TECHNICAL COMMENTARY

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Corpus callosum

Introduction

The corpus callosum is the bundle of inter-hemispheric white matter tracts and plays an essential role in the transfer and integration of sensory, motor and cognitive information between homologous regions in opposite hemispheres. It is the primary source of contralateral connections between the hemispheres and contains as many as 250 million axons. Connections from the prefrontal, parietal, motor, somatosensory and visual cortices are transmitted across the corpus callosum in a topographic manner.

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).

Results

We found four systematic reviews that met our inclusion criteria[3-6].

- Moderate to high quality evidence found volume reductions in the corpus callosum of people with schizophrenia compared to controls.
- There were also decreases in white matter integrity in the corpus callosum of people with schizophrenia. Specifically, in frontal white matter via genu of the corpus callosum extending to the body of the corpus callosum, incorporating fibers joining the left

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anterior thalamic radiation, cingulum fibers, inferior fronto-occipital fasciculus, and uncinate fasciculus in people with schizophrenia.

- High quality evidence found both male and female patients showed decreases of white matter 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 in males.
- There were similar decreases in white matter integrity in people with schizophrenia or bipolar disorder in the genu of the corpus callosum extending to the anterior thalamic radiation/cingulum, and inferior fronto-occipital fasciculus.

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Arnone D, McIntosh AM, Tan GM, Ebmeier KP, Tan GMY

Meta-analysis of magnetic resonance imaging studies of the corpus callosum in schizophrenia

Schizophrenia Research 2008; 101(1-3): 124-32

View review abstract online

Comparison	**Corpus callosum volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality (large samples, consistent, direct, mostly precise) evidence suggests reductions in the corpus callosum in people with schizophrenia, which was most pronounced in people with first-episode schizophrenia.**
Corpus callosum volume	
All patients vs. controls *Significant, small effect shows reduced callosal area in people with schizophrenia;* 28 studies, N = 1,703, *d* = -0.24, 95%CI -0.4 to -0.07, *p* value not reported, I^2 = 2% Patients with recurrent symptoms vs. controls *Significant, small effect shows reduced callosal area in people with schizophrenia;* 24 studies, N = 1,476, *d* = -0.17, 95%CI -0.33 to -0.001, *p* value not reported, I^2 = 1% First-episode schizophrenia vs. controls *Significant, large effect shows reduced callosal area in people with first-episode schizophrenia;* 4 studies, N = 227, *d* = -0.70, 95%CI -1.29 to -0.10, *p* value not reported, I^2 = 3%	
Consistency in results‡	Consistent
Precision in results§	Precise for all patients and recurrent patients, imprecise for first-episode patients.
Directness of results‖	Direct

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

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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) found decreases in white matter integrity in frontal white matter via genu of the corpus callosum extending to the body of the corpus callosum, incorporating fibers joining the left anterior thalamic radiation, cingulum fibers, inferior fronto-occipital fasciculus, and uncinate fasciculus in people with schizophrenia.**
White matter	
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 the left anterior thalamic radiation, cingulum fibers, inferior fronto-occipital fasciculus and uncinate fasciculus: 356 voxels, MNI coordinates = -20,34, 8, $p < 0.001$	
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 the anterior thalamic radiation/cingulum and inferior fronto-occipital fasciculus.**
White matter	
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 the anterior thalamic radiation/cingulum and inferior fronto-occipital fasciculus: 288 voxels, MNI coordinates = -18, 38, 2, $p < 0.001$	
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

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 white matter 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 in males.**

White matter

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.
Precision in results	Precise
Directness of results	Direct

TECHNICAL COMMENTARY

Corpus callosum

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.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found white matter reductions in the corpus callosum of people with schizophrenia.**
White matter	
34 studies, N = 2,231 *There were white matter reductions in;* Corpus callosum: 114,544 voxels, *p* = 0.000655, MNI = 17, 35, 35	
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

Explanation of acronyms

CI = confidence interval, *d* = Cohen's *d* and *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), N = number of participants, *p* = probability of obtaining that result ($p < 0.05$ generally regarded as significant), 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[7].

† 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 structural difference 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.

Fractional similarity network analysis refers to a network analysis technique in which secondary networks are identified within the larger framework of activity, creating a matrix for regional co-activity.

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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[7].

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[8]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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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).

‡ 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[9].

‖ 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 indirectcomparisons 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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