Special issue: Research report

Fronto-striatal circuitry and inhibitory control in autism: Findings from diffusion tensor imaging tractography

Marieke Langen [a,d,*], Alexander Leemans [b,c,1], Patrick Johnston [a,1], Christine Ecker [a], Eileen Daly [a], Clodagh M. Murphy [a], Flavio dell'Acqua [a], Sarah Durston [d], the AIMS Consortium[2] and Declan G.M. Murphy [a]

[a] *Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, King's College London, UK*
[b] *Cardiff University Brain Research Imaging Centre (CUBRIC), School of Psychology, Cardiff University, UK*
[c] *Image Sciences Institute, University Medical Center Utrecht, The Netherlands*
[d] *Neuroimaging (NICHE) Lab, Department of Child and Adolescent Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, The Netherlands*

A R T I C L E   I N F O

A B S T R A C T

Introduction: Repetitive behaviour and inhibitory control deficits are core features of autism; and it has been suggested that they result from differences in the anatomy of striatum; and/or the 'connectivity' of subcortical regions to frontal cortex. There are few studies, however, that have measured the micro-structural organisation of white matter tracts connecting striatum and frontal cortex.

Aims: To investigate differences in bulk volume of striatum and micro-structural organisation of fronto-striatal white matter in people with autism; and their association with repetitive behaviour and inhibitory control.

Methods: We compared the bulk volume of striatum (caudate nucleus, putamen and nucleus accumbens) and white matter organisation of fronto-striatal tracts using (respectively) structural magnetic resonance imaging (sMRI) and tract specific diffusion tensor imaging (DTI) measures in 21 adults with autism and 22 controls. We also assessed performance on a cognitive inhibition (go/nogo) task.

Results: Bulk volume of striatal structures did not differ between groups. However, adults with autism had a significantly smaller total brain white matter volume, lower fractional anisotropy of white matter tracts connecting putamen to frontal cortical areas, higher mean diffusivity of white matter tracts connecting accumbens to frontal cortex and worse performance on the go/nogo task. Also, performance on the go/nogo task was significantly

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* *Corresponding author.* Neuroimaging (NICHE) Lab, Department of Child and Adolescent Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, HP A01.468-431, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands.
E-mail address: m.langen@umcutrecht.nl (M. Langen).
[1] These authors contributed equally.

related to anatomical variation when both groups were combined; but not within the autism group alone.

Conclusions: These data suggest that autism may be associated with differences in the anatomy of fronto-striatal white matter tracts.

1. Introduction

Autism is characterised by a triad of (1) stereotyped and repetitive behaviours, and pervasive abnormalities in (2) socio-emotional and (3) communicative behaviour. While a considerable body of work has investigated brain differences associated with the last two clusters of symptoms, relatively few studies have investigated those putatively associated with stereotyped and repetitive behaviour. Hence, the biological associates of this core symptom domain are poorly understood.

Studies of people with other neuropsychiatric disorders, such as obsessive compulsive disorder and Tourette's syndrome, have highlighted the relationship between stereotyped and repetitive behaviours and abnormalities within the striatum (Albin and Mink, 2006; Bloch et al., 2005; Hyde et al., 1995; Van den Heuvel et al., 2009; Whiteside et al., 2004). Moreover, there is increasing evidence that autism is associated with differences in the developmental trajectory and volume of striatum (Hollander et al., 2005; Langen et al., 2007, 2009; McAlonan et al., 2002; Rojas et al., 2006; Sears et al., 1999) that, some have reported, are related to stereotyped and repetitive behaviour. Further, repetitive behaviour has been linked with executive function deficits (in particular inhibitory control) (Thakkar et al., 2008; Mosconi et al., 2009) and it has been suggested that the frontal cortex, and its connections to striatal and parietal regions, underpin these behavioural deficits (Christ et al., 2007; Garavan et al., 2002; Kana et al., 2007; Mosconi et al., 2009; Robinson et al., 2009; Schmitz et al., 2006). Hence, it has been suggested that differences in these brain regions play a central role in autism (Carper and Courchesne, 2005; Murphy et al., 2002; Rojas et al., 2006; Turner et al., 2006).

Recently, there has been increasing recognition that, in addition to — or instead of — focal differences in brain anatomy, people with autism may have altered brain 'connectivity' [e.g., see Bachevalier and Loveland (2006); Courchesne and Pierce (2005) and Just et al. (2004)]. For example, some have reported differences in intra-regional correlations of grey matter (McAlonan et al., 2004) and glucose metabolism (Horwitz et al., 1988) within corticostriatal circuits in autism, as well as altered functional connectivity (Belmonte et al., 2004a, 2004b; Just et al., 2004; Koshino et al., 2005; Ring and Serra-Mestres, 2002) within frontal cortex and in circuits linking frontal areas to other brain systems (Courchesne and Pierce, 2005; Kana et al., 2007; Turner et al., 2006).

Other investigators have used diffusion tensor imaging (DTI) to examine the micro-structural organisation of white matter in autism. This non-invasive MRI technique measures the diffusion profile of water molecules, which, in turn, can provide valuable insights in the underlying architectural organisation of white matter fibre tracts (Jones and Leemans, 2011; Tournier et al., 2011). Water molecules diffuse more readily in the direction parallel to a tract rather than perpendicular to it (Beaulieu,

2002). This directional dependence within a given voxel can be quantified using DTI, resulting in several outcome measures including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (Da), and radial diffusivity (Dr). These measures reflect directionality of diffusion (FA), amplitude of diffusion (MD), diffusion parallel to tracts (Da) and diffusion perpendicular to tracts (Dr) (Blain et al., 2011). Most prior DTI studies of autism used voxel based morphometry (VBM)-based approaches (Alexander et al., 2007; Barnea-Goraly et al., 2004; Ke et al., 2009; Keller et al., 2007; Thakkar et al., 2008), and reported widespread differences in white matter organisation. Although these studies are informative about overall changes in white matter, they do not provide direct measures of the micro-structural organisation of specific white matter tracts connecting brain regions. For example, VBM-based DTI approaches are able to describe regional differences in the anatomy of white matter — but not specific tracts — that are affected. Hence, evidence for the involvement of specific connections (i.e., tracts) is still lacking.

A technique that can partially overcome the limitations of VBM approaches is DTI-tractography (Conturo et al., 1999; Jones et al., 1999; Basser et al., 2000; Mori and Van Zijl, 2002). DTI based tractography uses the orientation of the diffusion profile to reconstruct the trajectories of fibre bundles and has been used extensively to explore the micro-structural organisation of white matter in a wide range of conditions including epilepsy (Ahmadi et al., 2009; Concha et al., 2007), and schizophrenia (Oh et al., 2009; Phillips et al., 2009). DTI-tractography is the only technique that allows the simultaneous quantification of both white matter volume and micro-structural organisation within specific tracts in the living human brain (Le Bihan, 2003; Catani et al., 2012; Bizzi et al., 2012; Thiebaut de Schotten et al., 2012).

Some investigators have applied tractography in autism and reported significant differences in cerebellar, frontal association and limbic tracts (Catani et al., 2008; Pugliese et al., 2009; Sundaram et al., 2008). However, no studies have yet examined the anatomy of the individual striatal structures alongside the micro-structural organisation of their fronto-striatal pathways in the same individuals; or related this to clinical symptoms. Therefore, we used structural MRI (sMRI) and DTI to compare bulk volume (i.e., grey and white matter) and micro-structural organisation of the basal ganglia and connecting fronto-striatal white matter in adults with autism and controls. Also we related anatomical differences to repetitive behaviours and inhibitory control.

2. Methods

2.1. Participants

Twenty-one right-handed males meeting International Classification of the Disease (ICD-10) criteria for autism and

twenty-two typically developing control males were included. Subjects were aged between 19 and 44 years; mean age was 26 ± 6 years for the autism group and 28 ± 6 years for the controls. All subjects had a full-scale IQ over 70. None of the subjects was using neuroleptic medication. There were no between-group differences in age or IQ (details in Table 1).

Subjects with autism were recruited from a clinical research program at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry (IoP) – part of the MRC (UK) Autism Imaging Multicentre Study (AIMS) network. Diagnosis was clinically established by a Consultant Psychiatrist from IoP's Department of Psychological Medicine and was confirmed in all subjects using the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989). None of the subjects had a history of head injury, major psychiatric disorder or medical illness affecting brain function or structure (e.g., psychosis or seizures). All had routine blood tests and a clinical examination to rule out biochemical and haematological abnormalities, or genetic disorders that may be associated with autism (including fragile X syndrome). Control subjects were recruited locally by advertisement. Control subjects with a history of head injury, major psychiatric disorder or medical illness affecting brain function or structure, or with a family history of psychiatric illness were excluded. All subjects were right-handed, and underwent a neuropsychological test battery including assessment of general intellectual functioning using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), and an online version of a go/nogo task that was adapted from Rubia et al. (2001). Participants were told to expect a series of arrows, which could point to the left, right or up. They were asked to press the '1' key in response to left arrows, the '2' key in response to right arrows and not to press anything if the arrow pointed upwards. There were 300 trials, presented in the same fixed order for each participant. There were 110 trails of each of left and right arrows (go trials) and 80 up arrows (nogo trials). Each trial was a maximum of 1200 msec long, with

a 100 msec white screen between trials. As soon as the participant responded, the next trial began. Accuracy and reaction times were recorded for each trial.

For all subjects, MRI scans were evaluated by independent clinical neuroradiologists. No gross abnormalities were reported for any of the subjects. The procedure was approved by the Joint Medical Ethical Committee of the IoP, Kings College London. Written informed consent was obtained for all subjects after complete description of the study.

2.2. MRI acquisition

All participants were scanned at the Centre for Neuroimaging Sciences, Institute of Psychiatry, London, UK, using a 3 T GE Signa System (General-Electric, Milwaukee, WI, USA). High-resolution structural T1-weighted volumetric images were acquired with full head coverage, 196 contiguous slices (1.1 mm thickness, with 1.09 mm × 1.09 mm in-plane resolution), a 256 × 256 × 196 matrix and a repetition time/echo time (TR/TE) of 7/2.8 msec (flip angle 20″, field of view (FOV) 28 cm). A (birdcage) head coil was used for radiofrequency transmission and reception. Consistent image quality was ensured by a semi-automated quality control procedure.

For white matter fibre tract reconstruction and computation of the FA, MD, Dr and Da maps, diffusion tensor MRI scans with a spin-echo echo-planar imaging (SE-EPI) double refocused sequence providing whole head coverage with isotropic image resolution ($2.4 \times 2.4 \times 2.4$ mm^3) were acquired (32 diffusion-weighted volumes with different non-collinear diffusion directions with b-factor 1300 sec/mm^2 and 6 non-diffusion-weighted volumes; 60 slices; no slice gap; TE 104.5 msec; TR 20 R–R intervals; 128 × 128 acquisition matrix; FOV = 30.7 cm^2; peripherally gated). A more detailed description of the acquisition protocol is reported in Jones et al. (2002).

2.3. MRI processing

2.3.1. Structural MRI: pre-processing
All scans were coded to ensure rater blindness to subject identity and diagnosis. The structural images were automatically placed in Talairach orientation, and were corrected for motion and magnetic field inhomogeneities using Freesurfer (Fischl et al., 2002, 2004a, 2004b). The corrected scans in Talairach orientation were used for hand-tracing of striatum. For calculating volumes of total brain, grey and white matter, Freesurfer was used (Fischl et al., 2002, 2004a, 2004b).

2.3.2. Structural MRI: manual segmentations
Striatal structures were traced manually using ITK-SNAP (Yushkevich et al., 2006) by one rater (ML), blind to subject identity, diagnosis and laterality. Caudate nucleus, putamen and nucleus accumbens were outlined in contiguous coronal slices in an anterior–posterior direction. The sagittal and axial planes were used for reference. We have previously reported the segmentation and tracing procedures in detail (Langen et al., 2007). Intra-rater reliabilities (estimated on a random duplicate set of 10 scans, using intra-class correlation coefficients; ICCs) were above .93 for all three structures.

Table 1 – **Characteristics of the sample (all right-handed males).**		
Variable	Normal controls (n = 22)	Subjects with autism (n = 21)
Age, mean ± SD (range), yrs	28.45 ± 6.39 (19–44)	25.57 ± 6.08 (19–39)
Full-scale IQ, mean ± SD (range)	109.82 ± 13.71 (83–133)	107.45 ± 15.08 (81–137)
ADI-R: social deficits		18.43 ± 5.86
ADI-R: abnormalities in communication		12.90 ± 4.43
ADI-R: ritualistic-repetitive behaviour		4.24 ± 2.02
ADOS: social deficits		6.70 ± 2.70
ADOS: abnormalities in communication		3.35 ± 1.53
ADOS: ritualistic-repetitive behaviour		1.33 ± 1.46

ADI-R: Autism Diagnostic Interview-Revised.
ADOS: Autism Diagnostic Observation Schedule.

2.3.3. DTI: pre-processing and generation of fibre tract data

The diffusion data were analysed using ExploreDTI (Leemans et al., 2009), analysis consisted of (i) correcting for eddy current distortion and subject motion (Leemans and Jones, 2009); (ii) diffusion tensor estimation using a non linear least square method (Jones and Basser, 2004), and (iii) whole brain tractography with a step-size of 1 mm, FA thresholds of .2 to initiate and continue tracking, and an angle threshold of 35° (Mori and Van Zijl, 2002).

2.3.4. DTI: visualisation and analysis of fibre tracts

For each individual subject, the high-resolution structural image and the manually segmented structures were registered to the fibre tract data using FLIRT (Jenkinson and Smith, 2001). TrackVis (Wang and Wedeen, 2007) was used for visualising and quantifying fibre tracts. With TrackVis, tract data can be reduced to specific tracts of interest by using a region-of-interest (ROI) selection method (Conturo et al., 1999). First, inclusion and exclusion ROIs are defined on the high-resolution structural image. Second, the tract is defined by including all fibres passing through the inclusion ROI(s), and excluding all fibres passing through the exclusion ROI(s). Separate tracts were defined for fibres passing through accumbens nucleus, caudate nucleus, and putamen and motor, pre-motor, pre-frontal and limbic cortices. The hand-traced segmentations of the striatum were used as inclusion ROIs. Exclusion ROIs were defined to exclude the corticospinal tracts, artifactual inter-hemispheric fibres and tracts originating or terminating in other cortical regions. Finally, for the generated fronto-striatal tracts, FA, MD, Da and Dr were calculated using the statistics tool in TrackVis (Fig. 1).

2.4. Statistical analysis

Statistical comparisons of the data were performed using SPSS software for Apple Mac (SPSS Inc, Chicago, IL). For all analyses, the level of statistical significance was defined as $p < .05$ (two-tailed).

2.4.1. Overall group-differences

First, overall group differences in age, IQ data, and performance on the go/nogo task were calculated using an independent samples t-test.

2.4.2. Group differences in striatal volumes and fronto-striatal white matter

We were especially interested in group differences in striatal grey and fronto-striatal white matter. To compare volumetric and tractography outcome measurements between groups, we used a general linear model (GLM) multivariate analysis of variance (MANOVA). Similar to Hardan et al. (2009), we computed univariate tests when marginally significant multivariate tests ($p < .10$) were present in the MANOVA. This balances Type I and II errors and identifies effects that may be promising for follow-up in future research.

Brain volumes and fronto-striatal FA, MD, Da, and Dr-values were included as the dependent variables, group was included as a fixed factor.

To further examine the specificity of findings to brain structures and fronto-striatal white matter, we used a multivariate analysis of covariance (MANCOVA). To control for potential confounding effects of overall brain volume on differences in brain volumes, we included intracranial volume as co-variate.

Last, a post-hoc t-test was used to confirm the significant results from the GLM and to establish the direction of the effects.

2.4.3. Brain–behaviour relationships

To investigate the relationship between brain and behavioural measures, correlations were calculated between anatomical variables that differed significantly between groups and performance measures of the go/nogo task. Finally, within the autism group, we related striatal volumes and fronto-striatal FA-values to measures of repetitive behaviour from the ADOS and ADI-R using Spearman rank-order correlations.

3. Results

3.1. Overall group-differences

There were no significant differences between groups in age and full-scale IQ. For the inhibitory control task, groups differed significantly on number of correct nogo-responses, with lower performance in the ASD group ($|t| = 3.897$,
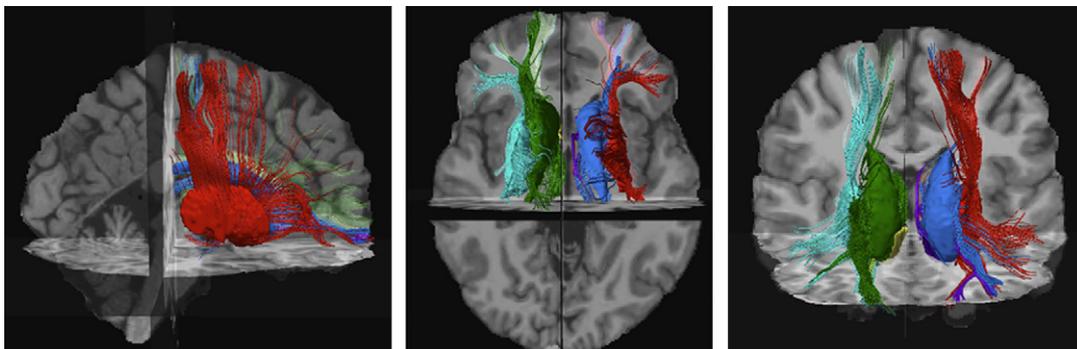
Fig. 1 – **Sagittal, axial, and coronal views of striatal structures and fronto-striatal tracts for one subject, superimposed on the T1-weighted scan. Yellow and purple = nucleus accumbens and accumbens tract; green and blue = caudate nucleus and caudate tract; turquoise and red = putamen and putamen tract.**

$p < .001$). Reaction time and performance on go trials did not differ between groups.

3.2. Group differences in striatal volumes and fronto-striatal white matter

There were no differences in bulk volume of any striatal structure we measured (bilateral, left or right hemisphere) ($F < 1.267$, $p > .267$). However, the autism group had a smaller total brain white matter volume bilaterally than controls ($F > 5.697$, $p < .022$).

For the DTI measures, people with autism had significant differences from controls in the anatomical microstructure of white matter tracts originating from putamen and accumbens: the autism group had a significantly lower FA than controls in the left, and total (left plus right) putamen tracts ($F > 6.002$, $p < .019$). The FA of tracts emerging from the right putamen was also lower than in controls, and this approached (but did not reach) statistical significance ($p = .055$). In addition, MD values in the right accumbens tract were significantly higher in the autism group ($F = 7.736$, $p = .008$). There were no other significant differences in DTI outcome measures ($F < 3.629$, $p > .064$).

See Table 2 for findings of brain volumes and white matter organisation, and laterality of the results.

3.3. Brain–behaviour relationships

For the behavioural measures, despite having no difference in overall intelligence, subjects with autism performed significantly worse than controls on nogo trials of the inhibitory control task ($F = 13.36$, $p = .001$). Furthermore, performance on this task was significantly related to FA of the putamen tract over both groups (Fig. 2), even when correcting for multiple comparisons using Bonferroni, but not to MD of the accumbens tract. However, we found no significant relationship when we examined the correlations within either of the individual groups alone. Lastly, within the autism group, there was no significant relationship between ADI-R or ADOS sub scale scores for repetitive behaviours and brain measures.

4. Discussion

Adults with autism have a significantly smaller total brain white matter volume and significant differences in white matter microstructure (as measured by FA and MD) of the tracts connecting putamen and accumbens to frontal cortical areas. Subjects with autism had worse performance than controls on a go/nogo task. Overall, when cases and controls were examined together, performance on this task was related to micro-structural organisation of fronto-striatal white matter in the putamen tract. However, within the autism group, there was no significant relationship between differences in FA and clinical symptoms.

Our finding of a significantly lower performance on the go/ nogo task by the autism group confirms other studies of response inhibition (Christ et al., 2007; Mosconi et al., 2009; Robinson et al., 2009). There is a vast literature discussing cognitive models of response inhibition, often as part of the broader concepts of 'executive functioning' and 'cognitive control'; and how these may be affected in ASD [for a review see Hill (2004) and Russo et al. (2007)]. However, although cognitive models can provide guiding hypotheses for how neurobiological circuitry might be disturbed in symptoms of psychiatric disorders such as ASD, it has proven difficult to parallel neuropsychological models to neurobiological findings. We found that differences in putamen tract FA were related to deficits in response inhibition – but only across groups (but not within each in isolation). One explanation for this may be that we lack statistical power. Alternatively the correlation when combining data from across groups may be spurious (i.e., it may simply reflect the significant between-group difference in performance on this task). To definitively address this issue larger samples are required; and this is a focus of future work in our laboratory.

Decreases in FA have been demonstrated before in people with autism in a number of brain regions (Alexander et al., 2007; Barnea-Goraly et al., 2004; Ke et al., 2009; Keller et al., 2007; Thakkar et al., 2008), as well as increases in frontal (Shukla et al., 2011; Sundaram et al., 2008) and temporal (Lee et al., 2007) white matter MD. Also, our findings converge with other reports of abnormal anatomy of corticostriatal circuitry in autism, such as differences in striatal grey matter (Hollander et al., 2005; Langen et al., 2007; Rojas et al., 2006), as well as with findings of altered 'connectivity' (Belmonte et al., 2004a, 2004b; Catani et al., 2008; Just et al., 2004; Koshino et al., 2005; Pugliese et al., 2009; Ring and Serra-Mestres, 2002; Sundaram et al., 2008). However, differences in specific (frontal) corticostriatal fibre tracts, and/or their relationship to deficits in inhibitory control have not previously been reported in autism.

The biological cause of the differences in white matter we found is unknown. Decreased myelination, decreased axonal density, and abnormal axonal organisation are some of the important mechanisms which are known to cause this previously reported pattern of decreased FA and increased diffusivity (Groen et al., 2011; Lee et al., 2007; Sundaram et al., 2008). In addition: are these findings primary effects or do they originate from pathology in other brain regions, for example striatum, the frontal lobe or both? Furthermore, it is unclear why we only found differences in tracts connecting putamen and accumbens (but not caudate) to frontal cortex and how these findings relate to the autism behavioural phenotype. Results from earlier studies investigating (1) white matter development in autism, and (2) involvement of putamen networks in inhibitory control may help explain our findings.

4.1. Fronto-striatal white matter abnormalities in autism: static or dynamic?

Results from our preliminary study suggest that adults with autism have significantly lower FA-values and higher MD values in white matter tracts connecting striatum to cortex. From our data, however, we cannot conclude whether these results reflect a static or dynamic difference between autism and controls. Findings from typically developing populations have shown that FA increases up to late childhood and then decreases with age (Lebel et al., 2008), where white matter maturation follows regionally specific trajectories (Barnea-Goraly et al., 2005; Salat et al., 2005). Hence our results could;

(1) reflect a general decrease of fronto-striatal white matter organisation in autism, non-specific to a particular age-group; (2) indicate typical development in childhood, but with an accelerated decrease of white matter quality in adulthood; or (3) arise from an earlier age of onset of age-related decline in white matter quality, possibly related to accelerated white matter maturation in (early) childhood.

Based on earlier findings, it seems unlikely that our results reflect the first option, i.e., a general decrease of fronto-striatal white matter organisation in autism. For example, the findings by others of both increased (Ben Bashat et al., 2007) and similar FA-values (Sundaram et al., 2008) in frontal circuits of younger people with ASD than we included in the present study, argue against this. The currently available evidence also does not strongly support the second option, as there are no reports of an accelerated decrease of white matter in autistic individuals during adulthood [albeit we have recently reported preliminary evidence for significantly greater age-related loss of cortical grey matter in adults with autism as compared to controls (Hallahan et al., 2009)]. Therefore, the third option seems the most likely, i.e., our results may reflect an earlier peak in white matter maturation and an earlier onset of an age-related decrease in FA in autism. This suggestion is supported by prior reports of an abnormally early, and accelerated, maturation of white matter FA, (predominantly affecting frontal lobe) in very young children with autism (1.8−3.3 years) (Ben Bashat et al., 2007). Furthermore, others have reported that early overgrowth of brain volume in autism is disproportionately accounted for by increased white matter volume (Courchesne et al., 2001; Hazlett et al., 2005), potentially related to an earlier peak in white matter maturation. Nevertheless, further (and preferably longitudinal) work investigating development of corticostriatal white matter in younger age-groups, and specifically examining regional differences in frontal white matter organisation, is required to further evaluate these issues.

4.2. Involvement of fronto-striatal white matter in inhibitory control

We found that young adults with autism have reduced FA in corticostriatal circuitry localised to the tract connecting putamen to frontal cortical areas. Cortical areas in this circuit (prefrontal, parietal, anterior cingulate and pre-superior motor) are typically associated with deliberate and controlled inhibition of unwanted responses (Garavan et al., 2002). Hence we related the differences we found in white matter tracts to inhibitory control in both groups. Although we did find a significant relationship when we combined data from both groups to examine inhibitory control; there was no significant association for the autism group separately. Therefore, although previous work has implicated the putamen circuit in inhibition of responses in a go/nogo paradigm (Garavan et al., 2002; Kana et al., 2007; Liddle et al., 2001; Rubia et al., 2003; Watanabe et al., 2002), from our data, we cannot conclude that the reduced micro-structural organisation in the autism group affects performance on the inhibitory control task. Our study does, however, support the suggestion that in humans (i.e., when we combined data from both groups) differences in the micro-structural organisation of this tract are associated with variation of inhibitory control − at least in adults. The directionality

of this association is, nevertheless, unknown. That is, the anatomy of these pathways is likely also to be modulated by life-long abnormalities in the behaviour itself. Further studies are required, and particularly of autistic individuals who have, or go on to later develop, more severe obsessional and/or repetitive symptoms.

4.3. Specificity of our findings to putamen tracts

Given the involvement of putamen in inhibitory control and the performance on the go/nogo task of our autism group, we were not surprised by our finding that these individuals have a significant reduction in the organisation of the white matter tracts connecting putamen and frontal regions. However, although differences in putamen grey matter (Langen et al., 2009; Toal et al., 2009), putamen connectivity (Supekar et al., 2009), and frontal white matter volume (Carper et al., 2002; Carper and Courchesne, 2005; Herbert et al., 2004) have also been reported by others, we were surprised that this was the *only* effect in corticostriatal circuitry we found. Furthermore, several (but not all) previous studies have reported that autistic individuals have significant differences from controls in volume of the caudate nucleus. It is likely that the characteristics of our sample, including age and diagnostic inclusion criteria, as well as the heterogeneity of the disorder itself could explain differences in our results.

First, the age of people we included could have been a factor (Herbert et al., 2003; Hollander et al., 2005; Langen et al., 2009; McAlonan et al., 2002). For example, several studies demonstrating differences in caudate volume in autism (Langen et al., 2007; Sears et al., 1999) investigated much younger samples than ours. Another, more recent study investigating functional connectivity in autism (Lee et al., 2009), supports this view. This reported that functional connectivity of the motor response inhibition circuit is *not* reduced in children with autism, but it is in adults. Taken together, our work, and that of Lee et al. (2009) suggests that age may play a significant modulatory role in the synchronisation of fronto-striatal brain regions supporting response inhibition in autism.

Furthermore, and unlike much prior work, our results are not confounded by factors such as exposure to antipsychotic medication, the presence of intellectual disability and/or epilepsy, or differences in overall intelligence between cases and controls. This is because we only included physically healthy adults that were medication-free and we excluded those with intellectual disability. Also, we only included individuals fulfilling diagnostic criteria for autism, whereas many other studies also included individuals with Asperger's syndrome [who display a slightly different behavioural (language) phenotype than those we studied].

Nevertheless, although the use of stringent inclusion criteria did reduce the potential confounds affecting our results they also limit the translation of our findings to the broader autism spectrum (e.g., to children, and those with an intellectual disability).

4.4. Limitations

As discussed in the previous section, we only included individuals fulfilling 'gold standard' diagnostic criteria (i.e., who

Table 2 — Overall and striatal brain volumes and fronto-striatal DTI measures for both samples.

	Autism group	Control group	p value
Brain structure	**Mean ± SD, cm^3**	**Mean ± SD, cm^3**	
Intracranial volume	1759.86 ± 183.21	1809.77 ± 169.34	n.s.
Left hemisphere grey matter	244.32 ± 22.36	238.90 ± 15.92	n.s.
Right hemisphere grey matter	244.30 ± 22.36	239.14 ± 16.60	n.s.
Total brain grey matter	488.60 ± 43.65	478.03 ± 32.20	n.s.
Left hemisphere white matter	255.10 ± 23.42	272.52 ± 24.41	.022
Right hemisphere white matter	255.88 ± 23.93	275.48 ± 25.27	.013
Total brain white matter	511.00 ± 47.26	548.00 ± 49.38	.016
Left caudate nucleus	4.59 ± .66	4.66 ± .46	n.s.
Right caudate nucleus	5.16 ± .65	5.018 ± .47	n.s.
Total caudate nucleus	9.79 ± 1.23	9.74 ± .90	n.s.
Left putamen	5.54 ± .42	5.43 ± .54	n.s.
Right putamen	5.55 ± .45	5.57 ± .52	n.s.
Total putamen	11.09 ± .81	11.00 ± 1.02	n.s.
Left accumbens nucleus	1.16 ± .20	1.20 ± .23	n.s.
Right accumbens nucleus	1.12 ± .18	1.19 ± .23	n.s.
Total accumbens nucleus	2.28 ± .35	2.39 ± .45	n.s.
White matter tract	**Mean ± SD, FA**	**Mean ± SD, FA**	
Left caudate nucleus tract	.43 ± .025	.43 ± .019	n.s.
Right caudate nucleus tract	.42 ± .018	.43 ± .028	n.s.
Total caudate nucleus tract	.43 ± .018	.43 ± .021	n.s.
Left putamen tract	.44 ± .022	.46 ± .017	.019
Right putamen tract	.44 ± .024	.45 ± .019	.055
Total putamen tract	.44 ± .020	.45 ± .015	.014
Left accumbens nucleus tract	.42 ± .026	.41 ± .023	n.s.
Right accumbens nucleus tract	.43 ± .020	.43 ± .025	n.s.
Total accumbens nucleus tract	.42 ± .017	.42 ± .021	n.s.
White matter tract	**Mean ± SD, MD ×10^{-4} mm^2/sec**	**Mean ± SD, MD ×10^{-4} mm^2/sec**	
Left caudate nucleus tract	8.11 ± .28	8.05 ± .28	n.s.
Right caudate nucleus tract	8.18 ± .31	8.01 ± .25	n.s.
Total caudate nucleus tract	16.27 ± .50	16.05 ± .45	n.s.
Left putamen tract	7.61 ± .26	7.52 ± .24	n.s.
Right putamen tract	7.59 ± .22	7.54 ± .22	n.s.
Total putamen tract	15.20 ± .42	15.06 ± .42	n.s.
Left accumbens nucleus tract	8.28 ± .42	8.22 ± .38	n.s.
Right accumbens nucleus tract	8.21 ± .33	7.93 ± .29	.008
Total accumbens nucleus tract	16.49 ± .61	16.15 ± .58	n.s.
White matter tract	**Mean ± SD, Da ×10^{-4} mm^2/sec**	**Mean ± SD, Da ×10^{-4} mm^2/sec**	
Left caudate nucleus tract	12.13 ± .42	12.04 ± .48	n.s.
Right caudate nucleus tract	12.22 ± .52	12.04 ± .47	n.s.
Total caudate nucleus tract	24.35 ± .84	24.08 ± .86	n.s.
Left putamen tract	11.59 ± .38	11.60 ± .33	n.s.
Right putamen tract	11.52 ± .34	11.57 ± .26	n.s.
Total putamen tract	23.11 ± .68	23.18 ± .55	n.s.
Left accumbens nucleus tract	12.30 ± .55	12.13 ± .63	n.s.
Right accumbens nucleus tract	12.32 ± .68	11.92 ± .54	n.s.
Total accumbens nucleus tract	24.62 ± 1.08	24.05 ± 1.11	n.s.
White matter tract	**Mean ± SD, Dr ×10^{-4} mm^2/sec**	**Mean ± SD, Dr ×10^{-4} mm^2/sec**	
Left caudate nucleus tract	6.10 ± .31	6.05 ± .22	n.s.
Right caudate nucleus tract	6.17 ± .26	5.99 ± .25	n.s.
Total caudate nucleus tract	12.29 ± .48	12.04 ± .38	n.s.
Left putamen tract	5.62 ± .26	5.48 ± .24	n.s.
Right putamen tract	5.63 ± .25	5.53 ± .24	n.s.
Total putamen tract	11.25 ± .45	11.01 ± .42	n.s.
Left accumbens nucleus tract	6.28 ± .43	6.26 ± .31	n.s.
Right accumbens nucleus tract	6.15 ± .24	5.94 ± .25	n.s.
Total accumbens nucleus tract	12.42 ± .52	12.20 ± .46	n.s.

FA = fractional anisotropy; MD = mean diffusivity; Da = axial diffusivity; Dr = radial diffusivity; n.s. = non significant.
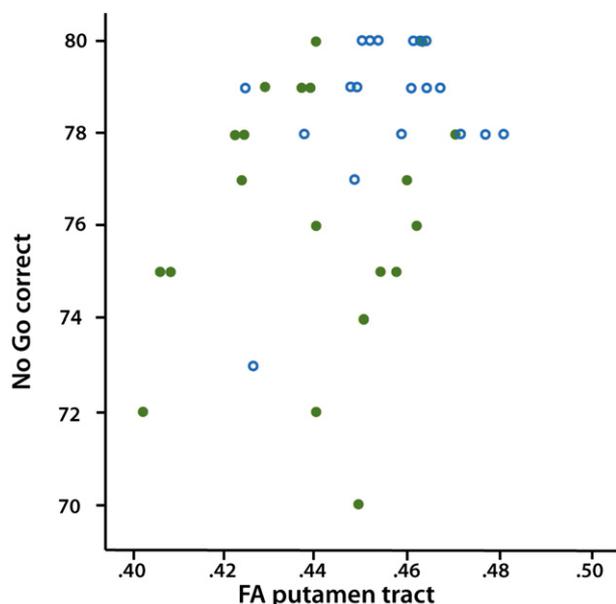
Fig. 2 — Associations of micro-structural organisation of putamen tract (FA-values) and inhibitory control (percentage correct on nogo trials of go/nogo task). Green = autism group; blue = control group. Correlation analyses: total group: r = .356, p = .021; autism group: r = .151, p = .52; control group: r = 277, p = .21.

were above threshold in both the ADI and ADOS) and who did not differ in age or overall intellectual functioning from controls. We suggest that this lends confidence to our finding of between-group differences. Nevertheless, there are some limitations to our study. First, although most DTI studies in autism included smaller samples, the size of the present study is still only moderate. To better evaluate the present findings, replication of our work (and in a larger sample) is required. Second, although the anatomical localisation of our findings is consistent with a growing body of literature that implicates corticostriatal abnormalities in autism, it needs to be acknowledged that DTI-tractography cannot visualise axons directly. Rather, DTI-tractography provides a reconstruction of axonal trajectories and is therefore merely an indirect measure of white matter tracts (Pugliese et al., 2009), though reflecting highly reproducible features of human brain anatomy (Catani et al., 2007).

Furthermore, although FA is generally accepted as an indicator of white matter organisation, methodological considerations potentially impacting measurement of FA (partial volume effects, signal-to-noise ratio of the data) need to be acknowledged (Kubicki et al., 2005; Sundaram et al., 2008; Vos et al., 2011). Additional imaging techniques such as magnetisation transfer imaging (MTI), MR spectroscopy, and relaxation time measurements can be used to increase the specificity of FA findings (Kubicki et al., 2005).

Fourth, as noted above, we only included adults without intellectual disability; and so it is unknown if our findings will generalise to other groups of autistic individuals (e.g., children, or low-functioning individuals with autism). We accept that a study of children is of great interest. However, brain anatomy [e.g., in grey and white matter volumes (Giedd et al., 1999)], connectivity, and function change throughout childhood and adolescence. A study of children therefore, takes place when brain maturation is incomplete, and maturational differences, including pubertal stage and cognitive developmental level may blur the abnormalities associated with the disorder itself. Indeed, several authors have highlighted that discrepancies in results between neuroimaging studies of autism could in part reflect differences in developmental stage between samples (Herbert et al., 2003; Hollander et al., 2005; Langen et al., 2009; McAlonan et al., 2002). To reduce this confound we would need to employ either longitudinal designs, or large cross sectional studies in different age cohorts. Most importantly, we should acknowledge that studying children and adults are complementary: by studying adults we are able to identify brain systems which differ in anatomy and connectivity in the 'end-state', whereas by studying children we can detect differences in *development* of brain structure and function.

4.5. Conclusion

This study investigated differences in bulk volume of striatal regions and fronto-striatal white matter in autism; and their involvement in repetitive behaviour and inhibitory control. We report differences in overall white matter volume and fronto-striatal FA between adults with autism and matched controls, where subjects with autism have smaller total white matter volumes and altered micro-structural organisation in the tracts connecting putamen and nucleus accumbens to frontal cortical areas. These findings emphasise the importance of fronto-striatal circuitry in autism.

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