $P=0.01$, HC: $6.55 \pm 4.94\%$, range 1.43–16.59%; ASD: $12.41 \pm 9.02\%$, range 2.37–26.67%], but did not differ significantly in the error rate for prosaccades [$t(22)=1.62$, $P=0.21$, HC: $2.04 \pm 1.50\%$, ASD: $4.82 \pm 4.06\%$] (Fig. 2A). ASD participants responded more quickly on correct trials [$F(1,21)=9.74$, $P=0.005$] and there was a trend to a group by task interaction [$F(1,21)=3.33$, $P=0.08$] reflecting a greater group latency difference for antisaccade than prosaccade trials [antisaccade: $t(21)=3.47$, $P=0.002$, HC: 309 ± 40 ms, ASD: 253 ± 20 ms; prosaccade: $t(21)=2.56$, $P=0.02$, HC: 254 ± 50 ms, ASD: 212 ± 29 ms] (Fig. 2B). ASD participants were slightly more likely to correct antisaccade errors [trend: $t(22)=1.77$, $P=0.09$; HC: $85 \pm 13\%$; ASD: $93 \pm 5\%$] (Fig. 2C), and did not differ from controls in the proportion of long versus short self-corrections [$t(22)=1.50$, $P=0.15$, HC: $67 \pm 29\%$; ASD: $51 \pm 20\%$]. Controls did not show significant post-error slowing for either antisaccades [0 ± 26 ms, $t(12)=0.06$, $P=0.95$] or prosaccades [14 ± 29 ms, $t(12)=1.71$, $P=0.11$]. ASD participants showed post-error speeding for antisaccades [-11 ± 15 ms, $t(9)=2.48$, $P=0.04$] and no post-error change in latency for prosaccades [ASD: 3 ± 13 ms; $t(9)=0.73$, $P=0.48$].

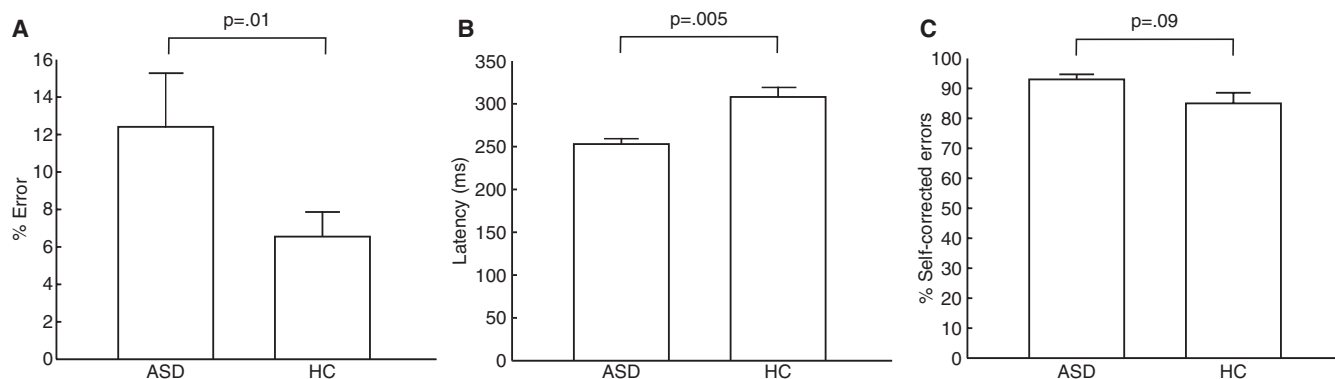


Fig. 2 Bar graphs of performance for each group as measured by mean and standard errors of (A) antisaccade error rate, (B) latency of correct antisaccades and (C) percentage of antisaccade errors that were self-corrected.

fMRI analyses of response monitoring in the ACC

Patients and controls did not differ in mean motion during functional scans [controls: 1.71 ± 0.81 mm, patients: 1.78 ± 0.47 mm, $t(22) = 0.62$, $P = 0.83$]. As group differences in activation were more pronounced at the 8 s than the 6 s time point, we report findings from 8 s only.

Controls showed a more differentiated response to error versus correct trials than ASD participants in the right rACC, extending into the dACC (Fig. 3A, Table 2). The basis of this group difference was that ASD participants showed significantly greater activation to correct responses in bilateral rACC (Fig. 3B, Table 2). In this region, the group difference in the response to errors was not significant (Fig. 3C), and within group analyses revealed that while both groups showed a significant response to errors bilaterally (Control: left maximum $-9, 37, 12$, cluster size = 1204 mm^2 , cluster-wise probability (CWP) = 0.0001; right maximum $7, 26, 18$, cluster size = 1561 mm^2 , CWP = 0.0001; ASD: left maximum $-5, 34, 5$, cluster size = 1112 mm^2 , CWP = 0.0001; right maximum $9, 38, 12$, cluster size = 850 mm^2 , CWP = 0.0001), only the ASD group showed a significant response to correct trials (left maximum $-7, 40, 1$, cluster size = 1107 mm^2 , CWP = 0.0001; right maximum $7, 39, 11$, cluster size = 1498 mm^2 , CWP = 0.0001). Compared with controls, ASD participants also showed significantly greater activation for correct trials in another more anterior perigenual rACC region bilaterally (Fig. 3B), and in the left hemisphere this region also showed a significantly greater response to errors (Fig. 3C). Controls did not activate this perigenual rACC region for either correct or error responses. When multiple comparisons correction was applied to the entire cortical surface, the finding that the ASD group showed an exaggerated response to correct trials in right rACC extending into dACC remained significant (CWP = 0.0001). The only other significant group difference in cortical activation was a less differentiated response for ASD participants to error versus correct responses in the medial aspect of the right superior frontal gyrus.

Four of our ASD participants were taking medications that could affect ACC function. A re-analysis of the data with only unmedicated ASD participants confirmed the main findings that in the right rACC, ASD participants showed significantly less discrimination between correct and error trials and greater activation to correct trials (Table 2, Supplementary Figure).

DTI analyses

ASD participants showed significantly reduced FA in the WM underlying rACC and dACC bilaterally (Fig. 4, Table 2). The maxima in both hemispheres were in rACC WM, near the border with dACC and FA reductions extended into the corpus callosum. These reductions met multiple comparisons correction for the entire cortical surface. Significantly reduced activation FA in ASD was also seen in the WM underlying bilateral frontopolar cortex, which, extended into dorsolateral and ventrolateral prefrontal cortex in the left hemisphere; bilateral intraparietal and parietal transverse sulci; and left precentral gyrus. The only region showing significantly greater FA in ASD participants versus controls was in the WM underlying right insula.

Relations of ACC function and structure to ADI-R scores of restricted and repetitive behaviour in ASD

Regression analyses showed that in ASD, higher ADI-R restricted and repetitive behaviour scores were associated with greater activation during correct trials versus fixation at 8 s in the right rACC (Fig. 5A, Table 2). This right rACC region overlapped with the regions showing both significantly increased activation to correct trials and reduced FA. Repetitive behaviour scores were not significantly associated with ACC activation in other contrasts at either 6 or 8 s. The only other cortical region showing a significant relation at 8 s was the right paracentral gyrus extending into the postcentral gyrus in the error versus correct contrast.

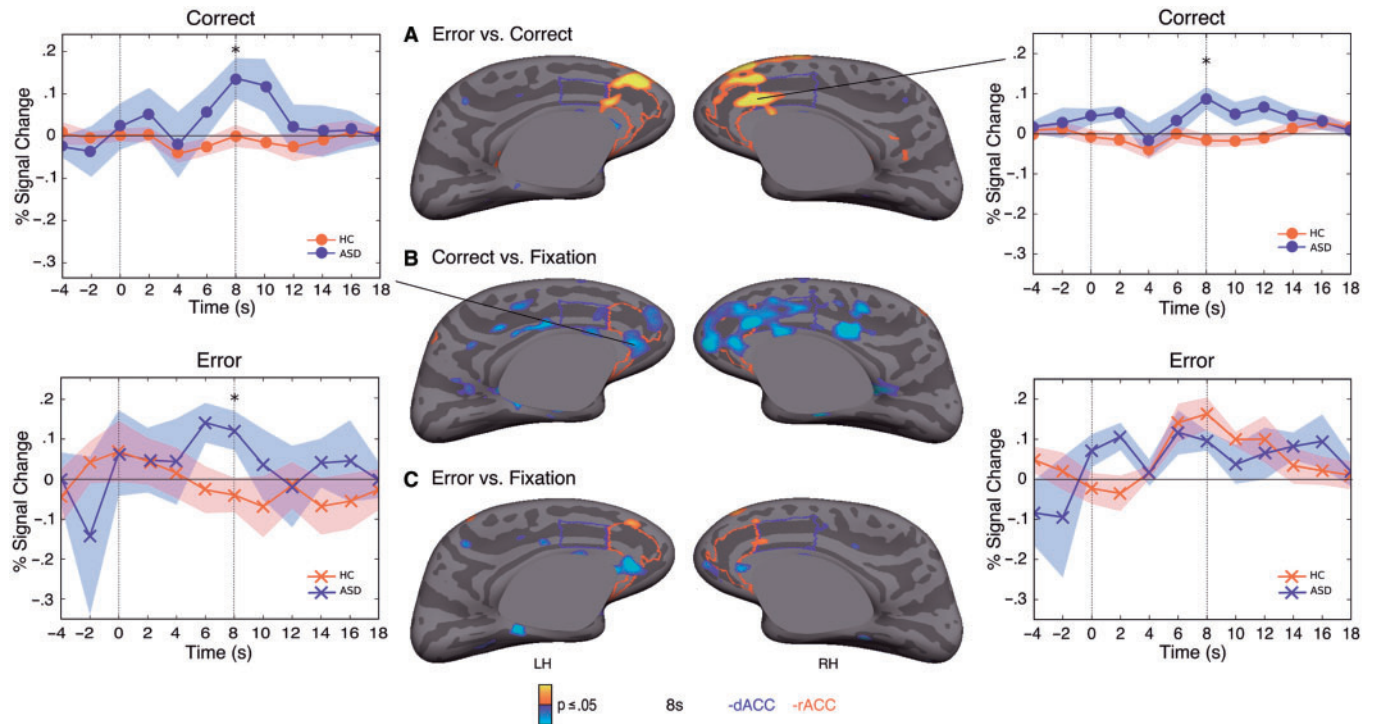


Fig. 3 Statistical maps of group differences in fMRI activation at 8s for contrasts of (A) error versus correct antisaccades; (B) correct antisaccades versus fixation; (C) error antisaccades versus fixation. Statistical maps are displayed on the inflated medial cortical surfaces of the template brain at $P \leq 0.05$. Regions of greater activation in controls are depicted in warm colours; greater activation in ASD patients is depicted in blue. The rACC is outlined in red and the dACC is outlined in blue. The gray masks cover non-surface regions in which activity is displaced. Haemodynamic response time course graphs with standard error bars are displayed for the indicated vertices with peak activation in the group comparisons.

Lower FA in the WM underlying ACC was significantly related to higher repetitive behaviour scores in left subgenual rACC, with a maximum vertex in subcallosal gyrus (Fig. 5B, Table 2). No other cortical regions showed significant relations in underlying WM.

The literature on repetitive behaviour in autism supports a division into ‘low-level’ repetitive motor behaviour and more complex behaviours that appear to be driven by ideation (for review see, Turner, 1999). To assess the relative importance of ‘sensorimotor’ versus ‘ideational’ forms of repetition in accounting for the observed relations with ACC activation and structure, we first divided each participants’ ADI-R repetitive behaviour score into ‘sensorimotor’ (i.e. D3/D4: stereotypies, mannerisms, repetitive object use, unusual sensory interests) and ‘ideational’ (i.e. D1/D2: narrow restricted interests and rituals) subscores (Hollander *et al.*, 2003). On average, the ideational subscore accounted for $65 \pm 14\%$ of the total repetitive behaviour score. We then performed multiple regression analysis with BOLD or FA value at the ACC maxima of the regression with total score as the dependent variable, and the two subscores as covariates. Sensorimotor subscores were more strongly related to activation in the ACC ($P=0.04$) than ideational subscores ($P=0.17$). The opposite was true for FA, which showed a stronger correlations with ideational subscores ($P=0.05$) than sensorimotor

subscores ($P=0.18$). The subscores did not differ significantly in their contribution to activation or FA, and neither improved on the relations seen with the total repetitive behaviour score (activation: $P=0.0009$; FA: $P=0.04$) suggesting that both subscores contributed to the relations observed.

Discussion

The present study demonstrates functional and structural abnormalities of the ACC in ASD that may contribute to restricted, repetitive and stereotyped patterns of behaviour, a defining feature of ASD. Compared with controls, ASD participants showed increased rACC activation to both correct and error responses and reduced microstructural integrity of the WM underlying ACC, including in regions showing abnormally increased response monitoring activation. Moreover, in rACC increased activation to correct trials and reduced FA were related to ratings of rigid, repetitive behaviour. These findings support the hypothesis of hyperactive response monitoring in ASD and link it to repetitive behaviour.

Relative to controls, ASD participants showed reduced discrimination between error and correct trials in a rACC region that responds to errors (Polli *et al.*, 2005). This was primarily due to an exaggerated response to correct trials,

Table 2 Maxima and locations of clusters showing significant group differences and significant relations to ADI-R repetition scores in ASD

	Approximate Talairach coordinates					CWP
	Cluster size (mm)	x	y	z	t-value (max)	
fMRI group comparisons						
Error versus correct						
<i>HC > ASD</i>						
Right rostral anterior cingulate gyrus	488	7	38	12	3.31	0.0001
<i>Unmedicated ASD participants</i>	424	7	38	12	2.18	0.008
Right medial superior frontal gyrus ^a	2071	9	50	38	3.53	0.001
Correct versus fixation						
<i>ASD > HC</i>						
Left pericollous sulcus (rACC)	413	-6	30	-6	2.22	0.0001
<i>Unmedicated ASD participants</i>	102	-6	31	-6	1.59	0.41
Right rostral anterior cingulate gyrus ^a	1746	7	39	11	3.47	0.0001
<i>Unmedicated ASD participants</i>	912	9	39	10	3.61	0.0002
Pericollous anterior cingulate gyrus		6	36	-6		
Error versus fixation						
<i>ASD > HC</i>						
Left rostral anterior cingulate gyrus	255	-2	26	-4	3.64	0.02
<i>Unmedicated ASD participants</i>	80	-1	26	-3	2.38	0.78
DTI-FA group comparison^b						
<i>HC > ASD</i>						
Left rostral anterior cingulate gyrus ^a	1598	-7	39	6	6.05	0.0001
Right rostral anterior cingulate gyrus ^a	6620	7	38	3	5.64	0.0001
<i>Frontopolar transverse sulcus</i>		20	61	14		
Left transverse gyrus, frontopolar ^a	6152	-20	59	6	7.2	0.0001
Left precentral gyrus ^a	1022	-47	-8	41	5.11	0.009
Left intraparietal and parietal transverse s ^a	4878	-40	-50	42	5.05	0.0001
Right intraparietal and parietal transverse s ^a	1465	21	-56	52	4.06	0.0008
<i>ASD > HC</i>						
Right anterior circular sulcus, insula*	838	35	31	-2	-2.91	0.05
fMRI regressions with ADI-R						
Correct versus fixation						
Right rostral anterior cingulate gyrus	684	6	37	-7	3.23	0.0001
Error versus correct						
Right paracentral gyrus ^a	1642	6	-25	51	-2.59	0.005
DTI-FA regressions with ADI-R						
Left subcollous gyrus (rACC)	148	-5	18	-8	-2.04	0.05

^aMeets correction for entire cortical surface. ^bCWP levels are based on correction for entire cortical surface. Important local maxima are indented. Results for fMRI group comparisons restricted to unmedicated ASD participants ($n = 6$) are indented and italicized.

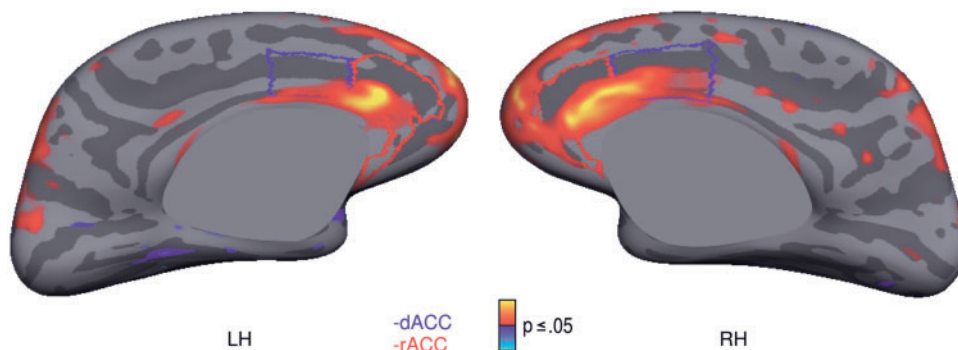


Fig. 4 Statistical map of group differences in FA displayed on the inflated medial cortical surfaces of the template brain at a threshold of $P \leq 0.05$. Regions of greater FA in controls are depicted in warm colours. The rACC is outlined in red and the dACC is outlined in blue.

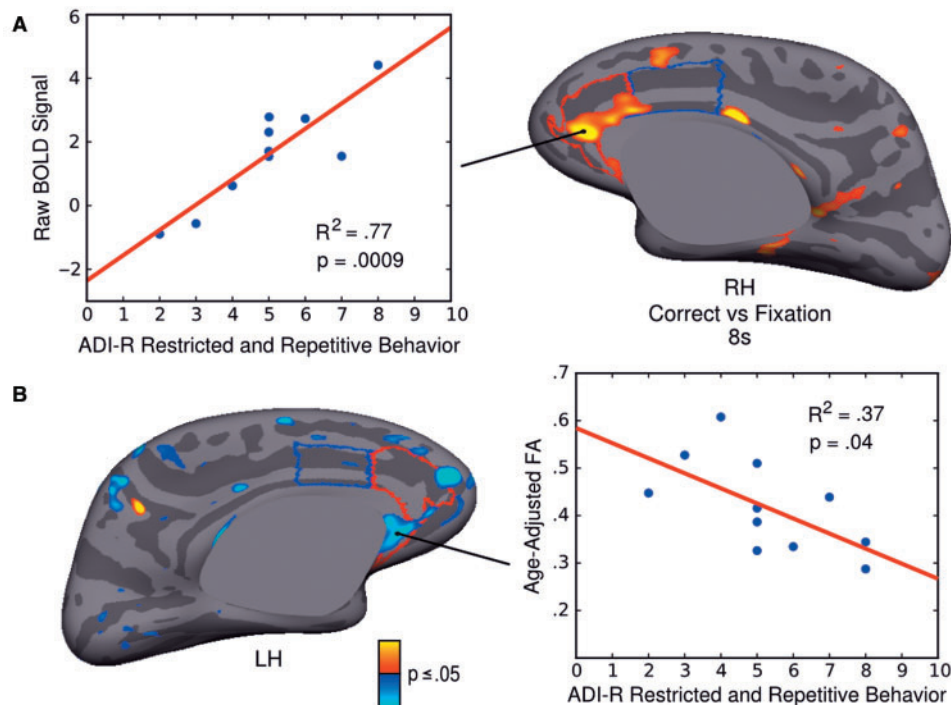


Fig. 5 Relations of ACC function and structure to restricted, repetitive behaviour in ASD. **(A)** Statistical map of regression of raw BOLD signal on ADI-R repetitive behaviour score. BOLD signal is from the correct antisaccade versus fixation contrast at 8 s. Results are displayed on the inflated right medial cortical surface. Scatter plot shows BOLD signal from the maximum vertex in right rACC for each ASD participant on the y-axis and ADI-R score on the x-axis. **(B)** Statistical map of regression of FA on ADI-R repetitive behaviour score. Results are displayed on the inflated left medial surface. Scatter plot shows FA from the maximum vertex in left rACC for each ASD participant on the y-axis and ADI-R score on the x-axis. The rACC is outlined in red and the dACC is outlined in blue.

rather than a blunted response to errors. Reduced discrimination between response outcomes may interfere with adjusting responses to obtain the most favourable outcome both with regard to subsequent trials and longer term modification of the strength of stimulus-response mappings. This could contribute to behaviour that is stimulus-bound and repetitive rather than flexible and responsive to contingencies. This provides a plausible explanation for the relation between increased rACC activity to correct trials and repetitive behaviour.

A complementary explanation has been offered for the relation of increased error signals to the severity of obsessions and compulsions in OCD (Gehring *et al.*, 2000; Ursu *et al.*, 2003). A longstanding theory of OCD posits that inappropriate and exaggerated error signals lead to a pervasive sense of incompleteness and self-doubt and behavioural repetition represents a vain attempt to reduce these error signals (Pitman, 1987). According to this theory, exaggerated ACC activation to correct trials reflects inappropriate error signalling and triggers a compulsion to repeat behaviours that were already successfully completed (Maltby *et al.*, 2005). Similar to individuals with OCD, ASD participants showed an exaggerated ACC response to correct trials (Ursu *et al.*, 2003; Maltby *et al.*, 2005). While in OCD fMRI activation to correct trials was maximal in dACC (Maltby *et al.*, 2005), in ASD it was

maximal in rACC and was related to repetitive behaviour. While dACC activity following errors is thought to reflect either conflict or error detection (for review see: Ullsperger and von Cramon, 2004), rACC activity following errors has been interpreted as appraisal of the affective or motivational salience of errors (van Veen and Carter, 2002; Luu *et al.*, 2003; Taylor *et al.*, 2006). Thus, one interpretation of this relation is that it reflects an inappropriate affective response to correct performance that triggers behavioural repetition. This exaggerated affective response may occur even with awareness that one has performed correctly. Regardless of its basis, the relation between increased rACC responses to correct trials and repetitive behaviour suggests that aberrant response monitoring contributes to a defining feature of ASD.

Both ASD and OCD are characterized by behaviour that is rigid and not optimally responsive to contingency, and there is evidence of both phenomenological overlap and distinctions between the obsessions and compulsions of OCD and the restricted and repetitive behaviours of ASD, both in terms of subjective experience and type of behaviour (Baron-Cohen, 1989; McDougle *et al.*, 1995; Russell *et al.*, 2005; Zandt *et al.*, 2007). Interestingly, a study of multiplex families of children with autism found that parents were significantly more likely to have obsessive-compulsive traits or disorder if the children had high ADI-R repetitive behaviour scores, and this was due to loading

on ideational but not sensorimotor items (Hollander *et al.*, 2003). This finding supports the distinction between repetition of movements and repetition of more complex, ideational behaviours (for review see, Turner, 1999) and suggests that the latter may share underlying mechanisms in OCD and ASD. In the present study, both sensorimotor and ideational subscores contributed to the relations seen with response monitoring activation and FA. At present, repetitive behaviours in autism are incompletely understood, and neurobiologically valid dimensions are yet to be delineated. The present findings suggest that ACC abnormalities may contribute to repetitive behaviour in ASD, possibly on the basis of their contribution to aberrant response monitoring, but linking ACC abnormalities to specific dimensions of repetitive behaviour and identifying the underlying mechanisms requires further study with large samples.

Abnormal response monitoring may also contribute to deficient cognitive control of behaviour in ASD, which, in the present study, was reflected in an increased antisaccade error rate, consistent with prior work (Manoach *et al.*, 1997, 2004; Minshew *et al.*, 1999; Goldberg *et al.*, 2002; Luna *et al.*, 2007) and possibly in reduced dynamic performance adjustment. In spite of making more errors, ASD participants responded more quickly than controls on correct trials suggesting a disruption in the speed-accuracy trade-off. This apparent difficulty in modulating response speed to improve accuracy is unlikely to reflect reduced error awareness since ASD participants were as, or more likely than controls to self-correct errors. Nor is it likely to reflect a blunted neural response to errors given both the increased response to errors in left perigenual rACC and previous work showing normal or increased amplitude of the ERN in ASD (Henderson *et al.*, 2006). Deficient use of outcomes to adjust performance in a continuous, dynamic fashion may stem from response monitoring dysfunction in the ACC and/or from dysconnection of the ACC from ocular motor regions involved in saccade generation. Aberrant connectivity of ACC regions subserving response monitoring in ASD is suggested by our finding of reduced FA in the underlying WM. This finding is consistent with a previous report of reduced FA in ACC white matter in autism (Barnea-Goraly *et al.*, 2004) and with evidence of decreased functional connectivity of the ACC to other regions during a task involving response inhibition (Kana *et al.*, 2007).

How might information concerning the outcome of the prior response be communicated to ocular motor regions responsible for adjusting behaviour in the subsequent trial? Monkey electrophysiology studies suggest a basis for speed-accuracy trade-offs in the ocular motor system. Compared with prosaccades, antisaccades are associated with reduced pre-target activity of saccade-related neurons in the frontal eye field (Everling *et al.*, 1999; Everling and Munoz, 2000) and superior colliculus (Everling *et al.*, 1999), key regions in saccade generation. Moreover, lower pre-target frontal eye

field activity is correlated with increased saccadic latency and fewer antisaccade errors. Reduced preparatory neural activity in response to the instruction to perform an antisaccade presumably makes it more difficult for activity related to the incorrect, but prepotent prosaccade to reach the threshold for triggering an eye movement. However, the price for this improved accuracy is that the activity generating the correct antisaccade also takes longer to reach threshold, resulting in prolonged saccadic latencies. Thus, we hypothesize that the slowing of responses that follow an antisaccade error (i.e. post-error slowing; Nieuwenhuis *et al.*, 2001) stems from an ACC error response that signals the frontal eye field to reduce its preparatory activity during the subsequent trial. This hypothesis is consistent with previous work demonstrating that other aspects of trial history affect preparatory neural activity in the frontal eye field during antisaccades (Manoach *et al.*, 2007b). How might error signals be conveyed to frontal eye field? The use of outcomes to dynamically adjust responses has been attributed to ACC acting with lateral prefrontal cortex (Gehring and Knight, 2000; Paus, 2001; Garavan *et al.*, 2002) and lateral prefrontal cortex has been proposed to provide inhibitory input to frontal eye field during antisaccades (DeSouza *et al.*, 2003). Thus, in ASD, aberrant communication between response evaluation in the ACC and regions initiating compensatory adjustments, possibly lateral prefrontal cortex, could result in a failure to optimally reduce preparatory firing rates in frontal eye field in response to a prior error. This reduced dynamic performance adjustment could lead to faster responding and more errors. We are presently testing this hypothesis using an antisaccade paradigm that gives rise to post-error slowing (Rabbitt, 1966) and will allow a more direct examination of compensatory behaviour and its supporting neural circuitry. Unfortunately, although post-error slowing is seen when antisaccades are the only task (Polli *et al.*, 2006) the intermixed antisaccade and prosaccade paradigm employed here gives rise to other inter-trial factors that also affect latency (e.g. task-switching and prior antisaccades, Cherkasova *et al.*, 2002; Fecteau *et al.*, 2004; Barton *et al.*, 2006; Manoach *et al.*, 2007b) and may obscure the effects of a prior error. There is evidence of reduced post-error slowing in adults with high functioning autism, however, from a previous study that employed a memory search task (Bogte *et al.*, 2007). Generalizing beyond the ocular motor system, failures of dynamic performance adjustment due to ACC dysfunction and dysconnectivity may contribute to the rigid and perseverative behaviours that characterize ASD.

Repetitive behaviour scores in ASD were also associated with reduced FA in the WM underlying left subgenual rACC. Subgenual rACC is part of a network that is thought to play an important role in generating autonomic responses to motivationally salient stimuli, evaluating their significance in predicting reward and in using this

information to guide behaviour (Damasio *et al.*, 1990; Drevets, 2000). An important consideration in interpreting this relation of FA to repetition is that subgenual rACC region was not functionally or structurally abnormal in this ASD sample. This suggests that even normal variation in FA of the subgenual rACC may contribute to a tendency to repeat unreinforced stimulus-response mappings. More generally, the relations we observed between behavioural repetition and ACC function and structure may not be specific to ASD. Accumulating evidence suggests that the three symptom clusters that define autism—social impairment, communication deficits and restricted, repetitive behaviour—arise from distinct genetic and cognitive mechanisms and may represent continuous traits in the population (for reviews see: Happe *et al.*, 2006; London, 2007). Previous studies have reported relations between indices of response monitoring and repetition in OCD (Gehring *et al.*, 2000; Ursu *et al.*, 2003) and in non-clinically ascertained samples of children and adults with obsessive-compulsive characteristics (Hajcak and Simons, 2002; Santesso *et al.*, 2006).

Our findings also raise the question of whether the response monitoring abnormalities that we observed are specific to ASD. Similar abnormalities have been reported in OCD (Maltby *et al.*, 2005) and attention deficit hyperactivity disorder (van Meel *et al.*, 2007). While methodological differences preclude a direct comparison of these findings, we previously studied patients with schizophrenia using the identical paradigm (Polli *et al.*, 2008). Schizophrenia is also a neurodevelopmental disorder that is characterized by rigid and perseverative behaviour, response monitoring abnormalities (Carter *et al.*, 2001), reduced FA in ACC WM (Manoach *et al.*, 2007a) and a consistently elevated antisaccade error rate (Radant *et al.*, 2007; Manoach *et al.* 2002). Although both schizophrenia and ASD samples made more antisaccade errors than controls, ASD participants performed correct trials faster and schizophrenia patients performed more slowly. While both groups showed reduced discrimination between error and correct trials in the ACC, this occurred for different reasons. In ASD this reflected a hyperactive response to correct trials, while in schizophrenia it reflected a blunted ACC response to errors, consistent with numerous previous reports (Laurens *et al.*, 2003). These differences argue for distinct behavioural and neural signatures of response monitoring deficits in schizophrenia and ASD. These findings, along with those of recent neuroimaging studies suggesting genetic mediation of response monitoring (Fallgatter *et al.*, 2004; Klein *et al.*, 2007; Kramer *et al.*, 2007), support the candidacy of neuroimaging-based indices of response monitoring as neurocognitive endophenotypes. Whether response monitoring abnormalities can be distinguished in ASD, OCD and other neuropsychiatric disorders, whether they are related to diagnosis or specific traits, and whether they are also present in unaffected family members remains to be seen.

Several additional limitations to and alternative interpretations of our findings merit consideration. First, might the hyperactive rACC response to correct antisaccades in ASD reflect a less efficient response to conflict rather than response monitoring? The ACC is thought to play a role in detecting conflict and engaging cognitive control to resolve it (for review see: Carter and van Veen, 2007). Antisaccades involve a high degree of conflict as one must choose between two competing responses and inhibit the prepotent one. Errors give rise to another type of conflict when the actual response is compared with the intended one. Thus, both correct and erroneous antisaccades engender conflict. While it is not possible to entirely rule out the conflict explanation, several observations argue against it. If this rACC region were detecting conflict it should respond to both correct and error trials. Instead, controls showed a significant response only to errors. In addition, the timing of the haemodynamic response to correct antisaccades in ASD, which started ~ 4 s and peaked at ~ 8 s (Fig. 3), argues for a role in response monitoring rather than successful conflict resolution. In this paradigm, differential fMRI activation for correct antisaccade versus prosaccade trials, including in dACC, presumably reflecting conflict detection, response inhibition and saccade generation, peaks at ~ 4 s and is mostly gone by 8 s (Manoach *et al.*, 2007b; see also Polli *et al.*, 2005, for a discussion of ACC regions involved in saccade generation versus response monitoring). Finally, it is dorsal rather than rACC activation that is associated with engaging cognitive control on correct high-conflict and error trials (Carter and van Veen, 2007).

An important limitation is that the small sample size of the present study may have compromised our power to detect additional group differences and relations of interest, particularly in regions outside our *a priori* ACC regions of interest for which more stringent multiple comparisons corrections were applied. In spite of the relatively small sample size, our *a priori* hypotheses were confirmed. In addition, four of our ASD participants were taking medications that could affect ACC function. A re-analysis of the fMRI data with only unmedicated ASD participants, however, supported our main findings of significantly less discrimination between response outcomes in the rACC, and greater activation to correct trials. It is also important to note that our sample was limited to high functioning adults with ASD so it is not clear that our findings would generalize to lower functioning or younger samples. Although increased antisaccade error rates are seen in autism as early as ages 8–12 (Luna *et al.*, 2007), we limited our study to adults since saccadic inhibition may not fully develop until late adolescence (Klein and Foerster, 2001) and larger samples would be necessary to discriminate between the effects of diagnosis and those due to normal development. Another limitation concerns our interpretation of FA as reflecting connectivity. FA reflects the degree of directional coherence of water diffusion in tissue and is, therefore, an indirect measure of

WM microstructure. While FA correlates with axon myelination (Harsan *et al.*, 2006), not all of its biophysical determinants are fully understood (Beaulieu, 2002). Thus, it is not possible to attribute FA differences or the relations we observed to a particular WM property.

In summary, the present study reports hyperactive response monitoring in the rACC in ASD that is related to restricted, repetitive behaviour and is accompanied by reduced FA in the underlying white matter. This suggests a structural correlate to abnormal function that may compromise connectivity in the circuitry subserving response monitoring. These findings suggest that structural and functional abnormalities of the ACC compromise response monitoring and contribute to behavioural repetition in ASD. Impairments in evaluating and learning from errors may lead to behaviour that is rigid and repetitive rather than optimally guided by outcomes, and may compromise performance across a wide range of tasks. Illuminating the neural basis and clinical significance of response monitoring deficits in ASD represents a fruitful avenue for further research.

Supplementary material

Supplementary material is available at *Brain* online.

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