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White matter microstructural abnormalities in the frontal lobe of adults with antisocial personality disorder

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ABSTRACT

Antisocial personality disorder (ASPD) and psychopathy involve significant interpersonal and behavioural impairments. However, little is known about their underlying neurobiology and in particular, abnormalities in white matter (WM) microstructure. A preliminary diffusion tensor magnetic resonance imaging (DT-MRI) study of adult psychopaths employing tractography revealed abnormalities in the right uncinate fasciculus (UF) (Craig et al., 2009), indicating fronto-limbic disconnectivity. However, it is not clear whether WM abnormalities are restricted to this tract or are or more widespread, including other tracts which are involved in connectivity with the frontal lobe.

We performed whole brain voxel-based analyses on WM fractional anisotropy (FA) and mean diffusivity (MD) maps acquired with DT-MRI to compare 15 adults with ASPD and healthy age, handedness and IQ-matched controls. Also, within ASPD subjects we related differences in FA and MD to measures of psychopathy.

Significant WM FA reduction and MD increases were found respectively in ASPD subjects relative to controls. FA was bilaterally reduced in the genu of corpus callosum while in the right frontal lobe FA reduction was found in the UF, inferior fronto-occipital fasciculus (IFOF), anterior corona radiata and anterior limb and genu of the internal capsule. These differences negatively correlated with measures of psychopathy. Also in the right frontal lobe, increased MD was found in the IFOF and UF, and the corpus callosum and anterior corona radiata. There was a significant positive correlation between MD and psychopathy scores.

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Conclusions: The present study confirms a previous report of reduced FA in the UF. Additionally, we report for the first time, FA deficits in tracts involved in interhemispheric as well as frontal lobe connectivity in conjunction with MD increases in the frontal lobe. Hence, we provide evidence of significant WM microstructural abnormalities in frontal brain regions in ASPD and psychopathy.

1. Introduction

1.1. *The frontal lobe theory of antisocial personality disorder (ASPD) and psychopathy*

The importance of the frontal lobes to social behaviour was first recognised in the 19th century following the case of Phineas Gage, in whom frontal lobe damage resulted in profound personality change associated with markedly inappropriate social behaviour [Harlow, 1993 (1869)]. A 'frontal lobe' syndrome was subsequently delineated based on clinical observations of the behaviour of patients with frontal lobe damage (Lishman, 1998) where symptoms included apathy, emotional lability, a lack of social awareness, unconcern for social rules, impulsivity, and reactive aggression.

It is currently recognised that there is much overlap between frontal lobe syndrome and 'functional' or 'non-organic' personality disorders (PDs), particularly ASPD and psychopathy (Damasio, 2000). The definition of psychopathy has changed little since Hervey Cleckley published *The Mask of Sanity* in 1941 where he described the psychopath as a charming, callous, superficial individual, lacking conscience and genuine emotion (Cleckley, 1941). The *Psychopathy Checklist* (PCL, Hare, 1980) and the later *Psychopathy Checklist – Revised* (PCL-R, Hare, 1991) were designed to operationalise Cleckley's concept of psychopathy as a basis for diagnosing the disorder. The PCL-R consists of 20 items characterised broadly by two dimensions: Factor 1 items are primarily interpersonal or emotional traits such as remorselessness, deception, shallow affect and callousness, whereas Factor 2 items assess behavioural symptoms such as violence, criminality, and dysfunctional lifestyle. For a diagnosis of psychopathy, attributes from both of these factors need to be present. While PCL-R scores $\geq$30 have traditionally been used to classify an individual as having psychopathy (Hare, 2003), more recent studies have argued for a score of $\geq$25 as sufficient for diagnosis (Edens and Petrila, 2006; Edens et al., 2010; Rutherford et al., 1999).

While the related construct of ASPD in *DSM-IV-TR* (Diagnostic and Statistical Manual Fourth Edition – Text Revision, American Psychiatric Association, 2000) includes several traits present in psychopathy (e.g., lack of guilt/remorse, and impulsivity), diagnostic criteria can be met based entirely on antisocial behaviours (e.g., violation of social norms, irresponsibility, and criminality). Hence, the emotional deficits fundamental to psychopathy are not necessary for a diagnosis of ASPD, even if these are present in some cases. Estimates of the prevalence of the two disorders also differ, suggesting that these are non-equivalent diagnoses. While most adult psychopathic offenders meet criteria for ASPD, only approximately one third of those with ASPD are psychopathic (Hart and Hare, 1997). Psychopathy has therefore been postulated to be a particularly severe subtype of ASPD (Dolan and Doyle, 2007). Psychopathy and ASPD are however distinguished from behaviours secondary to frontal lobe lesions by high levels of both reactive (elicited by frustration) and instrumental (goal-directed) violence (Blair, 2001; Glenn and Raine, 2009). Nevertheless, overlaps between traits of both psychopathy and ASPD, and frontal lobe syndrome, have led to the suggestion that both PDs may result from frontal lobe abnormality (Damasio, 2000). Neuroimaging studies of both people with ASPD, and of individuals with psychopathy, have provided evidence of abnormalities of frontal lobe structure and function relative to control populations, together with deficits in temporal, limbic, and other brain regions (see Table 1).

For example, neuroimaging studies of adult psychopaths examining the frontal cortex have reported reduced grey matter volume in conjunction with reduction in the superior temporal gyrus (Muller et al., 2008), and in the prefrontal cortex (PFC) of 'unsuccessful' (caught) psychopaths, versus healthy controls (Yang et al., 2005). Furthermore, higher total and subfactor PCL-R scores (arrogant/deceptive, affective, and impulsive/unstable) were associated with reduced prefrontal grey matter volume (*ibid*). Similarly, prefrontal and temporal cortical grey matter thinning was found in psychopathic individuals, with right hemisphere reductions related to elevated PCL-R Factor 1 'Affective' facet scores (Yang et al., 2009b).

Other studies have identified associations between psychopathic traits and specific subregions of the PFC. In particular, the association found in brain injured patients between ventromedial PFC (vmPFC) damage and reactive aggression (Blair and Cipolotti, 2000; Grafman et al., 1996) is mirrored by vmPFC structural and functional impairments in psychopaths (Tiihonen et al., 2008). Functional neuroimaging studies of people with psychopathy have also provided evidence of abnormal frontal lobe perfusion and abnormalities of task-related activation in prefrontal and other brain regions on reversal learning paradigms (Table 1). Individuals with ASPD have shown similar structural and functional prefrontal abnormalities to psychopaths – for instance reduced prefrontal grey matter volume has been found in both antisocial adults (Raine et al., 2000) and conduct disordered children (Huebner et al., 2008), compared with healthy controls. Also, cortical thinning of the medial frontal lobe has been found in ASPD (Narayan et al., 2007).

Nevertheless, structural and functional abnormalities in people with psychopathy and ASPD are not restricted to the frontal lobe. For example, abnormal amygdala structure and function have each been found to correlate with the emotion processing deficits observed in ASPD and psychopathic individuals (Gordon et al., 2004; Kiehl et al., 2001; Yang et al., 2009a), as well as in regions (such as fusiform–extrastriate cortices) known to be modulated by the amygdala (Deeley

Table 1 – Summary of volumetry, functional and DT-MRI findings implicating fronto-limbic and other brain region abnormalities in antisocial populations.

Author	Method	Population	Comparison group	Finding	Region
(Barkataki et al., 2006)	MRI	ASPD	Violent and non-violent schizophrenia	Reduced volume	Whole brain, bilateral temporal lobe
				Increased volume	Putamen
(Laakso et al., 2000)	MRI	ASPD with alcoholism	Healthy controls	Reduced volume	Right hippocampus, posterior hippocampi
(Laakso et al., 2001)	MRI	ASPD with alcoholism	Psychiatric patients	Volume inversely related to PCL score	Bilateral posterior hippocampus
(Narayan et al., 2007)	MRI	ASPD	Violent and non-violent schizophrenics and healthy controls	Cortical thinning	Medial PFC
(de Oliveira-Souza et al., 2008)	MRI	ASPD with psychopathy	Healthy controls	Reduced volume Volumes inversely related to psychopathy score	Frontopolar cortex, orbitofrontal cortex, anterior temporal cortex, superior temporal sulcus, insula
(Raine et al., 2000)	MRI	Community ASPD	Alcohol dependents and healthy controls	Reduced volume	Prefrontal grey matter
(Raine et al., 2003)	MRI	Community ASPD with high psychopathy scores	Healthy controls	Increased length Increased volume Reduced thickness	Corpus callosum
(Tiihonen et al., 2008)	MRI	ASPD with alcohol dependence	Healthy controls	Increased WM volume	Bilateral occipital lobe, bilateral parietal lobe, left cerebellum
				Increased grey matter volume	Right cerebellum
(Volkow et al., 1995)	PET	Violent offenders	Healthy controls	Reduced glucose metabolism	PFC, medial temporal cortex
(Raine et al., 1997)	PET	Murderers	Healthy controls	Reduced glucose metabolism	PFC, corpus callosum, superior parietal gyrus, left angular gyrus
(Boccardi et al., 2010)	MRI	Psychopathic violent offenders	Healthy controls	Bilateral depression	Hippocampus – longitudinal axis
				Reduced CA1 segment	Hippocampus – anterior
				Abnormal enlargement	Hippocampus – lateral borders
(Craig et al., 2009)	DT-MRI	Psychopaths	Healthy controls	Reduced FA	Right UF
(Glenn et al., 2010)	MRI	Community sample – high psychopathy scorers	Community sample – low psychopathy scorers	Increased volume with greater psychopathy score	Striatum
(Muller et al., 2008)	MRI	Criminal psychopaths	Healthy controls	Reduced volume	Right superior temporal gyrus
(Shamay-Tsoory et al., 2010)	CT/MRI	ASPD males with psychopathic traits	Orbitofrontal cortex verus non-frontal lesioned males and healthy controls	Impaired affective empathy performance in both orbitofrontal cortex lesioned and psychopathy group	Orbitofrontal cortex
(Yang et al., 2005)	MRI	Unsuccessful community psychopaths	Successful community psychopaths and healthy controls	Reduced volume	Prefrontal grey matter
(Yang et al., 2009a)	MRI	Community psychopaths	Healthy controls	Reduced volume Surface deformations	Bilateral amygdala Amygdala nuclei: basolateral, central, cortical, lateral
(Yang et al., 2009b)	MRI	Community psychopaths	Healthy controls	Cortical thinning	Right frontal cortex, right temporal cortex
				Thinning associated with greater PCL factor 2 score	Right frontal cortex, right temporal cortex

Table 1 – (*continued*)

Author	Method	Population	Comparison group	Finding	Region
(Deeley et al., 2006)	fMRI	Psychopaths	Healthy controls	Reduced BOLD activation to fearful and happy faces in emotion processing task	Fusiform gyrus, extrastriate cortex
				Decreased, rather than increased, BOLD activation to fearful faces	Fusiform gyrus
(Soderstrom et al., 2002)	SPECT	Violent offenders with varying psychopathy scores		Negative correlation between interpersonal psychopathy factor and perfusion	Frontal and temporal regions, head of caudate, left hippocampus
(De Brito et al., 2009)	MRI	Community sample of boys – high versus low callous-unemotional trait scorers		Increased grey matter concentration	Medial orbitofrontal cortex, anterior cingulate cortex
				Increased grey matter concentration and volume	Bilateral temporal lobe
(Kruesi et al., 2004)	MRI	Conduct disordered adolescents	Healthy controls	Reduced grey matter volume	Right temporal lobe
(Huebner et al., 2008)	MRI	Conduct disordered adolescent males comorbid with ADHD	Healthy controls	Reduced grey matter volume	Bilateral temporal lobe Left hippocampus, left amygdala
(Sterzer et al., 2007)	MRI	Conduct disordered adolescent males	Healthy controls	Reduced grey matter volume	Bilateral anterior insular cortex Left amygdala
(Berns et al., 2009)	DT-MRI	Healthy adolescents – high versus low on risk taking measure		High scores positively correlated with FA and negatively with transverse diffusivity	Frontal WM tracts
(Marsh et al., 2008)	fMRI	Antisocial children with callous-unemotional traits	Children with ADHD; healthy controls	Reduced BOLD activation to fearful faces on emotional processing task	Amygdala
				Reduced functional connectivity	Between amygdala and vmPFC
(Finger et al., 2008)	fMRI	Antisocial children with callous-unemotional traits	Children with ADHD; healthy controls	Abnormal BOLD signal to punished errors on reversal learning task	vmPFC
(Jones et al., 2009)	fMRI	Antisocial boys with callous-unemotional traits	Healthy controls	Reduced BOLD activation to fearful faces on emotional processing task	Right amygdala
(Stadler et al., 2007)	fMRI	Conduct disordered adolescent males	Healthy controls	Reduced BOLD activation to negative affective pictures in emotional processing task	Right anterior cingulate cortex

et al., 2006). Reduced volume of temporal regions is also seen in ASPD (Barkataki et al., 2006). Taken together, these studies of antisocial adults and conduct disordered children (with and without psychopathic traits) illustrate reduced volume of the temporal lobe and its constituent structures, and deficits in amygdala structure and function.

Apart from these fronto-temporal structures, other regions potentially relevant to psychopathy have been less extensively investigated. For instance, there have been only limited magnetic resonance imaging (MRI) studies assessing the corpus callosum, a major white matter (WM) bundle supporting interhemispheric functional integration, where abnormalities have included increases in volume and length but reduction in thickness (Raine et al., 2003). Also, while reductions in functional connectivity between prefrontal and limbic regions may contribute to antisocial traits (Table 1), their underlying microstructural basis remains unknown. Overall, the wider network of abnormalities in psychopathy has been relatively understudied although such investigation has been made possible using diffusion tensor magnetic resonance imaging (DT-MRI) (Basser et al., 1994b; Thiebaut de Schotten et al., 2012; Catani et al., 2012) where the 'connectivity' of neural systems is assessed using proxy measures of microstructural integrity.

1.2. *Disconnectivity between frontal and other regions in psychopathy*

DT-MRI is particularly used in the assessment of tissue (such as WM networks) where water preferentially diffuses along a particular axis aligned with the tissue's internal structure and is predicated on the principle that microarchitectural structures, for instance, cell membranes, myelin sheaths, as well as intracellular micro-organelles, act as barriers to the diffusion and free movement of water, and thus limit the spatial motion of these molecules (Malhi and Lagopoulos, 2008). The assessment of the directional dependence of water molecule diffusion in WM is usually quantified through calculation of fractional anisotropy (FA). FA is a measure of the degree of anisotropy or directionality where values range from

0 (perfectly isotropic diffusion) to 1 (perfectly anisotropic diffusion) (Pierpaoli and Basser, 1996) – so providing a measure of tissue integrity (Horsfield and Jones, 2002; Mori and Zhang, 2006). Mean diffusivity (MD) is another DT-MRI derived parameter used for reporting tissue differences which is calculated by division of the sum of the eigenvalues of the diffusion tensor (which correspond to the magnitude of diffusion in three orthogonal directions) by three. There are however only limited studies examining neural disconnectivity using DT-MRI in people with psychopathy and/or ASPD.

A recent study by our group using DT-MRI tractography focusing on FA in the uncinate, inferior longitudinal and inferior fronto-occipital fasciculi reported a significant reduction of this measure in only the uncinate fasciculus (UF) of nine psychopaths compared with age- and IQ-matched controls (Craig et al., 2009). Additionally, a significant negative correlation was found between measures of antisocial behaviour (PCL-R Factor 2 scores) and tract volume within this WM pathway, suggesting abnormal connectivity in the amygdala–orbitofrontal cortex limbic network. However, as this study was confined to a limited number of WM tracts, it was not possible to assess WM networks on a whole brain level. Consequently, the presence of deficits affecting WM connectivity with other brain regions is yet to be established in either ASPD or psychopathy. Further, our previous study did not examine other indices of WM microstructure, such as MD.

In summary, there is increasing evidence that people with ASPD and psychopathy may have significant differences in the structure and function of frontal, limbic and other brain regions. However, few studies have examined the microstructural integrity or connectivity of their WM networks. Therefore, we undertook the first DT-MRI investigation on a whole brain level of ASPD and psychopathy. We examined WM networks and tested the main hypothesis that people with ASPD and psychopathy have significant differences, based on DT-MRI derived parameters of FA and MD, in microstructural integrity and connectivity as compared to healthy matched controls. Also, we tested an additional hypothesis that within ASPD, severity of psychopathy (as measured by PCL-R) is related to differences in these WM measures.

2. Methods

2.1. *Subjects*

Study participants were recruited from three specialist forensic inpatient units in south-east London (South London and Maudsley National Health Service Foundation Trust) and south-west London (St George's Healthcare NHS Trust) as part of our longitudinal work in assessing psychopathy, over a period of eight years. Healthy controls were recruited from the general population through the Institute of Psychiatry, King's College London by advertisement. Ethical approval was obtained from the Ethics Committee of the South London and Maudsley Trust and Institute of Psychiatry, and St George's Healthcare Trust. Written informed consent was obtained from participants after full description of the study. Student's *t* tests (two-tailed) were used to compare the distribution of continuous data between the two groups.

Participants in both groups were medication free, spoke English as their first language, and were right-handed as assessed by the Annett Handedness Questionnaire. The Wechsler Adult Intelligence Scale – Revised (Wechsler, 1981) was used to measure IQ. All participants (in both groups) were examined by formal psychiatric semi-structured interview using ICD-10 research criteria (World Health Organisation, 1993) in addition to assessment of case notes for a diagnosis of ASPD. Assessment for the presence of comorbid psychiatric illness (e.g., anxiety disorders, substance misuse, schizophrenia, major depression), neurological and extracerebral disorders that may affect brain function, and contraindications to MRI scanning was also performed. Though many individuals with ASPD have a past history of alcohol and/or substance misuse, we attempted to recruit (as far as possible) subjects without comorbidities rather than to control for these post hoc. None of the participants fulfilled criteria for substance misuse or dependence syndrome 6 months prior to recruitment, with the exception of one subject who had harmful use of cocaine.

45 participants were initially recruited into the study (20 ASPD *vs* 25 controls). However, five with ASPD and 10 controls respectively were unsuitable for further assessment following exclusion for comorbid psychiatric disorder and contraindications to MRI procedures. PCL-R scores were obtained from case notes derived from assessments based at their specialist forensic unit by forensic psychologists fully trained in the administration of the PCL-R, or by a researcher (QD) where the PCL-R had not been administered but where subjects otherwise met inclusion criteria. We therefore included 30 normal intelligence right-handed adult male subjects: 15 with ASPD and a mean PCL-R score of 26 (SD ± 7; range 13–34) aged 39 ± 10 years and with full-scale IQ (FSIQ) 92 ± 13, and 15 healthy controls aged 37 ± 11 years, with FSIQ 99 ± 12. There were no significant differences in age or IQ between participant groups. Those with ASPD had a history of violent offending that encompassed manslaughter, attempted murder and multiple rape with strangulation. In the UK it is accepted practice to define psychopathy as a score of 25 or above on the PCL-R (Cooke, 1996; Cooke and Michie, 1999) and 10 of the 15 in the ASPD group scored above this threshold. However, while we were able to obtain total PCL-R scores for the entire patient cohort, it was only possible to acquire Factor 1 and Factor 2 subscores for 12 of the 15 subjects from case notes.

2.2. *MRI acquisition protocol*

Data were acquired using a 1.5 T GE Signa LX system (General Electric, Milwaukee, WI, USA), with actively shielded magnetic field gradients (maximum amplitude 40 mT m^{-1}). A standard quadrature birdcage head coil was used for both radiofrequency transmission and signal reception. Each DT-MRI volume was acquired using a multi-slice peripherally-gated echo-planar imaging (EPI) sequence, optimised for precise measurement of the diffusion tensor in brain parenchyma, from 60 contiguous 2.5 mm thick slices with field of view (FOV) 240 × 240 mm and matrix size 96 × 96, zero-filled during reconstruction to 128 × 128, giving a final in-plane voxel size of 1.875 × 1.875 mm^2 (Jones et al., 2002; Kyriakopoulos et al.,

2008). Image acquisition was synchronised to the cardiac cycle using a peripheral gating device placed on the subject's forefinger. Echo time was 107 msec while the effective repetition time was 15 R–R intervals. Duration of the diffusion encoding gradients was 17.3 msec giving a maximum diffusion weighting of 1300 sec mm^{-2}. At each slice location, 7 images were acquired with no diffusion gradients applied, together with 64 diffusion-weighted images in which gradient directions were uniformly distributed in space. Total scan time was approximately 20 min and the relative orientations of the diffusion gradient vectors were based on the electrostatic repulsion algorithm (Jones et al., 1999, 2002).

Following correction of the diffusion-weighted images for image distortions introduced by the diffusion-weighting gradients, in-house software was used to 1) remove non-brain tissue and 2) determine the diffusion tensor in each voxel (Basser et al., 1994a, 1994b). Images of 1) mean T2-weighted intensity (with no diffusion gradients applied) and 2) FA and MD were computed for each subject. Full details are given elsewhere (Jones et al., 2002).

2.3. *Pre-processing DT-MRI data*

Scans were examined for image corruption or motion artefacts prior to inclusion in the imaging pipeline and none of the acquired scans demonstrated these abnormalities. The subsequent pre-processing steps and analytical methodology have been published previously (Bloemen et al., 2010; Kyriakopoulos et al., 2008, 2009; Sundram et al., 2010), and are summarised below.

After construction of maps of FA and MD, a voxel-based approach in standard space using SPM2 (Wellcome Department of Imaging Neuroscience, University College London) within MATLAB 6.5.2 (The MathWorks, Natick, MA, USA), aligned, smoothed and segmented the FA and MD images. In a manner analogous to the early voxel-based morphometry (VBM) analysis methods developed for structural T1 and/or T2-weighted MR images, we first performed a two-stage normalisation to standard Montreal Neurological Institute (MNI) space using a study-specific, intermediate template to reduce potential bias due to different degrees of warping that would otherwise be required to match ASPD and control brains to a standard (control subject-based) template.

The mean T2-weighted (nondiffusion-weighted, $b = 0$) images from each subject were initially registered to the standard EPI template provided by SPM2. The derived mapping parameters for each subject were then applied to the (inherently co-registered) FA images. The normalised FA images of all subjects were then averaged and smoothed (8 mm full-width at half maximum Gaussian filter) to create a new, study-specific, intermediate template to which each subject's FA and MD images were then re-registered. Smoothing the data in order to coerce it into the appropriate statistical distribution is a prerequisite for some analytical approaches, but is not necessary for our non-parametric statistical approach where it serves instead to aid between-subject anatomical matching, reduce confounds due to individual variation in WM anatomy and improve the signal-to-noise ratio. We therefore segmented the registered FA images (using SPM's default *a priori* tissue probability information) to give maps of the probability of a tissue being either white or grey matter and thresholded the resulting images at a low level (10%) to provide a (deliberately slightly overinclusive) binary mask of WM. We then smoothed the original FA and MD images, before applying these masks to restrict the subsequent statistical testing to WM only. As different smoothing levels can result in varying results (Jones et al., 2005), in the absence of a specific hypothesis about the spatial extent of any abnormalities, we applied a Gaussian smoothing filter of 5 mm full-width at half maximum. Because of our overinclusive mask, the smoothed images will include some mixed grey/WM voxels at the edges of the masked region; however, later analysis steps (see below) further restrict the statistical testing to only core WM regions.

2.4. *Image analysis and correlations*

2.4.1. *DT-MRI group mapping*

We examined the statistical significance of between group differences in FA and MD using a non-parametric permutation-based method. Locally developed software, XBAM (version 3.4) (Institute of Psychiatry, http://www.brainmap.co.uk/) measures between group differences in standard space at both voxel and cluster levels by fitting an analysis of variance (ANOVA) statistical model. As there were no differences in the mean values in either age or IQ between groups, and the ranges similar, these were not entered as covariates and so the ANOVA model utilised FA or MD as the dependent variable while group classification was the key predictor variable.

Given that brain changes are likely to extend over a number of contiguous voxels, test statistics incorporating spatial information such as 3D cluster mass (the sum of suprathreshold voxel statistics) are generally more powerful than other possible test statistics, which are informed only by data at a single voxel (Bullmore et al., 1999). The voxelwise statistic images were therefore thresholded at a relatively lenient level of $p \leq .05$, and voxels that were spatially contiguous in three dimensions in the thresholded maps were assigned to the same cluster. The sum of voxel statistics within each cluster was computed for each randomisation to form a distribution of cluster mass under the null hypothesis. As no parametric distribution is known for cluster mass (sum of voxel statistics within each cluster), permutation testing was used to assess statistical significance; the mass of each cluster in the observed data was compared to this randomised distribution, and significant clusters were defined as those that had a greater cluster mass than the randomised distribution at a particular significance level. The number of permutations at the voxel and cluster levels was 1000 which defines the distribution well enough to permit inference about changes between groups (Bullmore et al., 1999). Such a non-parametric approach also overcomes the assumption that parametric methods adopt that the residuals of the model tested will follow a Gaussian distribution (which has been shown to not always be true for DT-MRI data, even after extensive smoothing) (Jones et al., 2005).

At this stage, we considered only those voxels at which all subjects contribute data which, along with the masking procedure above, restricted the analysis to core WM regions, reducing the search volume (and thus the number of

comparisons made) and also avoided testing at the grey/white interfaces, where the high grey/white contrast of FA images exacerbates any edge effects. At the cluster level, rather than set a single *a priori* *p*-value below which we regard findings as significant, we calculated, for a range of *p*-values, the number of clusters which would be expected by chance alone. A stringent cluster significance threshold was then applied to render less than one false positive cluster per analysis. As SPM was used for image registration, XBAM yielded coordinates of significant clusters in MNI space and the identification of significant clusters and WM tracts intersecting them was based on an atlas approach where several WM atlases were used in conjunction to determine the projection and localisation of WM bundles; these atlases were based on both single and multiple subject DT-MRI datasets in MNI space (Catani and Thiebaut de Schotten, 2008; Mori et al., 2005; Thiebaut de Schotten et al., 2011; Wakana et al., 2004). Given that the Talairach coordinate system is most commonly used for reporting findings in the neuroimaging literature, MNI coordinates were subsequently converted to Talairach space via a non-linear transformation (Brett et al., 2002) (details at http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach) and the localisation of WM tracts and their respective anatomical course within cerebral lobes was additionally confirmed using the Talairach atlas (Talairach and Tournoux, 1988). Where significant differences were found on either FA or MD maps, the *p*-value of each significant cluster is reported in Table 2 alongside the anatomical locations of their respective WM tracts in Talairach space.

In the investigation of cluster level effects, there is an underlying assumption that all regions will equally 'smooth' and can therefore be treated equivalently (from a statistical point of view). However, while we restricted our analysis to core WM regions where signal-to-noise ratio is relatively uniform, the effects of physiological noise (e.g., motion artefacts) may still vary across the brain. We therefore concurrently inspected the voxel-level maps (which treat each voxel independently and therefore inherently allow for such local differences in statistics) (Kyriakopoulos et al., 2008).

2.4.2. *Post hoc analysis of PCL-R scores*

Where significant 3D clusters were found on DT-MRI group mapping analyses, we carried out post hoc tests to determine if significant differences in WM FA or MD were associated with behavioural variation within the entire group with ASPD. As the clusters detected by XBAM may encompass multiple anatomical regions (i.e., were not constrained to lie only within particular WM tracts), we first extracted mean FA in combination with MD for each ASPD subject. To do this, mask images were created from each of the clusters found by the group mapping analysis and applied to each subject's normalised FA and MD images thereby enabling mean FA and MD values to be calculated over each region for each subject. These were then correlated with PCL-R scores (Factor 1: 'emotion dysfunction'; Factor 2: 'antisocial behaviour' and; total PCL-R) using Pearson product–moment correlation coefficients with Statistical Package for the Social Sciences (SPSS 14.0 for Windows, SPSS Inc., Chicago, IL, USA). Significant correlations are reported where a Bonferroni adjusted alpha of .025 was applied.

3. Results

3.1. *Group contrasts of FA using DT-MRI group mapping*

3.1.1. *ASPD versus controls WM FA (Fig. 1, Table 2)*

People with ASPD, relative to controls, had a significant reduction in WM FA; 1) bilaterally in the frontal lobe in the anterior portion of the corpus callosum (genu); 2) in the right hemisphere, only in anterior regions of the brain and in WM tracts that included the genu of corpus callosum, anterior corona radiata and anterior limb and genu of the internal capsule, and frontal course of the uncinate and inferior fronto-occipital fasciculus (IFOF); 3) in the left hemisphere in both anterior and posterior regions of the brain including respectively the genu of corpus callosum and temporo-occipital course of the inferior longitudinal and IFOF, and the retrolenticular part of the internal capsule and posterior thalamic radiation.

3.1.2. *ASPD versus controls WM MD (Fig. 2, Table 2)*

People with ASPD, relative to controls, had a significant increase in MD only in the right frontal lobe. This was localised to a cluster containing the frontal course of the IFOF and UF, and the genu of corpus callosum and anterior corona radiata. No regions of increased MD were found in the control group.

3.1.3. *Within ASPD, an analysis of Factor 1, Factor 2 and total PCL-R scores and differences in WM FA and MD*

In the ASPD group, there were significant correlations between PCL-R scores and both WM FA and MD. Mean FA of the cluster in the frontal lobe (Cluster 2) was negatively correlated with Factor 2 ($r = -.771$, $p = .003$, $n = 12$) and total PCL-R ($r = -.685$, $p = .005$, $n = 15$) scores. Additionally in the frontal lobe, there was a significant positive correlation between increased MD (Cluster 3) with Factor 2 scores ($r = .669$, $p = .017$, $n = 12$). There were no significant correlations between the cluster in the temporo-occipital cortex (Cluster 1) and total or subfactor PCL-R scores.

4. Discussion

We used DT-MRI in conjunction with whole brain voxel-based analyses of MD and FA to compare WM microstructural integrity of 15 adult males with a diagnosis of ASPD and 15 healthy controls matched for age, handedness and IQ. Reductions of FA were present in the frontal lobe of the ASPD group, and these were significantly and inversely correlated with severity of psychopathy (Factor 2, and total PCL-R scores). Also, increased MD was concurrently found in the right frontal lobe of ASPD subjects which showed a significant positive correlation with measures of psychopathy (Factor 2 scores).

The frontal cluster (Cluster 2, Table 2) that showed significant FA reduction and negative correlations with severity of psychopathy in the ASPD group included the genu of corpus callosum. Furthermore, it included right hemisphere structures of the anterior corona radiata and anterior limb and

Table 2 – WM FA and MD differences in ASPD relative to healthy controls (cluster significance threshold for FA maps $p = .0025$; cluster significance threshold for MD maps $p = .005$).

Cluster label	Cluster size (number of voxels)	Talairach and Tournoux coordinates			Tract(s) within cluster	Region	Cluster mean FA ASPD (SD)	Cluster mean FA Control (SD)	p-value
		x	y	z					
Cluster 1	504	−36	−42	−6	Temporo-occipital course of left ILF and IFOF[a]	Temporal lobe	.433 (.022)	.466 (.029)	.001378
		−32	−59	4	Left posterior thalamic radiation and retrolenticular part of internal capsule	Occipital lobe			
Cluster 2	1027	16	47	−8	Right IFOF and genu of corpus callosum	Frontal lobe	.383 (.020)	.409 (.033)	.000469
		19	30	−8	Right UF	Frontal lobe			
		−14	36	2	Left genu of corpus callosum	Frontal lobe			
		18	2	6	Right genu of internal capsule	Sub-lobar			
		18	32	7	Right genu of corpus callosum	Frontal lobe			
		23	11	9	Right anterior limb of internal capsule and anterior corona radiata[a]	Sub-lobar			
	Cluster size (number of voxels)	Talairach and Tournoux coordinates			Tract(s) within cluster	Region	Cluster MD ASPD mm^2 $sec^{-1} \times 10^{-3}$ (SD)	Cluster MD Control mm^2 $sec^{-1} \times 10^{-3}$ (SD)	p-value
		x	y	z					
Cluster 3	325	13	48	−11	Right anterior corona radiata, genu of corpus callosum, and IFOF and UF	Frontal lobe	.750 (.026)	.729 (.031)	.004513

a Location of voxel showing maximum FA difference.

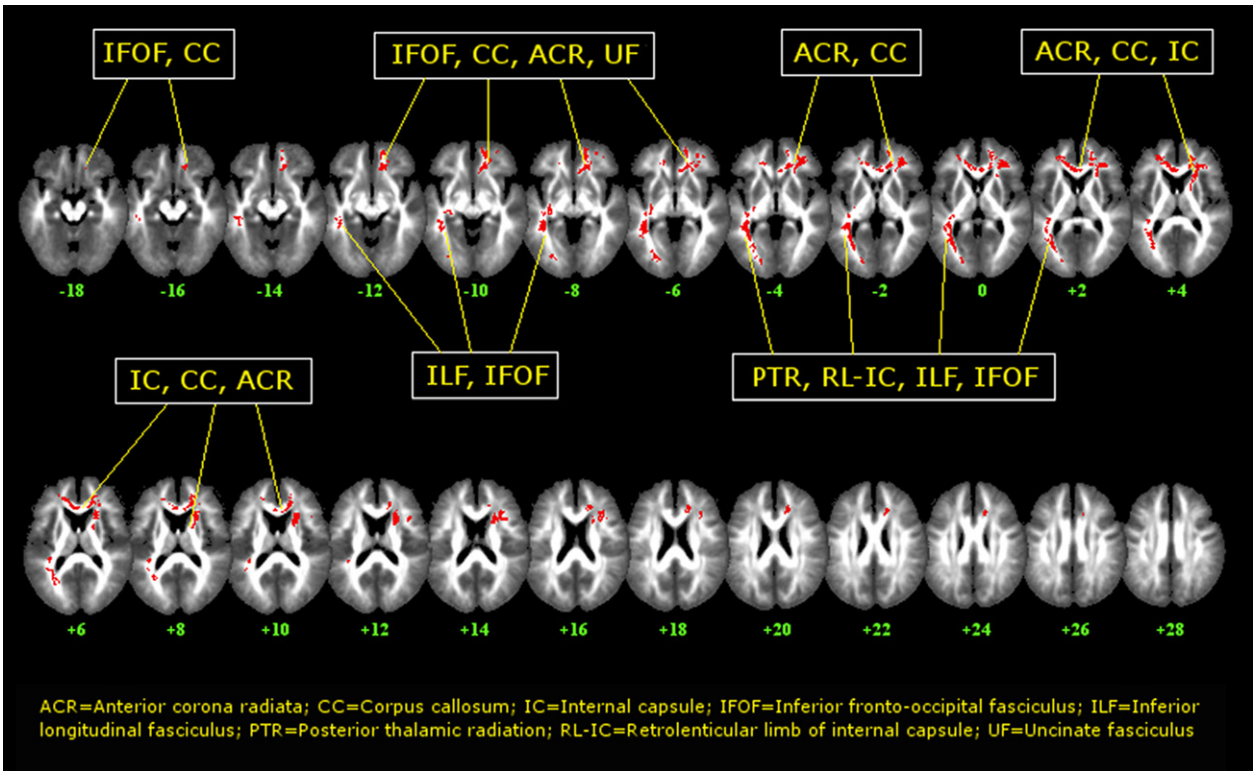

Fig. 1 – Reduced FA in ASPD relative to healthy controls [ascending 2 mm transverse sections].

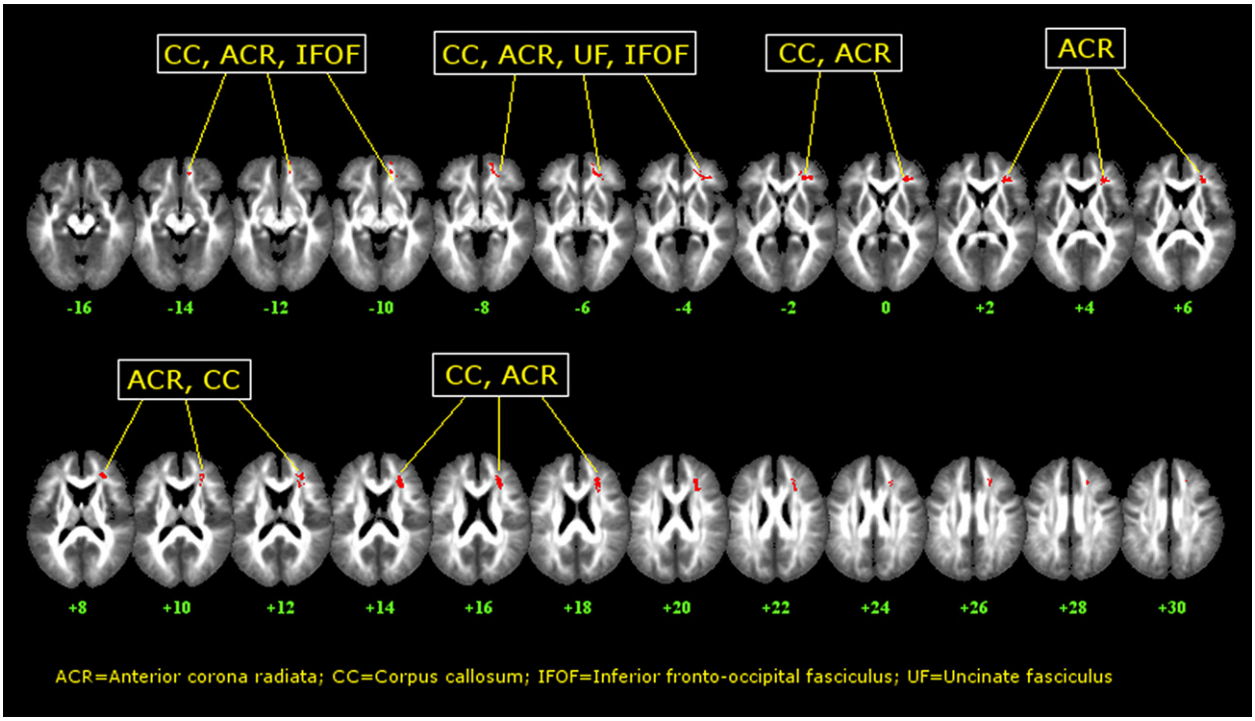

Fig. 2 – Increased MD in ASPD relative to healthy controls [ascending 2 mm transverse sections].

genu of the internal capsule in addition to the frontal course of the UF and IFOF. Additionally, a right frontal cluster (Cluster 3, Table 2) which encompassed the genu of corpus callosum and anterior corona radiata, as well as the frontal course of the IFOF and UF also showed a significant correlation between increased MD and psychopathy scores. Although FA reduction was also found in posterior regions of the left hemisphere in the temporo-occipital course of the inferior longitudinal fasciculus (ILF) and IFOF, in addition to the retrolenticular section and posterior thalamic radiation of the internal capsule (Cluster 1, Table 2), these did not correlate significantly with measures of psychopathy. Overall, our findings suggest that people with ASPD have WM microstructural abnormalities involving frontal WM networks, and particularly of the right hemisphere.

In a previous report by our group employing DT-MRI tractography examining FA and streamlines (a proxy measure of tract volume) of the UF, ILF and IFOF of nine individuals with psychopathy, FA was found to be reduced only in the right UF; additionally the number of streamlines in the UF bilaterally was correlated negatively with Factor 2 and total PCL-R scores though FA did not show any statistically significant correlations (Craig et al., 2009). The present finding of reduced FA in the right frontal lobe encompassing the UF replicates our original finding, noting that these nine subjects were also included in our larger sample of 15 individuals. The incorporation of more subjects in our current study may have provided additional power to detect further significant correlations with FA.

Apart from FA deficits in the UF, the frontal lobe of ASPD subjects in the current study also showed FA deficits in the corpus callosum, internal capsule, anterior corona radiata and IFOF; this is likely to indicate information relay impairments between prefrontal and other brain regions – e.g., interhemispherically and with the cingulum, pons, thalamus and temporo-occipital cortices (Catani et al., 2002; Schmahmann and Pandya, 2008). Impaired functioning of the corpus callosum in psychopaths has previously been postulated on the basis of evidence of prolonged interhemispheric transfer time relative to controls (Hiatt and Newman, 2007). Lesion studies of the corpus callosum have revealed its role in supporting sensory-motor functional integration, attention, language, interhemispheric transfer of associative learning, and emotional regulation (Bellani et al., 2009; Glickstein and Berlucchi, 2008; Zaidel and Iacoboni, 2003). Consequently, the present findings of reduced FA and increased MD in the corpus callosum of adults with ASPD, which also correlate with measures of psychopathy, may suggest that functions mediated predominantly by the left hemisphere (e.g., approach behaviour, language processing) may be relatively unmodulated by functions mainly mediated by the right hemisphere (including behavioural inhibition and emotion processing) as postulated by Hiatt and Newman (2007). This proposed mechanism may also help explain the association of reduced FA in the corpus callosum of dependent cocaine users with increased impulsivity (Moeller et al., 2005) and WM abnormalities in the corpus callosum of adolescents engaged in dangerous behaviour (Berns et al., 2009).

With regard to frontal lobe tracts, abnormalities in the UF are associated with impairments of conditional associative learning (Gaffan and Wilson, 2008; Gutnikov et al., 1997; Parker and Gaffan, 1998). Individuals with ASPD and/or psychopathy demonstrate deficits in reversal learning, a form of conditional associative learning characterised by a failure to 'reverse' a previously rewarded response when it is punished relative to controls (Table 1). Reversal learning deficits may contribute to the perseveration of antisocial behaviour and high levels of recidivism characteristic of the disorder. Further, fibres of the UF connect the orbitofrontal cortex and amygdala, while impaired regulation of amygdala activity by the orbitofrontal cortex may contribute to the behavioural disinhibition encountered both in 'acquired sociopathy' (Brower and Price, 2001) and ASPD and psychopathy (Sarkar et al., 2011). Although abnormalities in the IFOF and anterior corona radiata were also found in the frontal lobe in the current study, functional impairments attributable to these tracts are examined later in the discussion.

Additionally, FA deficits were found in the present study in the anterior limb of the internal capsule which contains thalamo-frontal (anterior thalamic radiation), fronto-thalamic and corticopontine fibres, and interconnects the dorsomedial and anterior thalamic nuclei with both the prefrontal and cingulate cortices. Lesions of the anterior limb of the internal capsule have been associated with 'acquired sociopathy' (Moll et al., 2003). Further, deficits in the anterior limb of the internal capsule have been suggested to lead to impairments in attention, perception and working memory (Buchsbaum et al., 2006; Sepulcre et al., 2008). The anterior limb of the internal capsule together with the anterior corona radiata (which connects the striatum with the anterior cingulate cortex) have been postulated respectively to contribute to attention impairments of alerting and conflict processing (Niogi et al., 2010). Disruption in tracts supporting the functional integration of cortical and subcortical regions involved in memory, attention, volition, learning and visual integration may contribute to the problems of people with ASPD in adaptively responding to altered contingencies in the social and physical environment (including social cues such as facial expressions), expressed in traits such as impulsivity or difficulty inhibiting motivated responses; a low threshold for the discharge of aggression; and failure to learn from aversive experiences.

We also report for the first time in ASPD, WM MD abnormalities of the frontal lobe. MD of the diffusion tensor reflects the magnitude of water molecule movement that is independent of direction and contrasts with FA that assesses the directional preference of such movement (Le Bihan et al., 2001). Increased MD has been reported for instance in vascular and neurodegenerative disorders affecting the brain (Herve et al., 2005; Scola et al., 2010), schizophrenia (Lee et al., 2009; Narr et al., 2009) and autism (Lee et al., 2007) indicating less restricted and thus, increased movement of water molecules. Similarly in our present study, increased diffusion of water molecules in the frontal lobe of those with ASPD suggests a less coherent underlying WM microstructure. Taken together with FA deficits concurrently found in the right frontal lobe, such disorganisation of WM microstructure may have arisen due to abnormal development of glial cells, axons or cell membranes (Dong et al., 2004; Herve et al., 2005). Furthermore, as frontal abnormalities in the current study are lateralised and involve the right hemisphere, there may be

a relationship between lateralisation of abnormalities and emergence of ASPD. Supporting this theory are findings from a previous study that demonstrated impairments in social conduct, social cognition and emotion processing in those with right-sided vmPFC lesions rather than left-sided damage (Tranel et al., 2002). Similarly, right-sided inferior frontal cortex lesions are associated with loss of inhibitory control (Aron et al., 2004) where disinhibition may result from a direct consequence of frontal lobe damage (Brower and Price, 2001) or indirectly through loss of frontal inhibition on temporal lobe structures, particularly, the amygdala (Hoffer et al., 2007). Given the lateralisation of brain functions noted above in our discussion of the corpus callosum [see also (Doron and Gazzaniga, 2008)], WM microstructural abnormalities localised to the right frontal lobe may further exacerbate the impaired modulation of left hemispheric processing that is potentially associated with abnormalities of the corpus callosum (Hiatt and Newman, 2007); this in turn may additionally contribute to emotion dysfunction (such as emotional shallowness and lack of empathy) and poor impulse control.

Although WM tracts in the posterior brain also showed FA deficits, these did not correlate significantly with psychopathy scores. The ILF and IFOF share projections at the posterior temporal and occipital lobes and are involved in connecting the visual association areas of the occipital lobe, and the auditory and visual association areas and the PFC respectively (Catani et al., 2002, 2003; Kier et al., 2004). Disconnection of the ILF has been associated with impaired communication between the occipital and temporal lobes (including the amygdala) – for instance involving the occipital and fusiform face areas (Catani and Thiebaut de Schotten, 2008; Thiebaut de Schotten et al., 2012) – which may lead to prosopagnosia and deficits in face processing (Fox et al., 2008) as well as visual memory disturbances (Shinoura et al., 2007). Further, the IFOF in humans represents the only direct long range association tract connecting the frontal and occipital lobes (Catani, 2006) and damage to the occipital portion of the IFOF has been associated with visual neglect as a result of impaired modulation by the frontal cortex (Urbanski et al., 2008). FA reduction in the present study was also found in the retrolenticular section and posterior thalamic radiation of the internal capsule which carries fibres of the optic radiation and is thus involved in the visual system. Overall, reduced microstructural integrity of these posterior tracts may contribute to deficits in face processing in antisocial populations, who show significant deficits in recognising fearful, sad, and surprised expressions, with a significantly greater deficit in fear recognition relative to other expressions (Marsh and Blair, 2008) and greater abnormalities of fusiform–extrastriate cortical responses to fearful than happy expressions relative to controls (Deeley et al., 2006). Deficits in fear processing in antisocial populations have been hypothesised to contribute to impaired moral socialisation, in which the 'at risk' child fails to learn to avoid behaviour that engenders distress in others (Marsh et al., 2008).

There were several limitations to our work. As this was a cross-sectional study, it is unclear whether the frontal deficits encountered are present early in life as a consequence of abnormal brain maturation and thus predispose to the emotional dysfunction and antisocial behaviour of psychopathy and ASPD, or whether they represent cumulative effects of later biopsychosocial factors such as the experience of recurrent involvement in antisocial behaviour or substance misuse. Future studies should therefore aim to assess child cohorts so as to longitudinally characterise WM integrity; and to identify whether WM anomalies predate detrimental lifestyle factors such as substance use, that frequently coexist in antisocial populations. Further, in order to match groups more closely, future studies would benefit from using non-psychopathic/non-ASPD offenders or patients as controls, rather than the healthy community sample used here. This would minimise potential confounds, including the higher incidence of substance misuse disorders, and differing lifestyle and socio-demographic factors. Overall, our current study represents the largest cohort of adults with ASPD analysed by DT-MRI to date, whilst recognising that recruiting suitable participants poses a challenge.

With regard to the PCL-R, while all subjects had total PCL-R scores, a limited number of participants did not have factor subscores (see Methods Section 2.1). Additionally, while controls were not assessed on the PCL-R, they were assessed through semi-structured interview using ICD-10 research criteria to assess for the presence of comorbid ASPD. Future studies may wish to implement the PCL-R or the shorter PCL-SV (Hart et al., 1995) to screen for psychopathy in control groups. Another weakness in the current study is that volumetry and neuropsychology measures were not assessed. The inclusion of neuropsychological tests within the present study may have helped to elucidate the type of information processing deficits that mediate the link between neural structural deficits and the behavioural profile of ASPD and psychopathy. Also, as WM FA/MD and structural volume may not be directly related (Lim et al., 1999), where possible, both conventional MRI and DT-MRI should be used in conjunction to investigate potential WM deficits as DT-MRI may be better able to detect pathology in normal appearing WM tissue while conventional MRI is able to ascertain independently occurring WM volumetric changes (Makki et al., 2007; Neil et al., 2002; Rugg-Gunn et al., 2001; Sundram et al., 2010). Moreover, when considering the results of our correlation analyses, it must be remembered that these may not be representative of other brain areas. In particular, as the ROIs over which these correlations were measured were defined by differences between ASPD subjects and controls, there is by definition, some relationship within these ROIs between FA and MD and overall behavioural scores, and our measurements cannot be considered truly independent. Future studies should therefore consider the use of ROIs based on the present study employed in independently acquired samples.

In summary, the current study showed reduced FA and increased MD respectively in areas consistent with a number of WM tracts within the frontal lobe in a group of males with ASPD compared to controls. Furthermore, frontal FA and MD abnormalities in the right hemisphere showed significant correlations with severity of psychopathy. Taken together, these findings suggest that frontal lobe WM microstructural abnormalities in ASPD particularly involve the right hemisphere. Given our pilot investigation, future work is required to longitudinally evaluate frontal lobe abnormalities through methods assessing brain structure, function and connectivity.

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