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 23 systematic reviews that met our inclusion criteria[3-25].

Structural changes

- Moderate quality evidence found significant reductions of grey matter in the bilateral cerebellum of people with chronic or first-episode schizophrenia, particularly treatment naïve patients.
- Moderate quality evidence found white matter reductions in the bilateral cortico-ponto-cerebellum tract, and in the bilateral inferior and superior cerebellar penduculus of people with schizophrenia compared to controls.
- High quality evidence found no changes in the reduction of cerebellum volume over time (1-10 years).
- Moderate to high quality evidence suggests better overall functioning was associated with larger cerebellum volume.
- Moderate to low quality evidence showed reduced white matter volume in the cerebellum was associated with increased severity of neurological soft signs in people with schizophrenia.

Functional changes

- Moderate to high quality evidence found decreased functional activity in the right cerebellum (lobule VIII and crus I) and the left cerebellum (lobule IX), with no increases in functional activity. Functional connectivity strength was reduced in the left cerebellum (lobule IV/V) extending to the left fusiform gyrus (BA 30) and increased in the left cerebellum (crus I/II) of medication-naïve people with first-episode schizophrenia.
- Moderate quality evidence found reductions in functional activation in the left cerebellum of people with schizophrenia (vs. controls) during episodic memory retrieval tasks. There was reduced activity in the right cerebellum lobule VI during explicit threat processing, and decreased activity in the fusiform gyrus extending into the cerebellum lobule IV/VI during implicit threat processing in people with schizophrenia compared to controls. There was decreased activity in the cerebellum during reward anticipation tasks. There was increased activation in the cerebellum of people with schizophrenia during facial emotion recognition tasks.
- Moderate to low quality evidence found functional activity in the cerebellum of first-degree relatives of people with schizophrenia is reduced (compared to controls) during working memory and executive functioning, with no differences during cognitive control, long-term memory, or language processing.
- Moderate to low quality evidence found increased activation in the cerebellum during auditory hallucinations in people with schizophrenia.
- Moderate quality evidence suggests decreased metabolic N-acetyl aspartate in the cerebellum of people with schizophrenia.

Structural and functional changes

- Moderate quality evidence found increased grey matter volume and decreased functional activity in the left cerebellum and increased grey matter volume and increased

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functional activity in the left cerebellum (lobule IX).

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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 to low quality evidence (medium-sized sample, direct, unable to assess precision and consistency) found reductions in functional activation in the left cerebellum of people with schizophrenia during episodic memory retrieval tasks.**
Cerebellum functional activation	
Reduced activation in the left cerebellum of patients during episodic memory retrieval tasks; 11 studies, N = 298, 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

Alustiza I, Radua J, Pla M, Martin R, Ortuno F

Meta-analysis of functional magnetic resonance imaging studies of timing and cognitive control in schizophrenia and bipolar disorder: Evidence of a primary time deficit

Schizophrenia Research 2017; 188: 21-32

View online review abstract

Comparison	**Brain activation during cognitive control tasks in people with schizophrenia vs. controls.** **Cognitive control is defined as the level of perceived difficulty of**

	the cognitive task and the subsequent mental effort that an individual applies to achieve the cognitive aim.
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) finds decreased activation during cognitive control tasks in the left cerebellum.**
Brain activity	
29 studies, N = 2,268 *Significant, decreased activation in people with schizophrenia was found in the left cerebellum.*	
Consistency in results	Unable to assess; no measure of consistent is reported.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
Directness of results	Direct

Brugger S, Davis JM, Leucht S, Stone JM

Proton magnetic resonance spectroscopy and illness stage in schizophrenia – a systematic review and meta-analysis

Biological Psychiatry 2011; 69: 495-503

View review abstract online

Comparison	**Comparison of metabolic N-acetyl aspartate (NAA) activity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, consistent, direct, unable to assess precision) suggests decreased NAA in the cerebellum of people with schizophrenia.**
NAA	
Significant, medium-sized reductions of NAA in the cerebellum of people with schizophrenia; 5 studies, N = 183, *d* = -0.50 95%CI not reported, *p* = 0.01, I^2 = 35%, Q*p* = 0.17	
Consistency in results	Consistent
Precision in results	Unable to assess; no measure of precision is reported.

Directness of results	Direct

Chan RCK, Di X, McAlonan GM, Gong Q

Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and Chronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression

Schizophrenia Bulletin 2011; 37(1) 177-188

View review abstract online

Comparison	**Cerebellum grey matter volume in people with first-episode schizophrenia vs. controls, people at high risk, and people with chronic schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found people with first-episode schizophrenia have grey matter reductions in the right cerebellum compared to 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

14 studies, N = 1,082

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

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 in;

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 in;

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

Cooper D, Barker V, Radua J, Fusar-Poli P, Lawrie SM

Multimodal voxel-based meta-analysis of structural and functional magnetic resonance imaging studies in those at elevated genetic risk of developing schizophrenia

Psychiatry Research - Neuroimaging 2014; 221(1): 69-77

View review abstract online

Comparison	**Comparison of functional activity in relatives of people with schizophrenia vs. controls during various tasks.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) suggest relatives show decreased activity in the left cerebellum.**
Functional activation or failure of deactivation	
13 studies, N = 561 *Relatives showed decreased activation in;* Left cerebellum: Talairach coordinates -2, -80, -14, p = 0.001	
Consistency in results	Authors report the results are consistent.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Ding Y, Ou Y, Pan P, Shan X, Chen J, Liu F, Zhao J, Guo W

Cerebellar structural and functional abnormalities in first episode and drug-naive patients with schizophrenia: A meta-analysis

Psychiatry Research - Neuroimaging 2019; 283: 24-33

View review abstract online

Comparison	**Cerebellar functionality in medication-naïve people with first-episode schizophrenia vs. controls.**

Cerebellum

Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) suggests decreased functional activity in the right cerebellum (lobule VIII and crus I) and left cerebellum (lobule IX), with no increases in functional activity. Functional connectivity strength was reduced in the left cerebellum (lobule IV/V) extending to the left fusiform gyrus (BA 30) and increased functional connectivity strength in the left cerebellum (crus I/II) in medication-naïve people with first-episode schizophrenia.**
Cerebellar functionality	
Functional activity 8 studies, N = 689 *Decreased functional activity was found in;* Right cerebellum, hemispheric lobule VIII: MNI coordinates 22, -62, -58, *p* = 0.000366390 Left cerebellum, hemispheric lobule IX: MNI coordinates -12 -58 -42, *p* = 0.000397384 Right cerebellum, crus I: MNI coordinates 48, -58, -32, *p* = 0.002353311 There were no increases in functional activity. Functional connectivity strength 3 studies, N = 188 *Decreased functional connectivity strength in;* Left cerebellum, hemispheric lobule IV/V: MNI coordinates -22, -34, -24, *p* = 0.000428319 Extending to the left fusiform gyrus, BA 30: MNI coordinates -20 -44 -16, *p* = 0.000185788 *Increased functional connectivity strength in;* Left cerebellum, crus II: MNI coordinates -16 -78 -34, *p* = 0.000015497 Left cerebellum, crus I: MNI coordinates -8 -70 -28, *p* = 0.000061929	
Consistency in results	Authors report consistent results.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Dong D, Wang Y, Jia X, Li Y, Chang X, Vandekerckhove M, Luo C, Yao D

Abnormal brain activation during threatening face processing in

schizophrenia: A meta-analysis of functional neuroimaging studies **Schizophrenia Research 2018; 197: 200-208** View review abstract online	
Comparison	**Functional activity during threatening face processing in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests decreased activity in the right cerebellum lobule VI during explicit threat processing, and decreased activity in the fusiform gyrus extending into the cerebellum lobule IV/VI during implicit threat processing.**
Functional activity	
19 studies, N = 728 Explicit threat processing *Decreased activity in;* Right cerebellum lobule VI: 200 voxels, MNI coordinates 32, -74, -24, $p < 0.001$ Implicit threat processing *Decreased activity in;* Fusiform gyrus extending into cerebellum lobule IV/VI: 2,137 voxels, MNI coordinates 26, 4, 88, $p < 0.001$	
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

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	**Cerebellum grey matter volume in people with first-episode**

	schizophrenia vs. controls.
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess consistency or precision) found grey matter reductions in the left cerebellum in people with first-episode schizophrenia.**
Cerebellum grey matter volume	
27 studies, N = 1,556 *Greater grey matter reduction in people with first-episode schizophrenia compared to controls in;* Left cerebellum: 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	**Cerebellum grey matter volume and grey matter concentration (grey matter as a proportion of the whole brain volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) found reductions in grey matter volume and concentrations in the left cerebellum of people with schizophrenia.**
Cerebellum grey matter volume and concentration	
Clusters where GMC reductions were significantly more frequent than GMV reductions; 37 studies, N = 3,336 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

Gao X, Zhang W, Yao L, Xiao Y, Liu L, Liu J, Li S, Tao B, Shah C, Gong Q, Sweeney JA, Lui S

Association between structural and functional brain alterations in drug-free patients with schizophrenia: A multimodal meta-analysis

Journal of Psychiatry and Neuroscience 2018; 43: 131-42

View review abstract online

Comparison	**Overlap between regions of functional and structural alteration in drug-free people with first-episode schizophrenia vs. controls.** **Note; most patients were drug naïve.**
Summary of evidence	**Moderate quality evidence (large sample, mostly consistent, direct, unable to assess precision) suggests increased grey matter volume and decreased functional activity in the left cerebellum and increased grey matter volume and increased functional activity in the left cerebellum (lobule IX).**
Structural and functional alteration	
15 structural MRI studies, N = 971, 16 functional MRI studies, N = 831 *Significant increased grey matter volume and decreased functional activity in;* Left cerebellum: 1,170 voxels, MNI coordinates -6, -28, -18, $p < 0.001$ *Significant increased grey matter volume and increased functional activity in;* Left cerebellum, lobule IX: 327 voxels, MNI coordinates -12, -56, -46, $p < 0.001$	

Consistency in results	Authors report most findings were consistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Goghari MV

Executive functioning-related brain abnormalities associated with the genetic liability for schizophrenia: an activation likelihood estimate meta-analysis

Psychological Medicine 2001; 41: 1239-1252

View review abstract online

Comparison	**Whole brain comparison of functional activation in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests relatives show decreased functional activation during executive functioning in the left cerebellum.**
Functional activity	
17 studies, N = 456 *Decreased activity during executive functioning in relatives of people with schizophrenia;* Left cerebellum: Talairach coordinates -8/-14, -42/-40, -32/-38, cluster volume 168 mm^3	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Haijma SV, Van Haren N, Cahn W, Koolschijn PCMP, Hulshoff Pol HE, Kahn RS

Brain volumes in schizophrenia: a meta-analysis in over 18000 subjects

Cerebellum

Schizophrenia Bulletin 2012; 39(5): 1129-1138 View review abstract online	
Comparison	**Cerebellum grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, mostly inconsistent, direct) suggests schizophrenia is associated with reductions in the grey matter volume of the cerebellum.**
Cerebellum grey matter volume	
Decreased in medicated patients; Cerebellum: 20 studies, N = 1,402, d = -0.15, 95%CI -0.30 to -0.01, p = 0.035, Q = 29.4, p = 0.06, I^2 = 35.3%	
Consistency in results	Mostly inconsistent
Precision in results	Precise
Directness of results	Direct

Huhtaniska S, Jaaskelainen E, Hirvonen N, Remes J, Murray GK, Veijola J, Isohanni M, Miettunen J

Long-term antipsychotic use and brain changes in schizophrenia - a systematic review and meta-analysis

Human Psychopharmacology 2017; 32: doi: 10.1002/hup.2574

View review abstract online

Comparison	**Association between long-term antipsychotic dose and changes in brain regions over time (>2 years) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) suggests antipsychotic dose is not associated with changes in cerebellum volume.**
Longitudinal changes in volume	

There were no associations between long-term antipsychotic use and; Cerebellum: 3 studies, N = 296, r = 0.01, 95%CI -0.10 to 0.13, $p > 0.05$, I^2 = 0% There were no moderating effects of antipsychotic type (first vs. second generation).	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Kompus K, Westerhausan R, Hugdahl K

The "paradoxical" engagement of primary auditory cortex in patients with auditory verbal hallucinations: a meta-analysis of functional neuroimaging studies

Neuropsychologia 2011; 49: 3361-9

View review abstract online

Comparison	**Functional activation in people with schizophrenia during auditory verbal hallucinations.**
Summary of evidence	**Moderate to low quality evidence (small sample, direct, unable to assess precision or consistency) suggests increased activation in the cerebellum during auditory hallucinations in people with schizophrenia.**
During hallucinations (endogenously evoked)	
12 studies, N = 103, showed increased activation during hallucinations in; Cerebellum: Talairach coordinates 20, -46, -16, cluster volume 248mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Leroy A, Amad A, D'Hondt F, Pins D, Jaafari N, Thomas P, Jardri R

Reward anticipation in schizophrenia: A coordinate-based meta-analysis

Schizophrenia Research 2020; Jan: doi.org/10.1016/j.schres.2019.12.041

View review abstract online

Comparison	**Functional activity during reward anticipation in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found reduced activation in the cerebellum during reward anticipation in people with schizophrenia.**
Functional activation	
11 studies, N = 488 *Schizophrenia was characterised by;* Reduced activation in the cerebellum	
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

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	**Cerebellum grey matter changes in people with first-episode schizophrenia (treated and medication naïve) vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large sample, direct, unable to assess consistency or precision) found reductions in the bilateral cerebellum in treatment-naïve, first-episode patients compared to controls. Only the left cerebellum was reduced in the**

	comparison with treated first-episode patients.
Cerebellum grey matter volume	
Grey matter reductions in treatment-naïve patients compared to controls; 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 *Grey matter reductions in treatment-naïve patients compared to 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

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

View review abstract online

Comparison	**Cerebellum functional activity in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, 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	

Working memory tasks *4 studies investigated functional activity during working memory tasks, N = 239;* 3/4 studies showed reduced activity compared to controls. Activity (hyper- or hypo-) was abnormal in 60% of reports. 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. 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 cerebellum grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) found no changes in cerebellum volume over time between people with schizophrenia and controls.**

Cerebellum grey matter volume	
No differences between patients and controls over 1-10 years; 6 studies, N = 476, *d* = -0.029, 95%CI -0.17 to 0.22, *p* = 0.773, I^2 = 5%	
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	**Cerebellum functional activity during episodic memory tasks in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to quality evidence (unclear sample size, direct, unable to assess precision or consistency) found reduced functional activity during episodic retrieval in the bilateral cerebellum of people with schizophrenia.**
Functional activity	
10 studies, N = unclear *Significantly decreased activity in patients in;* 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	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Sugranyes G, Kyriakopoulos M, Corrigall R, Taylor E, Frangou S

Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition

PLoS ONE 2011; 6(10): e25322

View review abstract online

Comparison	**Functional activation during social cognition processing in schizophrenia vs. autism spectrum disorders.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests increased activation in the cerebellum of people with schizophrenia during facial emotion recognition tasks.**
Facial emotion recognition	
17 studies, N = 511 *The following clusters showed increased activation in schizophrenia vs. autism spectrum disorders;* Left cerebellum culmen: Talairach coordinates -30, -46, -20, cluster volume 352mm^3 Right cerebellum culmen: Talairach coordinates 32, -44, -18, cluster volume 304mm^3 Left cerebellum declive: Talairach coordinates -30, -76, -20, cluster volume, 384mm^3 Right cerebellum declive: Talairach coordinates 26, 68, -14, cluster volume 376mm^3	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
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.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found white matter reductions in the bilateral cortico-ponto-cerebellum tract, and bilateral inferior and superior cerebellar penduculus.**
FA	
34 studies, N = 2,231 *There were white matter reductions in;* Left inferior cerebellar penduculus: 5,648 voxels, MNI coordinates -7, -33, -22, p = 0.000235 Right inferior cerebellar penduculus: 5,302 voxels, MNI coordinates 14, -38, -31, p = 0.000502 Left superior cerebellar penduculus: 8,012 voxels, MNI coordinates -7, -31, -22, p = 0.000772 Right superior cerebellar penduculus: 8,113 voxels, MNI coordinates 13, -24, -7, p = 0.000741 Left cortico-ponto-cerebellum tract: 2,176 voxels, MNI coordinates 16, -37, -32, p = 0.000226 Right cortico-ponto-cerebellum tract: 766 voxels, MNI coordinates 25, -17, 5, p = 0.000206	
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

Wojtalik JA, Smith MJ, Keshavan MS, Eack SM

A Systematic and Meta-analytic Review of Neural Correlates of Functional Outcome in Schizophrenia

Schizophrenia Bulletin 2017; 43: 1329-47

View review abstract online

Comparison	**Association between functional outcomes and grey matter volume in people with schizophrenia.** **Functional outcomes include global functioning, social functioning, resource needs, quality of life, socioeconomic status, independent living, employment, and role functioning.**
Summary of evidence	**Moderate to high quality evidence (unclear sample size, consistent, precise, direct) suggests better overall functioning**

	was associated with larger cerebellum volume.
Brain volume and functional outcome	
Better functioning was associated with larger volumes in; Cerebellum: 4 studies, r = 0.17, 95%CI 0.09 to 0.26, p < 0.0001, Q = 10.96, p > 0.05	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Zhao Q, Li Z, Huang J, Yan C, Dazzan P, Pantelis C, Cheung EFC, Lui SSY, Chan RCK

Neurological soft signs are not "soft" in brain structure and functional networks: evidence from meta-analysis

Schizophrenia Bulletin 2013, doi:10.1093/schbul/sbt063

View review abstract online

Comparison	**Localised brain regions associated with neurological soft signs in patients with schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) showed reduced white matter volume in the cerebellum was associated with increased severity of neurological soft signs in people with schizophrenia.**
Neurological soft signs	
NSS severity correlated with white matter volume in: Cerebellar culmen: Talairach coordinates 0, -56, -16	
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

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, 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), 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 [26].

† 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 [26].

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[27]. 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[28].

‖ 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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