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Meta-analysis of diffusion tensor imaging studies in schizophrenia

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ABSTRACT

The objective of the study was to identify whether there are consistent regional white matter changes in schizophrenia. A systematic search was conducted for voxel-based diffusion tensor imaging fractional anisotropy studies of patients with schizophrenia (or related disorders) in relation to comparison groups. The authors carried out meta-analysis of the co-ordinates of fractional anisotropy differences. For the meta-analysis they used the Activation Likelihood Estimation (ALE) method hybridized with the rank approach used in Genome Scan Meta-Analysis (GSMA). This system detects three-dimensional conjunctions of co-ordinates from multiple studies and permits the weighting of studies in relation to sample size. Fifteen articles were identified for inclusion in the meta-analysis, including a total of 407 patients with schizophrenia and 383 comparison subjects. The studies reported fractional anisotropy reductions at 112 co-ordinates in schizophrenia and no fractional anisotropy increases. Over all studies, significant reductions were present in two regions: the left frontal deep white matter and the left temporal deep white matter. The first region, in the left frontal lobe, is traversed by white matter tracts interconnecting the frontal lobe, thalamus and cingulate gyrus. The second region, in the temporal lobe, is traversed by white matter tracts interconnecting the frontal lobe, insula, hippocampus–amygdala, temporal and occipital lobe. This suggests that two networks of white matter tracts may be affected in schizophrenia, with the potential for 'disconnection' of the gray matter regions which they link.

1. Introduction

Brain changes in schizophrenia may involve abnormalities in a network of gray and white matter regions (Csernansky and Cronenwett, 2008). However, the architecture of these changes has been more precisely mapped in gray matter than in white matter. Gray matter reductions have been located in limbic, paralimbic and frontal cortical regions and thalamus (Ellison-Wright et al., 2008a; Glahn et al., 2008; Wright et al., 2000; Shenton et al., 2001). However, the distribution of white matter changes remains uncertain (Kubicki et al., 2007; Kanaan et al., 2005). Two broad theories have been proposed to describe the pattern of white matter changes: the global and macro-circuit theories (Buchsbaum et al., 2006a).

According to the global theory, white matter reductions occur uniformly throughout the brain, possibly as a result of genetic abnormalities in the protein pathways controlling myelination (Konrad and Winterer, 2008). The alternative macro-circuit theory proposes that specific white matter tracts are disrupted in schizophrenia, either as a cause or a consequence of a disorder in the gray matter regions they connect (Konrad and Winterer, 2008).

At a functional level, considerable evidence has accrued for the abnormal integration of neural systems activated in patients with schizophrenia performing cognitive tasks. The evidence for this 'functional dysconnectivity' derives from a wide range of neurophysiologic and neuroimaging studies (Friston, 2005). Such abnormalities in functional connectivity could be due to abnormalities of axonal connectivity between regions (Bullmore et al., 1997), or they could be attributed to abnormal synapse formation and plasticity (Stephan et al., 2006).

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The objective of this meta-analysis was to test the different implications of these theoretical accounts of white matter changes in schizophrenia. We focused on neuro-imaging studies using diffusion tensor imaging (DTI). This is a magnetic resonance method which measures the diffusion properties of water molecules (Assaf and Pasternak, 2008). In general, the diffusion of water molecules is increased in white matter where it can occur parallel to the fibers. This property enables DTI to map both the distribution and integrity of white matter within the brain. One DTI measurement is called fractional anisotropy (FA). In the brain FA is high in white matter, low in gray matter and close to zero in cerebro-spinal fluid. We have selected studies employing voxel-based analyses of FA, since these analyse white matter throughout the brain, rather than region of interest studies which pre-select limited parts of the brain for analysis. Voxel-based analyses generally report the three-dimensional co-ordinates where there are maximal FA differences between patients and controls and these provide the data for meta-analysis.

Although most DTI studies of schizophrenia have identified FA reductions, with a few exceptions (Foong et al., 2002), diverse white matter regions have been implicated (Kubicki et al., 2007; Kanaan et al., 2005; Buchsbaum et al., 2006a; Friedman et al., 2008). Evidence that there is functional dysconnectivity in schizophrenia has recently been interpreted in terms of changes in micro-circuit synaptic plasticity rather than macro-circuit white matter abnormality (Stephan et al., 2006). An important part of the evidence cited against the macro-circuit theory was that 'diffusion weighted imaging studies have delivered negative results or widely varying findings'.

This meta-analysis tests whether there are consistently located white matter deficits (possibly super-imposed on global changes) whose detection in individual studies depends on statistical variation (i.e. the macro-circuit theory). Combining the results from multiple studies increases the power to detect these deficits. White matter regions which are preferentially affected may identify specific tract deficits contributing to functional disconnection of the regions they link (Burns et al., 2003). Our null hypothesis was that the coordinates of FA reductions (if present) followed a uniform random distribution (i.e. consistent with the global model of axonal disruption).

2. Methods

2.1. Data sources

A systematic search strategy was used to identify relevant studies. First, we carried out keyword searches of the MEDLINE and EMBASE databases (from 2000–2008; the search was conducted in August 2008). Second, a hand search was also conducted of the titles of published papers in five psychiatric journals for the period January 2007 to July 2008: *The American Journal of Psychiatry*, *Archives of General Psychiatry*, *Biological Psychiatry*, *The British Journal of Psychiatry* and *Schizophrenia Research*. Finally, we searched the reference lists of the studies identified for inclusion. Table 1 lists the articles included in the meta-analysis.

2.2. Study selection

Studies were considered for inclusion if they were published before August 2008 as an article, if they compared a group of subjects with schizophrenia (or schizophrenia and related diagnoses e.g., schizoaffective disorder, first episode psychosis) and a comparison group, if they utilised voxel-based analysis of fractional anisotropy to investigate differences in whole-brain (or whole white matter), and if they reported the three-dimensional co-ordinates of changes in stereotactic space.

Study data were excluded if insufficient data were reported to extract the number of subjects in each group, if there were fewer than six subjects in either the schizophrenia group or the comparison group, or if the data contributed to another publication, in which case the publication with the largest group size was selected. Co-ordinates were independently extracted by two psychiatrists (I.E-W. and H.S.). The results of one study were only given as a figure without co-ordinates (Ardekani et al., 2003) but the co-ordinates were quoted in the discussion section of another study (Buchsbaum et al., 2006b)

Table 1
Studies included in the meta-analysis

	Study	Male/Female/Both	Number of patients	Number of controls	Duration of illness (*) or treatment (#)	Number of coordinates
1	Ardekani et al., 2003	B	14	14	Not stated	12
2	Ashtari et al., 2007	B	23	21	2.4 years*	2
3	Buchsbaum et al., 2006b	B	63	55	18.2 years*	19
4	Cheung et al., 2008	B	25	26	0.5 years*	7
5	Hao et al., 2006	B	21	21	10.3 months#	17
6	Hubl et al., 2004	B	26	13	8.1 years*	17
7	Jones et al., 2005	M	14	14	8 years*	2
8	Kyriakopoulos et al., 2008	B	19	20	27.9 months#	3
9	Mori et al., 2007	B	42	42	16.8 years*	10
10	Schlösser et al., 2007	B	18	18	Not stated	3
11	Seok et al., 2007	B	30	22	8.6/6.3 years*	4
12	Serene et al., 2007	B	36	34	2.0 years*	6
13	Shergill et al., 2007	B	33	40	7 years*	3
14	Szeszko et al., 2005	B	10	13	15 days#	3
15	Szeszko et al., 2008	B	33	30	79 weeks*	4
	Total		407	383		112

All studies compared a patient group with a comparison group using voxel-based analysis of diffusion tensor imaging (DTI) fractional anisotropy (FA).

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and were used after cross-referencing with the figure in the original study. The results of one study (Kumra et al., 2005) were reported with an expanded patient group in another publication (Serene et al., 2007).

2.3. Data extraction

Co-ordinates that were reported in the stereotactic space of the Montreal Neurological Institute (MNI) were converted to Talairach coordinates (Talairach and Tournoux, 1988) using the Lancaster transform in GingerALE (Laird et al., 2005). Talairach co-ordinates that had been generated by the Brett transform applied to MNI co-ordinates were re-transformed to Talairach space using the Lancaster transform.

2.4. Meta-analysis

The analysis was carried out using the Genome Scan Meta-Analysis (GSMA) modification of Activation Likelihood Estimation (ALE) (Ellison-Wright et al., 2008b). Genome Scan Meta-Analysis was developed to deal with the diverse marker systems and analyses used in genome scan studies (Wise et al., 1999, Levinson et al., 2003). Structural neuro-imaging studies are also diverse in terms of image processing and statistical thresholds and a ranking method provides a systematic approach for integrating them. The GSMA method also permits weighting of studies in the meta-analysis based on sample size. The probability values can then be interpreted on an image-wide basis after correction for multiple testing (Koziol and Feng, 2005). We used the False Discovery Rate for this step, a method which controls the proportion of type 1 errors (false positives) among significant results (Verhoeven et al., 2005). A theoretical advantage over the standard ALE system is that extra weight is given to the spatial conjunction of co-ordinates when they derive from different studies rather than a single study. In standard ALE, if one study reports a dense cluster of co-ordinates in one region then this may provide a significant result after meta-analysis, even if no other study identifies co-ordinates in this region; using the GSMA ranking method, a dense cluster of co-ordinates in one study would only provide a single high rank for this region from one study and this would be unlikely to exceed the significance threshold derived from the null distribution.

Meta-analyses were carried out using a C++ program. For each study, the co-ordinates were modeled as the peaks of three-dimensional Gaussian probability density functions with full-width half-maximum of 7 mm, within a white matter mask of 153726 voxels of linear dimension 2 mm. The voxels in this probability image were then ranked from 153726 (highest probability) to 1 (lowest probability), giving voxels of equal probability a mean rank. This created a rank image for each study which was smoothed with a 7 mm Gaussian filter. These study images were weighted by the square root of the number of patients in the study. The weighted images were summated to create a sum-rank image.

A null distribution for the sum-rank image result was derived by 10000 permutations of the same process, but using an equal number of co-ordinates for each study derived from a random uniform distribution of coordinates within the white matter mask. The voxel-wise probability of a sum-rank under the null hypothesis was calculated as the proportion of permutations giving a value equal or greater than the actual value. The data set being tested was included in the ranking of all known outcomes (Levinson et al., 2003). The probability maps for the sum-rank images were ordered in magnitude and thresholded, controlling the image false discovery rate at $p<0.05$ (Verhoeven et al., 2005).

White matter tracts passing through clusters of voxels showing significant fractional anisotropy differences were mapped by reference to an atlas of human white matter anatomy (Mori et al., 2005), supplemented by DTIquery software (Sherbondy et al., 2005). With DTIquery software we used pre-computed pathways from DTI data on a normal 35 year old male subject (the standard set supplied with the software), mapped using Streamlines Tracking Techniques (STT) and filtered by tract length and region of interest.

3. Results

A total of fifteen studies were identified for inclusion in the meta-analysis (Table 1). These studies included a total of 407 patients with schizophrenia (or related disorders) and 383 comparison subjects and provided 112 co-ordinates of fractional anisotropy decreases. No regions of fractional anisotropy increase were reported.

Meta-analysis of the co-ordinates from these studies identified two regions of fractional anisotropy decreases in schizophrenia subjects compared with controls on sum-rank analysis. These regions are displayed on a brain template (Fig. 1) using the Mricron software program (Rorden et al., 2007).

The first region was in the left frontal deep white matter (Talairach co-ordinates of the maximum sum-rank at $x=-12$, $y=34$, $z=10$ with voxelwise $p<0.0001$; cluster size 2368 mm^3). Seven of the fifteen studies in the meta-analysis reported one or more co-ordinates (transformed into Talairach space) within 20 mm of the maximum focus of fractional anisotropy reduction in this region. White matter tracts traversing this region were visualized using DTIquery software. The region of

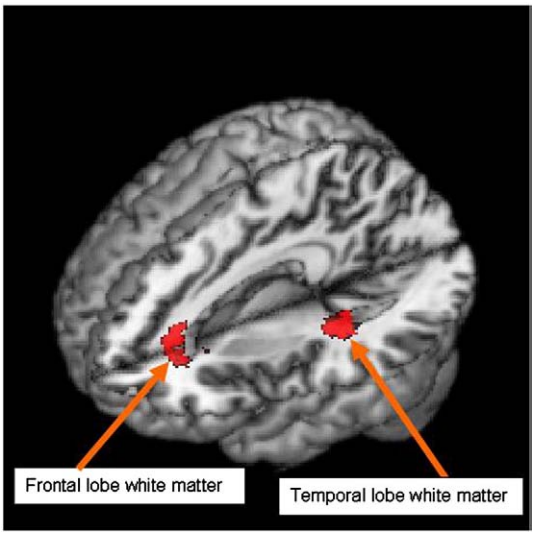

Fig. 1. Regional fractional anisotropy reductions in schizophrenia. Fractional anisotropy reductions in schizophrenia in the deep white matter of the left frontal lobe and the deep white matter of the left temporal lobe, displayed on a three-dimensional rendered brain with part of the left hemisphere removed.

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Table 2
Regions of fractional anisotropy decreases in schizophrenia subjects compared with controls

	Region	Talairach co-ordinates			Cluster size (mm^3)	White matter tracts traversing region
		x	*y*	*z*		
1	Left frontal white matter	−12	34	10	2368	Inter-hemispheric fibers (via genu of corpus callosum) Cingulum bundle Left anterior thalamic radiation Left corticobulbar tract Left inferior fronto-occipital fasciculus
2	Left temporal white matter	−30	−32	−2	2264	Inter-hemispheric fibers (via splenium of corpus callosum) Fornix/stria terminalis Left inferior longitudinal fasciculus Left inferior fronto-occipital fasciculus

Regions identified by meta-analysis of co-ordinates from fifteen studies (voxelwise $p<0.0001$ and false discovery rate for whole image $p<0.05$).

interest applied in DTIquery was a bounding box (size 15 mm diameter) centered on the co-ordinates of maximum sum-rank. These tracts include the anterior thalamic radiation and corticobulbar tracts, inter-hemispheric fibers running through the genu of the corpus callosum, the inferior fronto-occipital fasciculus and the cingulum bundle (Table 2, Fig. 2).

The second region was in the left temporal deep white matter ($x=-30, y=-32, z=-2$ with voxelwise $p<0.0001$; cluster size 2264 mm^3). Eleven of the fifteen studies in the meta-analysis reported one or more co-ordinates within 20 mm of the maximum focus of fractional anisotropy reduction in this region. White matter tracts traversing this region were visualized in DTIquery (using a smaller bounding box of 10 mm to improve visualization). These tracts included inter-hemispheric fibers running through the splenium of the corpus callosum, the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus and the fornix/stria terminalis (Table 2, Fig. 3).

4. Discussion

4.1. Regions of white matter changes in schizophrenia

The results of this meta-analysis identified two consistent locations of fractional anisotropy reduction in schizophrenia: one in the deep white matter of the left frontal lobe and the other in the deep white matter of left temporal lobe. Thirteen of the fifteen studies reported one or more coordinates within 20 mm of one or other of these regions' maxima. The two studies which did not report such coordinates only reported a total of six coordinates (Kyriakopoulos et al., 2008; Schlösser et al., 2007). Further evidence in support of changes in these regions comes from other voxel-based studies (not included in this meta-analysis because they did not report co-ordinate data) which found reduced fractional anisotropy in the splenium (Agartz et al., 2001) in the cingulum, fornix, left internal capsule and corpus callosum (Kubicki et al., 2005) and in the cingulum, left inferior longitudinal fasciculus and left anterior thalamic radiation (Skelly et al., 2008). A voxel-based study published after completion of this meta-analysis also reported reduced fractional anisotropy in the left temporal region (Hoptman et al., 2008). Region of interest studies have found reduced fractional anisotropy in the cingulum bundle (Smith et al., 2006, Rosenberger et al., 2008), the left inferior longitudinal fasciculus (Friedman et al., 2008) and the inferior fronto-occipital fasciculus (Rosenberger et al., 2008).

4.2. Interpretation of fractional anisotropy decreases

Fractional anisotropy varies according to the presence and integrity of white matter fibers (Assaf and Pasternak, 2008). However, each voxel examined in a DTI study may contain a mixture of gray matter, white matter and cerebro-spinal fluid. Therefore a decrease in FA may potentially represent a change

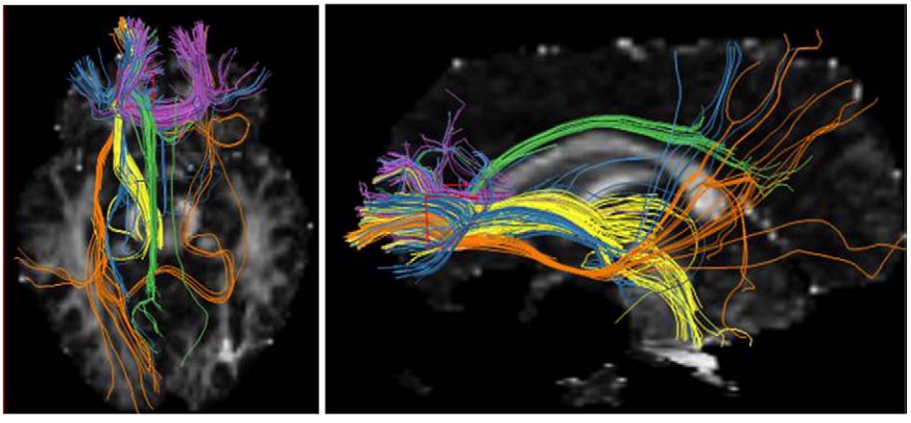

Fig. 2. White matter diffusion tensor tracts traversing left frontal white matter region. Three-dimensional images showing white matter tracts traversing a bounding box centered at $x=-12$, $y=34$, $z=10$, mapped using DTIquery in a single normal individual. Left image seen from above, right image seen from the left side of the brain. Tracts include the anterior thalamic radiation and corticobulbar tracts (yellow), inter-hemispheric fibers running through the genu of the corpus callosum (purple), the inferior fronto-occipital fasciculus (orange) and the cingulate bundle (green). The remaining tracts are blue. Axial and sagittal slices mapping fractional anisotropy values are shown in the background for illustrative purposes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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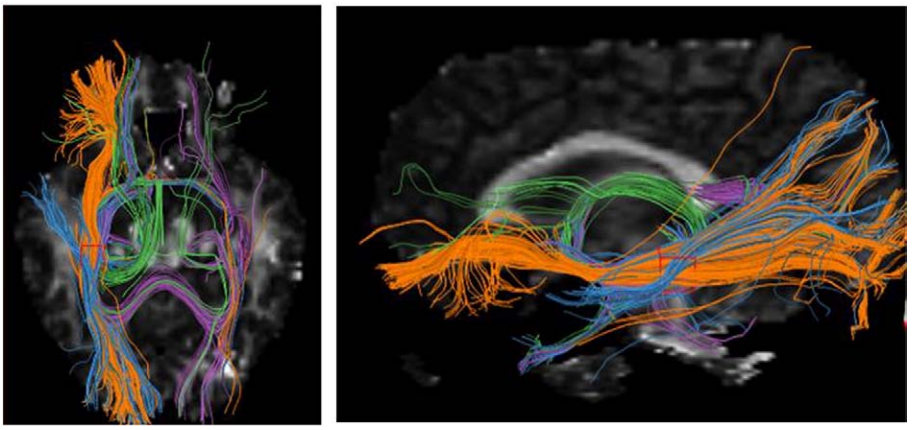

Fig. 3. White matter diffusion tensor tracts traversing left temporal white matter region. Three-dimensional images showing white matter tracts traversing a bounding box centered at $x=-30$, $y=-32$, $z=-2$, mapped using DTIquery in a single normal individual. Left image seen from above, right image seen from the left side of the brain. Tracts include inter-hemispheric fibers running through the splenium of the corpus callosum (purple), the inferior fronto-occipital fasciculus (orange), the inferior longitudinal fasciculus (some blue fibers), and the fornix/stria terminalis (green). Axial and sagittal slices mapping fractional anisotropy values are shown in the background for illustrative purposes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in any of these components. In disease states, FA reductions have been found in demyelination, oedema and inflammation. However, demyelination is not always accompanied by FA reduction and some studies of oedema after acute stroke have found increased FA (Assaf and Pasternak, 2008). Therefore the FA reductions identified in this meta-analysis are likely to indicate abnormality in regional white matter but do not specify the nature of this change. The possibilities include a reduction in one or more white matter fiber tracts passing through the regions, a change in the chemical composition of the white matter or differences in the proportion of axonal, oligodendrocyte and glial cellular components.

If white matter abnormality in these regions results from a neuro-developmental process interfering with white matter tract formation then there may be evidence for an absolute reduction in white matter in these regions. White matter density reductions have been found in both the left frontal white matter (Paillère-Martinot et al., 2001; Spalletta et al., 2003; Sigmundsson et al., 2001; McDonald et al., 2005) and left temporal white matter (Sigmundsson et al., 2001; Price et al., 2006; Whitford et al., 2007; McDonald et al., 2005). Region of interest studies of the internal capsule (Zhou et al., 2003) and corpus callosum (Arnone et al., 2008) have also identified white matter reductions. The well-established finding of ventricular enlargement in schizophrenia (Wright et al., 2000) has been related to a reduction in white matter adjacent to the ventricles (Christensen et al., 2004).

White matter tracts can be examined, indirectly, with DTI tractography which uses diffusion tensor data to construct their pathways. Pathways produced by tractography do not necessarily correspond to anatomical white matter bundles (Sherbondy et al., 2005) but represent abstract pathways derived from the diffusion data. However, evidence from post mortem studies has demonstrated that there is significant correspondence between the computed pathways and anatomical data (Mori et al., 2005; Sherbondy et al., 2005). White matter tract length in the anterior limb of the internal capsule has been found to be reduced in patients with schizophrenia (Buchsbaum et al., 2006a), consistent with disruption of a frontal–striatal–thalamic circuit in schizophrenia (Csernansky and Cronenwett, 2008; Ellison-Wright et al., 2008a). In patients with first-episode schizophrenia, an abnormal distribution of FA values has been found in the left uncinate fasciculus, the largest white matter tract connecting the frontal and temporal lobes, interpreted as reflecting a disruption in axonal packing within the core of the tract (Price et al., 2008).

The results of this meta-analysis, in identifying two separate regions of FA reduction, suggest the intriguing possibility that there may be two overlapping networks of white matter abnormalities in schizophrenia. The first network, with a focus in the frontal white matter, interconnects the frontal lobe, thalamus and cingulate gyrus. The second network, with a focus in the temporal white matter, interconnects the frontal lobe, insula, hippocampus–amygdala, and occipital lobe. Disruption of these white matter networks may contribute to cognitive deficits and symptoms in schizophrenia (Kubicki et al., 2007). Memory impairment has been associated with reduced FA in the fornix (Nestor et al., 2007) while performance monitoring deficits have been associated with reduced FA in the left cingulum bundle (Nestor et al., 2004). It has been postulated that inferior longitudinal fasciculus disruption may contribute to impaired social cognition in schizophrenia (Ashtari et al., 2007) and auditory hallucinations in schizophrenia have been associated with FA changes in multiple tracts including the cingulum bundle, corpus callosum and left inferior longitudinal fasciculus (Hubl et al., 2004, Shergill et al., 2007).

4.3. Methodological issues

This meta-analysis utilised a robust approach for identifying consistent regional changes between studies. It employed the Genome-Scan Meta-Analysis (GSMA) modification of Activation Likelihood Estimation (ALE). This method treats the spatial conjunction of co-ordinates from different studies as more significant than the conjunction of co-ordinates from the same study and permits the weighting of studies by sample size. The voxel-based analysis studies which provided the co-ordinates for the meta-analysis analyse the whole brain (or white matter

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within a mask) and therefore should avoid *a priori* bias in the identification of regional white matter changes. In addition, our analysis of regions of FA reduction was assisted by DTIquery. This permits mapping of white matter tracts traversing the regions on the basis of pre-computed tensor tracts from an individual normal subject, enhancing the information available from the MRI white matter atlas.

There are also a number of potential methodological limitations of this study. The power to detect regional changes was limited by the number of studies and their sample sizes. Heterogeneity in study results (also reducing the likelihood of detecting regional changes) may occur because the pattern of brain changes in schizophrenia may depend on the stage of the illness (Ellison-Wright et al., 2008a) and age effects (Jones et al., 2006) and because the smoothing filter used in voxel-wise analysis of DTI influences the results (Jones at al., 2005). Therefore, regional FA reduction may extend beyond the regions which were identified as significant. In particular, we cannot rule out the possibility that changes are bilateral. Although there is some intriguing evidence that brain changes in schizophrenia are greater on the left than right (Wright et al., 2000), this needs specific statistical testing which is beyond the scope of this meta-analysis. The FA changes may be affected by confounding factors such as medication, substance misuse or comorbidity. There is some evidence that medication can affect FA values (Minami et al., 2003). These effects would need to be explored in larger patient samples.

4.4. Future directions

This meta-analysis suggests two candidate regions for more intensive examination of white matter changes in schizophrenia. In the future, the detection of fractional anisotropy changes may be enhanced by improved registration of subject data (Gee and Alexander, 2007). A number of approaches have been developed, for example Tract-Based Spatial Statistics (TBSS) which registers subject data to a white matter skeleton (Smith et al., 2006) and a method which registers segmented fiber bundles (Ziyan et al., 2007). Tractography may also be used to measure the length of specific tracts traversing regions of interest (Buchsbaum et al., 2006a). An improved understanding of the nature of the white matter disruption in areas of reduced FA may come from co-registering FA data with magnetization transfer imaging (MTI), a technique sensitive to myelin and axonal alterations (Kubicki et al., 2005). Changes in the constituent parameters of FA, axial and radial diffusivity, may also indicate distinct forms of white matter pathology (Wozniak and Lim, 2006). Increased radial diffusivity has been found to accompany reduced FA in white matter tracts in schizophrenia, interpreted as resulting from demyelination or changes to the axonal cytoskeleton rather than gross axonal damage (Seal et al., 2008).

A more complete model of schizophrenia pathology would identify the relationship between schizophrenia susceptibility genes and white matter tract architecture in the brain. Evidence that an abnormality in genes regulating white matter architecture may lead to alterations in white matter fiber directionality comes from DTI studies of genetic disorders such as Williams Syndrome. This involves hemideletion of approximately 25 genes on chromosome 7q11.23, results in specific cognitive impairments and DTI has identified mis-routing of white matter tracts compared with control subjects (Marenco et al., 2007).

Finally, neuropathological studies of schizophrenia have detected some abnormalities in white matter, including axonal atrophy and swelling of periaxonal oligodendrocyte processes especially in the prefrontal cortex (Uranova et al., 2007). Identification of particular fiber tracts differentially affected in schizophrenia would provide specific targets for neuropathological investigation.

5. Conclusion

This meta-analysis identified two consistent locations of fractional anisotropy reduction in schizophrenia. One region, in the left frontal lobe, is traversed by white matter tracts interconnecting the frontal lobe, thalamus and cingulate gyrus. The second region in the temporal lobe, is traversed by white matter tracts interconnecting the frontal lobe, insula, hippocampus–amygdala, temporal and occipital lobe. This suggests that two networks of white matter tracts may be affected in schizophrenia, with the potential for 'disconnection' of the gray matter regions which they link.

These findings, taken in conjunction with the results of white matter volume, tractography and magnetic resonance spectroscopy studies (Tang et al., 2007), provide evidence for macro-circuit white matter changes in schizophrenia. The challenge for the future is to identify the precise white matter tracts affected, and whether this involves a reduction in fiber content or a misrouting of fibers to inappropriate destinations.

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This study was supported by a grant from The Salisbury Hospitals Foundation towards computer equipment. No funding source had a role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Contributors

Dr Ellison-Wright ascertained studies, carried out the statistical analysis and wrote the first draft of the manuscript. Professor Bullmore participated in the design and coordination and helped draft the manuscript. Both authors contributed to and approved the final manuscript.

Conflict of interest

Professor Bullmore is employed half-time by the University of Cambridge and half-time by GlaxoSmithKline (GSK) and is a stockholder in GSK.

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