TECHNICAL COMMENTARY

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Cerebellum

Introduction

The cerebellum sits below the larger cerebrum of the brain, and is connected via the brainstem. The cerebellum is divided into two hemispheres separated dorsally by a midline zone called the vermis. It contains three primary lobes, the flocculonodular lobe, anterior lobe and posterior lobe.

Broadly, the cerebellum is thought to function in fine motor control (coordination and precision) and motor learning, balance, posture, as well as some cognitive and emotional capacity. The interaction of sensory, cognitive and motor functions may also contribute to proprioception (the awareness of self in space), planning movements, and evaluating information for action. The detailed functions of each region of the cerebellum are determined largely by their connectivity.

Schizophrenia has been associated with altered structure and function of the cerebellum. Understanding of any brain alterations in people with schizophrenia may provide insight into changes in brain development associated with the illness onset or progression. Reviews contained in this technical summary encompass both structural (MRI) and functional imaging investigations (fMRI, PET), as well as metabolic imaging (MRS) of the cerebellum in schizophrenia. Several studies have utilized a voxel-based method of meta-analysis known as Anatomical (or Activation, in functional studies) Likelihood Estimation. This analysis estimates consistent regions of altered grey or white matter among studies. For ease of description, the results reported in these studies are referred to here as “volume” or “density” changes, though it is recognized that they are not exclusively representing alterations of regional volume.

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

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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 fourteen systematic reviews that met our inclusion criteria[3-16].

Structural changes: MRI and DTI

- Moderate quality evidence suggests significant reductions of grey matter in the bilateral cerebellum of people with chronic or first episode schizophrenia, particularly treatment naïve patients.
- Moderate to low quality evidence suggests reduced white matter integrity (fractional anisotropy) in the cerebellum.
- High quality evidence suggests no difference in reduction of cerebellum volume over time in schizophrenia compared to controls.

Functional changes: fMRI, PET, MRS

- Moderate to low quality evidence suggests changes in functional activity in the cerebellum in people with schizophrenia were most frequently identified during motor, cognitive/executive, and emotional tasks.
- Moderate quality evidence suggests functional activation is decreased in the left cerebellum during episodic memory retrieval tasks.
- Moderate to low quality evidence suggests functional activity in the cerebellum in first degree relatives of people with schizophrenia is reduced compared to controls during working memory tasks, with no differences during cognitive control, long-term memory, and language processing tasks.

Cerebellum

Abbott C, Bustillo J

What have we learned from proton magnetic resonance spectroscopy about schizophrenia? A critical update

Current Opinion in Psychiatry 2006; 19(2): 135-9

View review abstract online

Comparison	**Metabolic N-acetyl aspartate (NAA) and Creatine (Cr) activity (measured by ^{1}H-MRS) in people with schizophrenia vs. healthy controls (NAA and Cr are reported as a ratio, NAA/Cr).**
Summary of evidence	**Low quality evidence (1 small study, direct, unable to assess precision or consistency) is unable to determine NAA levels.**
Vermis and cerebellum NAA/CR	
1 study, N = 28 NAA/Cr levels were decreased in chronic schizophrenia.	
Consistency in results‡	No measure of heterogeneity is reported.
Precision in results§	No confidence intervals are reported.
Directness of results‖	Direct

Achim AM, Lepage M

Episodic memory-related activation in schizophrenia: meta-analysis

British Journal of Psychiatry 2005; 187: 500-509

View review abstract online

Comparison	**Functional activation in people with schizophrenia vs. healthy controls during episodic memory retrieval tasks.**
Summary of evidence	**Moderate quality evidence (large sample sizes, direct, unable to assess precision and consistency) suggests significant decreases in functional activation during episodic memory retrieval tasks in the left cerebellum of people with schizophrenia.**

Cerebellum functional activation	
Reduced activation in schizophrenia patients compared to controls for episodic memory retrieval tasks; 11 observational studies, N = 298 Left cerebellum: Talairach coordinates (-22, -62, -42) ALE: 0.00675 Voxel probability: 0.000003	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Chan RCK, Di X, McAlonan GM, Gong Q

Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, andChronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of IllnessProgression

Schizophrenia Bulletin 2011; 37(1) 177-188

View review abstract online

Comparison	**Grey matter volume in people with first-episode schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess consistency or precision) suggests people with first-episode schizophrenia have grey matter reductions in the right cerebellum compared to healthy controls and high risk individuals. People with chronic schizophrenia showed greater reduction in the left cerebellum compared to people with first-episode schizophrenia.**
Cerebellum grey matter volume	

Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies.

FWHM 10mm, FDR corrected at $p < 0.01$

14 studies, N = 1082

First-episode schizophrenia, right cerebellum: Talairach coordinates (28, -44, -34), cluster 184mm^3, ALE 0.0117

Greater grey matter reduction in people with first-episode schizophrenia compared to people at high risk for psychosis;

Right cerebellum: Talairach coordinates (28, -44, -34), cluster 320mm^3, ALE 0.0116

Greater grey matter reduction in people with chronic schizophrenia compared to people with first-episode schizophrenia;

Left cerebellum: Talairach coordinates (-2, -70, -4), cluster 168mm^3, ALE 0.0124

Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E

The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis

American Journal of Psychiatry 2008; 165(8): 1015-23

View review abstract online

Comparison	**Grey matter volume in people with first-episode schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess consistency or precision) suggests grey matter reductions in the left cerebellum in people with first-episode schizophrenia.**

Cerebellum grey matter volume

Voxel-based morphometry whole brain grey matter volume reported at baseline.

27 studies, N = 1556

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First-episode schizophrenia: Talairach coordinates (-4, -66, -26), cluster 320mm^3, ALE 0.008, p = 0.0008	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Fornito A, Yucel M, Patti J, Wood SJ, Pantelis C

Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies

Schizophrenia Research 2009; 108(1-3): 104-113

View review abstract online

Comparison	**Grey matter volume and grey matter concentration (grey matter as a proportion of the whole brain volume), using voxel-based morphometry structural MRI analysis in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests significant reductions in grey matter volume and concentrations in the left cerebellum of people with schizophrenia.**

Cerebellum grey matter volume and concentration

Meta-analysis was performed using Activation Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies.

FWHM 12mm, FDR corrected at $p < 0.05$

Clusters where GMC reductions were significantly more frequent than GMV reductions

37 studies, N = 3336

Left cerebellum: Talairach coordinates (-1.35, -70.86, -3.42), Voxel cluster size 336mm^3, ALE 0.73 x 10^{-3}

Clusters where GMV reductions were significantly more frequent than GMC reductions

Left cerebellum: Talairach coordinates (-19.99, -82.02, -16.2), Voxel cluster size 800mm^3, ALE -0.76 x 10^{-3}

Left cerebellum: Talairach coordinates (-52.75, -47.02, -22.41), Voxel cluster size 128mm^3, ALE 0.59 x 10^{-3}	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Caverzasi E, Cortesi M, Veggiotti P, Politi P, Barale F, McGuire P

Neurofunctional correlates of vulnerability to psychosis: A systematic review and meta-analysis

Neuroscience & Biobehavioral Reviews 2007; 31(4): 465-484

View review abstract online

Comparison	**Functional activity in relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Low quality evidence (one small study) is unclear as to any changes in functional activity in the cerebellum of relatives.**
Cerebellum functional activity	
1 study, N = 63 Medium effect size suggests reduced activation of cerebellum (*d* = 0.5) in non-psychotic relatives of schizophrenia patients compared to controls for visual initiation tasks.	
Consistency in results	No measure of heterogeneity 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	**Functional activity in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Low quality evidence (1 study, sample size unclear, direct, unable to assess precision and consistency) is unclear of functional activity levels in the cerebellum of people with schizophrenia.**
Cerebellum functional activity	
Cerebellum illustrated decreased FA in one study between schizophrenia patients and controls	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Leung M, Cheung C, Yu K, Yip B, Sham P, Li Q, Chua S, McAlonan G

Gray Matter in First-Episode Schizophrenia Before and After Antipsychotic Drug Treatment. Anatomical Likelihood Estimation Meta-analyses With Sample Size Weighting

Schizophrenia Bulletin 2011; 37(1): 199-211

View review abstract online

Comparison	**Grey matter changes in people with first-episode schizophrenia (treated and medication naïve) vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample size, indirect, unable to assess consistency or precision) suggests greater reduction in bilateral cerebellum in treatment naïve, first episode schizophrenia patients than healthy controls or treated first-episode schizophrenia patients.**
Cerebellum grey matter volume	

Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies.

FWHM 8mm, FDR corrected at p <0.05

Treatment naïve, first-episode schizophrenia patients

6 studies, N = 327

Left cerebellum: Talairach coordinates (-4, -50, -22), cluster 296mm^3, ALE 0.0024

Right cerebellum: Talairach coordinates (28, -42, -34), cluster 280mm^3, ALE 0.0023

Regions where grey matter reductions were larger magnitude in treatment naïve patients than treated patients;

Left cerebellum: Talairach coordinates (-4, -50, -22), cluster 200mm^3, ALE 0.0102

Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Lungu O, Barakat M, Laventure S, Debas K, Proulx S, Luck D, Stip E

The incidence and nature of cerebellar findings in schizophrenia: a quantitative review of fMRI literature

Schizophrenia Bulletin 2013; 39(4): 797-806

View review abstract online

Comparison	**Functional activity in the cerebellum of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (large sample, direct, unable to assess precision or consistency) suggests changes in functional activity in the cerebellum in patients with schizophrenia were most frequently identified during motor, cognitive/executive and emotional tasks.**

Cerebellar functional activity

From 234 fMRI studies in schizophrenia, 96 studies (41%) reported at least one focus of activation in the cerebellum in schizophrenia compared to controls during task performance.

This proportion varied considerably depending on the type of task utilised:

Motor tasks: 69.9% of studies identified cerebellum activation. Of these, 50% reported hypoactivation in schizophrenia compared to controls. Cognitive tasks: 43% of studies identified cerebellum activation Of these, 67% reported hypoactivation in schizophrenia compared to controls. Perceptual tasks: 7.7% of studies identified cerebellum activation Of these, 100% reported hypoactivation in schizophrenia compared to controls. Linguistic/language tasks: 26% of studies identified cerebellum activation Of these, 100% reported hypoactivation in schizophrenia compared to controls. Emotional tasks: 41% of studies identified cerebellum activation Of these, 46% reported hypoactivation in schizophrenia compared to controls. Executive tasks: 43% of studies identified cerebellum activation Of these, 60% reported hypoactivation in schizophrenia compared to controls.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct measures and comparison of functional activity

MacDonald AW, Thermenos HW, Barch DM, Seidman LJ

Imaging genetic liability to schizophrenia: systematic review of FMRI studies of patients' nonpsychotic relatives

Schizophrenia Bulletin 2009; 35(6): 1142-1162

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Comparison	**Functional activation in first-degree relatives of people with schizophrenia vs. healthy controls**
Summary of evidence	**Moderate to low quality evidence (large sample size, direct, unable to assess precision or consistency) suggests functional activity in the cerebellum is reduced in first-degree relatives of people with schizophrenia during working memory tasks, with no differences between relatives and controls during cognitive control tasks, long-term memory, and language processing tasks.**
Cerebellum functional activity	

Cognitive control tasks *7 studies investigated functional activity during cognitive control tasks, N = 308;* 6 studies investigated the cerebellum, 2/6 showed altered activity compared to controls. Working memory tasks *4 studies (5 independent samples) investigated functional activity during working memory tasks, N = 239;* 3 studies showed reduced activity compared to controls. Activity (hyper- and hypo-) was abnormal in 60% of reports. Long-term memory tasks *3 studies investigated functional activity during episodic long-term memory tasks, N = 195;* 2 studies showed no group differences, one showed increased activity compared to controls. *1 study investigated functional activity during procedural long term memory tasks, N = 27;* No group difference was reported. Language processing tasks *4 studies investigated functional activity during language processing tasks, N = 164;* 3/4 showed no task-related response in the cerebellum, 1/4 showed reduced activity.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM

Are There Progressive Brain Changes in Schizophrenia? A Meta-Analysis of Structural Magnetic Resonance Imaging Studies

Biological Psychiatry 2011; 70(1): 88-96

View review abstract online

Comparison	**Progressive changes in grey matter volume in people with schizophrenia vs. healthy controls.**
Summary of evidence	**High quality evidence (large sample sizes, consistent, precise, direct) suggests no differences in reductions in cerebellum volume over time between people with schizophrenia and**

	controls.
Cerebellum grey matter volume	
Progressive changes in grey matter volume reported across longitudinal MRI scans over 1-10 years. *No differences between patients and controls;* Cerebellum: N = 476, 6 studies, *d* = -0.029, 95%CI -0.17 to 0.22, *p* = 0.773, I^2 = 5.2%	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Ragland JD, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC

Prefrontal activation deficits during episodic memory in schizophrenia

American Journal of Psychiatry 2009; 166(8): 863-874

View review abstract online

Comparison	**Functional activation following episodic memory tasks in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests functional activity during episodic retrieval is reduced in the bilateral cerebellum of people with schizophrenia.**
Functional activity	
Ten studies contributing 76 foci investigated functional activity during episodic retrieval tasks. ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model *p* < 0.05 *Significantly increased activity in controls compared to schizophrenia patients;* Left cerebellum: cluster volume 1488mm^3, Talairach centre of mass (-24, -62, -42) Right cerebellum: cluster volume 624mm^3, Talairach centre of mass (30, -80, -34) *Subgroup analysis:* Seven of ten studies (63 foci) controlled for group performance differences. ALE analysis excluding those studies which did not control for performance differences, showed all	

foci had similar activation patterns.	
Consistency in results	No measure of consistency is reported, results are consistent across subgroup analyses.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Smieskova R, Fusar-Poli P, Allen P, Bendfeldt K, Stieglitz RD, Drewe J, Radue E W, McGuire PK, Riecher-Rossler A, Borgwardt SJ

The Effects of Antipsychotics on the Brain: What Have We Learnt from Structural Imaging of Schizophrenia? - A Systematic Review

Current Pharmaceutical Design 2009; 15(22): 2535-2549

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Comparison	**Grey matter volume changes in cross-sectional and longitudinal assessments in treated and untreated people with schizophrenia compared to healthy controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) is largely unclear as to the role of medication in mediating cerebellar structural alterations in people with schizophrenia.**
Cerebellum grey matter	
Two studies used VBM methodology to assess structural changes in cerebellum following administration of antipsychotics. First-episode patients treated with risperidone in the short-term showed reduced white matter in cerebellum. In early-onset patients, atypical treatment was associated with reduced cerebellar volume compared to healthy controls.	
Consistency in results	No measure of consistency is reported, results appear inconsistent.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Cerebellum

Steen RG, Hamer RM, Lieberman JA

Measurement of brain metabolites by ^{1}H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis

Neuropsychopharmacology 2005; 30(11): 1949-1962

View review abstract online

Comparison	**NAA activity (measured by ^{1}H-MRS) in grey matter regions in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Low quality evidence (sample size unclear, direct, inconsistent, unable to assess precision) is unclear of NAA levels in the cerebellum.**
NAA levels	
3 studies, N is unclear Patient average 92.3% of control levels	
Consistency in results	Significant heterogeneity reported, $p<0.0001$.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Explanation of acronyms

ALE = activation likelihood estimate, CI = Confidence Interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardized mean differences (see below for interpretation of effect size), FA = fractional anisotropy, FDR = false discovery rate correction for multiple comparisons, fMRI = functional magnetic resonance imaging, FWHM = full-width at half maximum smoothing kernel, GMC = grey matter concentration, GMV = grey matter volume, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PET = positron emission tomography, SPECT = single-photon emission computed tomography, Q = Q statistic (chi-square) for the test of heterogeneity, vs = versus

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 [17].

† 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, 0.5 a medium effect, and over 0.8 represents a large effect [17].

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[18]. 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).

‡ 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[19].

‖ 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.

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal*. 2009; **151**(4): 264-9.
2. GRADEWorkingGroup. Grading quality of evidence and strength of recommendations. *British Medical Journal*. 2004; **328**: 1490.
3. Abbott C, Bustillo J. What have we learned from proton magnetic resonance spectroscopy about schizophrenia? A critical update. *Current Opinion in Psychiatry*. 2006; **19**(2): 135-9.
4. Achim AM, Lepage M. Episodic memory-related activation in schizophrenia: meta-analysis. *British Journal of Psychiatry*. 2005; **187**: 500-9.
5. Fornito A, Yucel M, Patti J, Wood SJ, Pantelis C. Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophrenia Research*. 2009; **108**(1-3): 104-13.
6. Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Caverzasi E, Cortesi M, Veggiotti P, Politi P, Barale F, McGuire P. Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*. 2007; **31**(4): 465-84.
7. 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): 255-73.
8. Steen RG, Hamer RM, Lieberman JA. Measurement of brain metabolites by 1H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis. *Neuropsychopharmacology*. 2005; **30**(11): 1949-62.
9. MacDonald AW, 3rd, Thermenos HW, Barch DM, Seidman LJ. Imaging genetic liability to schizophrenia: systematic review of FMRI studies of patients' nonpsychotic relatives. *Schizophrenia Bulletin*. 2009; **35**(6): 1142-62.
10. Ragland JD, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC. Prefrontal activation deficits during episodic memory in schizophrenia. *American Journal of Psychiatry*. 2009; **166**(8): 863-74.
11. Chan RCK, Di X, McAlonan GM, Gong Q-y. Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and Chronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression. *Schizophrenia Bulletin*. 2009.
12. Leung M, Cheung C, Yu K, Yip B, Sham P, Li Q, Chua S, McAlonan G. Gray Matter in First-Episode Schizophrenia Before and After Antipsychotic Drug Treatment. Anatomical Likelihood Estimation Meta-analyses With Sample Size Weighting. *Schizophrenia Bulletin*. 2009.
13. Smieskova R, Fusar-Poli P, Allen P, Bendfeldt K, Stieglitz RD, Drewe J, Radue EW, McGuire PK, Riecher-Rossler A, Borgwardt SJ. The Effects of Antipsychotics on the Brain: What Have We Learnt from Structural Imaging of Schizophrenia? - A Systematic Review. *Current Pharmaceutical Design*. 2009; **15**(22): 2535-49.
14. Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *American Journal of Psychiatry*. 2008; **165**(8): 1015-23.
15. Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM. Are There Progressive Brain Changes in Schizophrenia? A Meta-Analysis of Structural Magnetic Resonance Imaging Studies. *Biological Psychiatry*. 2011.
16. Lungu O, Barakat M, Laventure S, Debas K, Proulx S, Luck D, Stip E. The Incidence and Nature of Cerebellar Findings in Schizophrenia: A Quantitative Review of fMRI Literature. *Schizophrenia Bulletin*. 2012.
17. CochraneCollaboration. Cochrane Handbook for Systematic Reviews of Interventions. 2008: Accessed 24/06/2011.
18. Rosenthal JA. Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research*. 1996; **21**(4): 37-59.

19. GRADEpro. [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*. 2008.