TECHNICAL COMMENTARY

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Diffusion tensor imaging

Introduction

Diffusion tensor imaging (DTI) is a specialised imaging technique that uses MRI technology to investigate the movement of water within tissues of interest. By applying a magnetic field, the movement ("diffusivity") of water molecules can be visualised in vivo.

The diffusion of water is influenced by the cellular structure of the surrounding tissues, and measures such as fractional anisotropy (FA) were derived as an approximate measurement for the freedom of movement. In areas of high structural coherence such as white matter (WM), FA is highest, indicating that water is moving in relatively fixed directions. It is lower in grey matter (GM), and close to zero in cerebrospinal fluid (CSF), indicating that water is moving freely[1-3]. Consequently, changes in FA values are interpreted to be representing alterations in the structural integrity of the regional white matter[1-4].

Schizophrenia has been associated with structural alterations in many brain regions. Understanding neurological structural alterations using DTI in patients with schizophrenia may provide insight into the molecular neurobiology of aberrant neurotransmission, by highlighting brain regions where reduced cellular integrity may contribute to symptom expression. Studies have focused on individual regions but also whole brain investigations to identify differences between people with schizophrenia and controls[1-3].

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[5]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[6]. The resulting table represents an objective summary of the available evidence, although the conclusions

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are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found seven systematic reviews that met our inclusion criteria[1-4, 7-9].

- Moderate to high quality evidence suggests schizophrenia is associated with significantly reduced fractional anisotropy (compromised white matter integrity) in the frontal lobe (medial and lateral); splenium of corpus callosum; anterior cingulate gyrus; middle and superior temporal gyri; internal and external capsules; parahippocampal gyrus; and occipital lobe. First episode schizophrenia was associated with changes in internal and external capsules only.
- Moderate to low quality evidence suggests reduced FA in the genu of corpus callosum, posterior cingulate, hippocampus, entorhinal gyrus, fusiform gyrus, amygdala, parietal lobe, arcuate fasciculus, and cerebellum.

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Diffusion tensor imaging

Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, Yücel M, Velakoulis D, Pantelis C

Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis

Schizophrenia Research 2011; 127: 46-57

View review abstract online

Comparison	**Whole brain comparison of white matter (fractional anisotropy, FA) in chronic and first episode schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample size, direct, unable to assess consistency or precision) suggests people with chronic schizophrenia show FA matter reductions in the corpus callosum, medial frontal lobe and temporal lobe white matter (including internal and external capsules), but only in the internal and external capsules in first episode schizophrenia.**
FA	
Chronic schizophrenia N = 1380, 24 studies *Bilateral genu of corpus callosum and anterior cingulate/medial frontal;* Talairach coordinates (18, 24, 10), cluster 2501mm^3, $p < 0.000001$ *Left temporal white matter and left retrolenticular internal capsule/external capsule;* Talairach coordinates (-32, -26, -2), cluster 349mm^3, $p = 0.00006$ *Right temporal white matter;* Talairach coordinates (38, -32, -4), cluster 154mm^3, $p = 0.0002$ First episode schizophrenia *Left temporal white matter and left retrolenticular internal capsule/external capsule;* Talairach coordinates (-28, -48, 12), cluster 900mm^3, $p = 0.00004$ *Right internal capsule (posterior limb);* Talairach coordinates (14, -8, 2), cluster 45mm^3, $p = 0.0003$	
Consistency in results‡	No measure of consistency is reported

Diffusion tensor imaging

Precision in results§	No confidence intervals are reported.
Directness of results‖	Direct

Ellison-Wright I, Bullmore E

Meta-analysis of diffusion tensor imaging studies in schizophrenia

Schizophrenia Research 2009; 108(1-3): 3-10

View review abstract online

Comparison	**Whole brain comparison of foci of reduced white matter fractional anisotropy (FA) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to fully assess precision and consistency) suggests schizophrenia is associated with significant reductions in white matter integrity in the frontal and temporal lobes.**

FA

Meta-analysis was performed using a hybrid of Anatomical Likelihood Estimate (ALE) analysis and Genome Scan Meta-analysis (GSMA) which combines activation foci from multiple studies, and permits weighting for sample size

FWHM 7mm, FDR corrected at $p < 0.05$

15 studies, N = 790

Decreased FA was reported for 112 coordinates

Significant foci of reduced FA were identified in two regions of deep white matter: frontal and temporal lobes;

Frontal lobe reduction

Talairach coordinates (-12, 34, 10), $p < 0.0001$, Voxel cluster size 2368mm^3

7/15 studies reported 1 or more coordinate that lay within 20mm of this maximal focus of decreased FA.

White matter tracts traversing this region include inter-hemispheric fibres (genu of corpus callosum) cingulum bundle, left anterior thalamic radiation, left corticobulbar tract, left inferior fronto-occipital fasciculus.

Temporal lobe reduction

Talairach coordinates (-30, -32, -2), $p < 0.0001$, Voxel cluster size 2264mm^3

11/15 studies reported 1 or more coordinate that lay within 20mm of this focus of decreased FA. White matter tracts traversing this region include inter-hemispheric fibres (splenium of corpus callosum, fornix/stria terminalis, left inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus.	
Consistency in results	No measure of consistency is reported, results appear inconsistent particularly for frontal lobe data.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Geoffroy PA, Houenou J, Duhamel A, Amad A, De Weijer AD, Curcic-Blake B, Linden DEJ, Thomas P, Jardri R.

The arcuate fasciculus in auditory-verbal hallucinations: A meta-analysis of diffusion-tensor-imaging studies

Schizophrenia Research 2014; 159(1): 234-7

View review abstract online

Comparison	**The relationship between white-matter integrity and auditory-verbal hallucinations in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, precise, inconsistent) suggests decreased FA in the left, but not the right arcuate fasciculus in people with schizophrenia who are experiencing auditory hallucinations compared to controls.**
FA	
There was reduced fractional anisotropy in the left arcuate fasciculus of people with hallucinations compared to controls; 5 studies, N = 256, g = -0.42, 95%CI -0.69 to -0.16, $p < 0.10^{-3}$, I^2 = 58% *There was no significant effect in the right arcuate fasciculus;* 5 studies, N = 256, g = -0.19, 95%CI -0.47 to 0.09, p = 0.18, I^2 = 75%	
Consistency in results	Inconsistent
Precision in results	Precise

Directness of results	Direct

Kanaan RA, Kim JS, Kaufmann WE, Pearlson GD, Barker GJ, McGuire PK

Diffusion tensor imaging in schizophrenia

Biological Psychiatry 2005; 58(12): 921-929

View review abstract online

Comparison	**Whole brain comparison of regions of reduced white matter fractional anisotropy (FA) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to fully assess precision and consistency) suggests decreased FA in the splenium of corpus callosum, anterior cingulate gyrus, middle temporal gyrus, parahippocampal gyrus, superior temporal gyrus, frontal lobe, and occipital lobe.**
FA	
19 studies, N = 640 *Regions with decreased FA in at least one study in people with schizophrenia;* Splenium of corpus callosum, anterior cingulate gyrus, middle temporal gyrus, parahippocampal gyrus, superior temporal gyrus, frontal lobe, and occipital lobe. *Regions which did not report reduced FA in people with schizophrenia;* Prefrontal cortex, temporo-parietal cortex, parieto-occipital cortex, uncinate fasciculus, middle and superior peduncles, internal capsule, and hippocampus.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Kuswanto CN, Teh I, Lee TS, Sim K

Diffusion tensor imaging findings of white matter changes in first episode

schizophrenia: a systematic review **Clinical Psychopharmacology and Neuroscience 2012; 10(1): 13-24** View review abstract online	
Comparison	**Regions of altered white matter fractional anisotropy (FA) in first episode schizophrenia patients vs.controls.**
Summary of evidence	**Moderate to low quality evidence (large sample size, direct, unable to assess precision or consistency) suggests decreased FA in the corpus callosum, longitudinal fasciculi, cingulate gyrus, and temporal lobe of people with first episode schizophrenia.**
FA	
22 studies, N = 1713 *Regions showing decreased FA;* Corpus callosum (6 studies), superior longitudinal fasciculus (5 studies), inferior longitudinal fasciculus (5 studies), fronto-occipital fasciculus (5 studies), uncinate fasciculus (1 study), temporal lobe gyri (3 studies), temporal-occiptal region (1 study), posterior temporal region (3 studies), medial and middle frontal lobe (3 studies), precuneus and parietal lobe (3 studies), anterior and posterior cingulate cortex (3 studies), internal capsule (1 study), fornix (1 study), and hippocampus/parahippocampus (2 studies).	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Kyriakopoulos M, Bargiotas T, Barker GJ, Frangou S **Diffusion tensor imaging in schizophrenia** **European Psychiatry: the Journal of the Association of European Psychiatrists 2008; 23(4): 255-273** View review abstract online	
Comparison 1	**Whole brain comparison of regions of reduced white matter integrity, assessed by voxel-based analysis, in people with schizophrenia vs. controls.**

Summary of evidence	**Moderate to low quality evidence (unclear sample, direct, unable to assess precision and consistency) suggests reduced FA in the prefrontal cortex, parietal lobe, temporal lobe, occipital lobe, corpus callosum, cingulum bundle, internal capsule, arcuate fasciculus, and cerebellum in people with schizophrenia.**
FA	
15 studies, N = unclear *Regions that illustrated decreased FA in at least one study in people with schizophrenia;* Prefrontal cortex (12 studies), parietal lobe (4 studies), temporal lobe (12 studies), occipital lobe (5 studies), corpus callosum (6 studies), cingulum bundle (3 studies), internal capsule (4 studies), arcuate fasciculus (5 studies), and cerebellum (1 study).	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct
Comparison 2	**Whole brain comparison of regions of reduced white matter integrity, assessed by region-of-interest analysis, in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess precision and consistency) suggests reduced white matter integrity in the frontal lobe, genu of corpus callosum, anterior cingulate, occipital lobe, splenium of corpus callosum, posterior cingulate, hippocampus, entorhinal gyrus, fusiform gyrus, amygdala, temporal lobe, and parietal lobe of people with schizophrenia.**
FA	
17 studies, N = unclear *Regions that illustrated decreased FA in at least one study in people with schizophrenia;* 9 studies report decreased FA in anterior regions (frontal lobe, genu of corpus callosum, anterior cingulate). 7 studies reported decreases in posterior regions (occipital lobe, splenium of corpus callosum, posterior cingulate). 8 studies report decreases in temporal regions (hippocampus, entorhinal gyrus, fusiform gyrus, amygdala, temporal lobe). 3 studies show decreases in parietal regions.	

Diffusion tensor imaging

Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct
Comparison 3	**Association of alterations in white matter integrity with disease characteristics, medication effects and cognitive variables.**
Summary of evidence	**Low quality evidence (small sample sizes) is unclear as to the association of white matter integrity with disease variables.**
Disease characteristics	
One study showed positive correlation between right insular white matter FA and negative symptoms PANSS score; N = 40, r = 0.747, p <0.0001 No other disease characteristics showed correlation with white matter changes. 9/12 studies reported no correlation with medication effects.	
Cognitive variables	
One study (N = 33) showed lower right FA values were correlated with worse Trail Making performance (r = -0.71, p <0.01) and with WAIS III subtest scores (r = 0.55, p <0.05). Lower left uncinate fasciculus FA values were correlated with worse immediate recall in the verbal paired associate subtest of the WMS (r = 0.79, p <0.01). One study (N = 34) showed lower left cingulum bundle FA values were correlated with increased wrong responses in the WCST (r = -0.546, p = 0.04) and with increased non-perseverative errors (r = -0.658, p = 0.01). One study (N = 47) showed lower left cingulum bundle FA values were correlated with WCST totals incorrect (r = -0.471, p = 0.042); perseverative responses (r = -0.478, p = 0.038); and increased perseverative errors (r = -0.517, p = 0.023). One study (N = 42) showed lower left superior cerebellar peduncle FA values were correlated with higher PANSS cognitive cluster scores (r = -0.72, p = 0.002).	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Not applicable

Diffusion tensor imaging

Patel S, Mahon K, Wellington R, Zhang J, Chaplin W, Szezko PR

A meta-analysis of difusion tensor imaging studies of the corpus callosum in schizophrenia

Schizophrenia Research 2011; 129: 149-55

View review abstract online

Comparison	**Mean fractional anisotropy (FA) in the corpus callosum of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to hith quality evidence (direct, precise, inconsistent) suggests medium-sized decreases of FA in the corpus callosum - specific to the splenium, in people with schizophrenia. This effect may be largest for females and for antipsychotic-naïve patients.**

FA

7 studies, N = 415

Splenium of corpus callosum

Signficant, medium-sized effect of decreased mean splenium FA In people with schizophrenia;

g = 0.526, 95%CI 0.216 to 0.837, p = 0.001, Q = 16.91, p = 0.02, I^2 = 58.60%

Subgroup analyses suggests this effect was significantly larger in the antipsychotic-naive sample compared to the medicated sample (antipsychotic-naïve g = 1.001 vs. medicated g = 0.379, Q = 5.14, p = 0.023).

Meta-regression with gender (% male) showed a significant association (p < 0.01) suggesting studies with a higher number of males showed less difference in mean splenium FA between groups.

Genu of corpus callosum

No significant difference between groups;

g = 0.223, 95%CI -0.081 to 0.528, p = 0.15

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Diffusion tensor imaging

Explanation of acronyms

ALE = Anatomical Likelihood Estimate, CI = Confidence Interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardized mean differences (see below for interpretation of effect sizes), FDR = False Discovery Rate correction for multiple comparisons, FA = Fractional Anisotropy, FWHM = full width at half maximum, applied as a smoothing kernel, GSMA = Genome Scan Meta-analysis, MRI = magnetic resonance imaging, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, vs = versus, WAIS, Weshler Adult Intelligence scale, WCST = Wisconsin Card Sorting Test, WMS = Weshler Memory Scale

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Diffusion tensor imaging

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[10].

† Different effect measures are reported by different reviews.

ALE analysis (Anatomical Likelihood Estimate) refers to a voxel-based meta-analytic technique for structural imaging in which each point of statistically significant fractional anisotropy is spatially smoothed into Gaussian distribution space, and summed to create a statistical map estimating the likelihood of difference in each voxel, as determined by the entire set of included studies. Incorporated with the Genome Scan Meta-analysis (GSMA), the meta-analysis of coordinates from multiple studies can be weighted for sample size to create a random effect analysis. The ALE statistic (if reported) represents the probability of a group difference occurring at each voxel included in the analysis.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[10].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[11]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to

possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[12].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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