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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. Consequently, changes in FA values are interpreted to be representing alterations in the structural integrity of the regional white matter.

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.

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[1]. 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)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

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Results

We found five systematic reviews that met our inclusion criteria[3-7].

- Compared to controls, moderate quality evidence finds white matter reductions in people with schizophrenia in the anterior commissure, corpus callosum, fornix, internal capsule, bilateral arcuate fasciculus, bilateral cingulum, bilateral cortico-ponto-cerebellum tract, bilateral cortico-spinal tract, bilateral inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, bilateral inferior cerebellar penduculus, bilateral optic radiation, bilateral anterior and posterior segment of the arcuate fasciculus, bilateral superior longitudinal fasciculus 1, 2 and 3, bilateral superior cerebellar penduculus, and bilateral uncinate fasciculus.
- Moderate quality evidence finds similar decreases in white matter integrity in people with schizophrenia and people with bipolar disorder in the genu of the corpus callosum extending to anterior thalamic radiation/cingulum fibres/inferior fronto-occipital fasciculus, and in left posterior cingulum fibres.
- Compared to controls, moderate quality evidence finds reduced white matter in the left, but not the right, arcuate fasciculus in people with schizophrenia who are experiencing auditory hallucinations.
- Moderate to high quality evidence found decreased whole brain white matter was associated with a small decrease in positive and general symptoms, and a small increase in negative symptoms. Authors state these relationships could be explained by older age, which was associated with decreased whole brain white matter. This is because older age has been associated with less severe positive symptoms and more prominent negative symptoms.
- High quality evidence found similar reductions in white matter in the genu, but not splenium, of the corpus callosum of male and female patients compared to controls. Although not significant, the reductions were slightly larger in females than in males.

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Dong D, Wang Y, Chang X, Jiang Y, Klugah-Brown B, Luo C, Yao D

Shared abnormality of white matter integrity in schizophrenia and bipolar disorder: A comparative voxel-based meta-analysis

Schizophrenia Research 2017; 185: 41-50

View online review abstract

Comparison 1	**White matter integrity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, some inconsistency, unable to assess precision, direct) finds decreases in white matter integrity in frontal white matter via genu of the corpus callosum extending to the body of the corpus callosum, in right cingulum fibres, in anterior thalamic projections/caudate nucleus, and in left superior longitudinal fasciculus. Reduced white matter in the right cingulum fibers was associated with older age and longer illness duration.**
FA	
25 studies, N = 1,529 *Significant decreases in white matter integrity in people with schizophrenia were found in;* Frontal white matter via genu of the corpus callosum extending to the body of the corpus callosum, incorporating fibers joining left anterior thalamic radiation, cingulum fibers, inferior fronto-occipital fasciculus and uncinate fasciculus: 356 voxels, MNI = -20,34, 8, $p < 0.001$ Right cingulum fibres: 325 voxels, MNI = 10, -38, 20, $p < 0.001$ Anterior thalamic projections/caudate nucleus: 92 voxels, MNI = -4, -20, 18, $p < 0.001$ Left superior longitudinal fasciculus: 43 voxels, MNI = -34, -52, 30, $p < 0.001$ Meta-regression analysis indicated that the reduced white matter in the right cingulum fibers was associated with older age and longer illness duration. There were no significant moderating effects of image acquisition parameters or schizophrenia chronicity (chronic and first-episode).	
Comparison 2	**White matter integrity in people with schizophrenia vs. people with bipolar disorder, controlling for age, sex and illness duration.**
Summary of evidence	**Moderate quality evidence (large sample, some inconsistency, unable to assess precision, direct) suggests similar decreases in white matter integrity in the genu of the corpus callosum**

	extending to anterior thalamic radiation/cingulum fibers/inferior fronto-occipital fasciculus, and in left posterior cingulum fibers.
FA	
47 studies, N = 1,459 *Both groups showed significant decreases compared to controls, with no differences between patients in;* The genu of the corpus callosum extending to anterior thalamic radiation/cingulum fibers/inferior fronto-occipital fasciculus: 288 voxels, $p < 0.001$, MNI = -18, 38, 2 Left posterior cingulum fibers: 74 voxels, $p < 0.001$, MNI = -18, -36, 34	
Consistency in results‡	Authors report some of the results were inconsistent.
Precision in results§	Unable to assess; no measure of precision is reported (CIs).
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	**White matter integrity and auditory-verbal hallucinations in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, 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%	

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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

Shahab S, Stefanik L, Foussias G, Lai MC, Anderson KK, Voineskos AN

Sex and Diffusion Tensor Imaging of White Matter in Schizophrenia: A Systematic Review Plus Meta-analysis of the Corpus Callosum

Schizophrenia Bulletin 2017; 44: 203-221

View review abstract online

Comparison	**White matter integrity in the corpus callosum in males and females with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) found both male and female patients showed decreases of FA in the genu, but not in the splenium, of the corpus callosum when compared to controls. The effect was non-significantly higher in females than males.**
FA	
Both male and female patients showed decreases of FA in the genu, but not in the splenium, of the corpus callosum when compared to controls; Genu of the corpus callosum Males: 10 studies, N = 1,161, *g* = -0.282, 95%CI -0.473 to -0.091, *p* = 0.004, I^2 = 30%, *p* = 0.167 Females: 10 studies, N = 1,161, *g* = -0.417, 95%CI -0.686 to -0.148, *p* = 0.002, I^2 = 29%, *p* = 0.175 Splenium of the corpus callosum Males: 10 studies, N = 1,161, *g* = -0.203, 95%CI -0.418 to 0.012, *p* > 0.05, I^2 = 44%, *p* = 0.085 Females: 10 studies, N = 1,161, *g* = -0.232, 95%CI -0.553 to 0.088, *p* > 0.05, I^2 = 49%, *p* = 0.039 The differences in effect sizes between males and females were not statistically significant.	
Consistency in results	Consistent, apart from females; splenium.

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Precision in results	Precise
Directness of results	Direct

Vitolo E, Tatu MK, Pignolo C, Cauda F, Costa T, Ando A, Zennaro A

White matter and schizophrenia: A meta-analysis of voxel-based morphometry and diffusion tensor imaging studies

Psychiatry Research: Neuroimaging 2017; 270: 8-21

View review abstract online

Comparison	**White matter integrity in people with schizophrenia vs. controls.** **The meta-analysis combined MRI and DTI studies.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found white matter reductions in the anterior commissure, corpus callosum, fornix, internal capsule, bilateral anterior segment of the arcuate fasciculus, left long segment of the arcuate fasciculus, bilateral arcuate fasciculus, bilateral cingulum, bilateral cortico-ponto-cerebellum tract, bilateral cortico spinal tract, bilateral inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, bilateral inferior cerebellar penduculus, bilateral optic radiation, bilateral posterior segment of the arcuate fasciculus, bilateral superior longitudinal fasciculus 1, 2 and 3, bilateral superior cerebellar penduculus and bilateral uncinate fasciculus.**

FA

34 studies, N = 2,231

There were white matter reductions in;

Anterior commissure: 16,636 voxels, $p = 0.000904$, MNI = -25, 8, -25

Corpus callosum: 114,544 voxels, $p = 0.000655$, MNI = 17, 35, 35

Fornix: 26,318 voxels, $p = 0.000924$, MNI = -29, 10, -27

Internal capsule: 63,671 voxels, $p = 0.000525$, MNI = -19, -1, 17

Left anterior segment of arcuate fasciculus: 5,391 voxels, $p = 0.000036$, MNI = -51, -7, 15

Right anterior segment of arcuate fasciculus: 8,780 voxels, MNI coordinates (50, -10, 29), $p = 0.000378$

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Left long segment of arcuate fasciculus: 7,639 voxels, *p* = 0.000218, MNI = -34, -40, -1

Left arcuate fasciculus: 24,480 voxels, *p* = 0.000112, MNI = -34, -40, -1

Right arcuate fasciculus: 23,307 voxels, *p* = 0.000258, MNI = 44, -38, -1

Left cingulum: 42,476 voxels, *p* = 0.000566, MNI = -19, -43, 39

Right cingulum: 38,840 voxels, *p* = 0.001913, MNI = 18, 35, 32

Left cortico-ponto-cerebellum tract: 2,176 voxels, *p* = 0.000226, MNI = 16, -37, -32

Right cortico-ponto-cerebellum tract: 766 voxels, *p* = 0.000206, MNI = 25, -17, 5

Left cortico spinal tract: 29,175 voxels, *p* = 0.000409, MNI = -19, -1, 17

Right cortico Spinal tract: 23,730 voxels, *p* = 0.000592, MNI = 29, -19, 5

Left inferior fronto-occipital fasciculus: 22,154 voxels, *p* = 0.000725, MNI = -31, -22, -7

Right inferior fronto-occipital fasciculus: 23,185 voxels, *p* = 0.001700, MNI = 41, -31, -7

Left inferior longitudinal fasciculus: 20,131 voxels, *p* = 0.000900, MNI = -34, -40, -1

Right inferior longitudinal fasciculus: 16,338 voxels, *p* = 0.002284, MNI = 41, -31, -7

Left inferior cerebellar penduculus: 5,648 voxels, *p* = 0.000235, MNI = -7, -33, -22

Right inferior cerebellar penduculus: 5,302 voxels, *p* = 0.000502, MNI = 14, -38, -31

Left optic radiation: 7,923 voxels, *p* = 0.000797, MNI = -34, -40, -1

Right optic radiation: 5,982 voxels, *p* = 0.002349, MNI = 29, -19, 5

Left posterior segment of arcuate fasciculus: 11,088 voxels, *p* = 0.000313, MNI = -34, -40, -1

Right posterior segment of arcuate fasciculus: 12,107 voxels, *p* = 0.001262, MNI = 41, -34, -4

Left superior longitudinal fasciculus1: 109,025 voxels, *p* = 0.000169, MNI = -19, -43, 39

Right superior longitudinal fasciculus1: 98,037 voxels, *p* = 0.001150, MNI = 20, 35, 35

Left superior longitudinal fasciculus2: 112,229 voxels, *p* = 0.000059, MNI = -20, -4, 53

Right superior longitudinal fasciculus2: 117,581 voxels, *p* = 0.000437, MNI = 20, 35, 35

Left superior longitudinal fasciculus3: 72,219 voxels, *p* = 0.000115, MNI = -49, -37, 14

Right superior longitudinal fasciculus3: 119,900 voxels, *p* = 0.000078, MNI = 23, 27, 31

Left superior cerebellar penduculus: 8,012 voxels, *p* = 0.000772, MNI = -7, -31, -22

Right superior cerebellar penduculus: 8,113 voxels, *p* = 0.000741, MNI = 13, -24, -7

Left uncinate fasciculus: 12,282 voxels, *p* = 0.000883, MNI = -25, 9, -21

Right uncinate fasciculus: 13,022 voxels, *p* = 0.000888, MNI = 16, 27, 2

Older patients showed reduced white matter in the right splenium of corpus callosum and the right cortico spinal tract. Younger patients showed white matter reductions of the left cortico spinal tract, the right cingulum bundle, the right superior temporal gyrus, and the left superior longitudinal fasciculus3.

Longer duration of illness was associated with white matter reductions in the bilateral uncinate fasciculus, the left inferior longitudinal fasciculus, the right inferior fronto-occipital fasciculus and the right posterior cingulum bundle. Shorter duration of illness was associated with white matter reductions in the right anterior cingulum bundle, the right median cingulate gyrus, and the left superior longitudinal fasciculus3. A higher percentage of male patients showed reduced white matter traits in the right superior longitudinal fasciculus2, the left inferior temporal gyrus, the bilateral superior longitudinal fasciculus3, the right superior temporal gyrus, the right posterior segment of arcuate fasciculus, and the left body of corpus callosum. Female patients showed reduced white matter traits in the right genu of corpus callosum, the right inferior fronto-occipital fasciculus, the right superior longitudinal fasciculus3, the left superior cerebellar penduculus, the left optic radiation, and the left long segment of the arcuate fasciculus.

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Yang X, Cao D, Liang X, Zhao J

Schizophrenia symptomatic associations with diffusion tensor imaging measured fractional anisotropy of brain: a meta-analysis

Neuroradiology 2017; 59: 699-708

View review abstract online

Comparison	**Association between white matter integrity and symptoms in people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) found decreases in whole brain FA were associated with small increases in negative symptoms and small decreases in positive and general symptoms. Authors state these relationships were not clinically significant and could be explained by increased age which was associated with decreased FA (positive symptoms tend to be more prominent early on in the disorder, while negative symptoms tend to be more prominent in older age).**
FA	

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33 studies, N = 1,121 *Small, significant effects of associations between increases in whole brain FA and decreases in negative symptoms and increases in positive and general symptoms;* Negative symptoms: r = -0.29, 95%CI -0.23 to -0.35, p < 0.00001, I^2 = 48% Positive symptoms: r = 0.16, 95%CI 0.04 to 0.27, p = 0.007, I^2 = 75% General symptoms: r = 0.26, 95%CI 0.15 to 0.35, p = 0.004, I^2 = 77% There was a significant moderating effect of age; decreased age was associated with increased FA.

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

Explanation of acronyms

CI = confidence interval, FA = fractional anisotropy, *g* = Hedges' g = standardised mean differences, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MNI = Montreal Neurological Institute, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), *r* = correlation coefficient, vs. = versus

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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[8].

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† 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[8].

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[9]. 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[10].

‖ 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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