TECHNICAL COMMENTARY

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Hippocampus

Introduction

The hippocampus is located deep within the medial temporal lobe and has extensive connections, largely to cortical association areas including the sensory modalities. This widespread connectivity facilitates multimodal integration of sensory information, and likely contributes to the role of the hippocampus in generating memory and facilitating spatial navigation. The medial temporal lobes, particularly the hippocampus and the surrounding cortical regions, have been implicated as crucial facilitators in the formation of new declarative memories.

Schizophrenia has been associated with altered structure and function of the hippocampus. Understanding brain alterations in people with schizophrenia may provide insight into changes in brain development associated with the illness onset or progression. The hippocampus is often identified in imaging studies as a complex with the amygdala, due to their close spatial proximity. Reviews contained in this technical summary encompass both structural imaging investigations (MRI, DTI), and functional imaging (fMRI, PET), as well as metabolic investigations (MRS) of the hippocampus in schizophrenia.

Method

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

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

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Results

We found eighteen systematic reviews that met our inclusion criteria[3-20].

Structural changes: MRI and DTI

- High quality evidence suggests there are hippocampal grey matter reductions in chronic and first-episode schizophrenia compared to controls. Moderate to high quality evidence suggests first-degree relatives of people with schizophrenia also have reduced hippocampal volume compared to controls.
- Moderate quality evidence suggests there are reductions in white matter integrity in the hippocampus, entorhinal gyrus, and parahippocampal gyrus in people with schizophrenia.
- Moderate to low quality evidence suggests increased hippocampal volume after treatment with second generation antipsychotics.

Functional changes: fMRI, PET and MRS

- Moderate quality evidence suggests decreased activation in the hippocampus of people with schizophrenia during memory encoding and retrieval tasks. Moderate to low quality evidence suggests decreased activation of the parahippocampus during emotion processing tasks.
- Moderate to low quality evidence suggests decreased hippocampal N-acetyl aspartate/creatine (NAA/Cr) ratio in people with schizophrenia and their first-degree relatives of people when compared to controls.

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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 activity (measured by ^{1}H-MRS) in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Low quality evidence (small samples, direct, unable to assess precision or consistency) is uncertain of N-acetyl aspartate/creatine (NAA/Cr ratio) and glutamate (Glu) levels in schizophrenia.**
NAA/Cr	
NAA/Cr levels were decreased in people with schizophrenia; 1 study, N = 30 *Glu levels were increased in people with chronic schizophrenia with acute exacerbation;* 1 study, N = 42	
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	**Whole brain comparison of functional activation in people with schizophrenia vs. healthy controls during episodic memory tasks.**

Summary of evidence	**Moderate quality evidence (medium to large sample sizes, direct, unable to assess precision and consistency) suggests decreased activation in the hippocampus of people with schizophrenia during memory encoding and retrieval tasks.**
Activation during memory encoding tasks	
Reduced activation in people with schizophrenia; 8 studies, N = 176 Right posterior hippocampus: Talairach coordinates (20, -34, 2) ALE: 0.003231 Voxel probability: 0.000141	
Activation during memory retrieval tasks	
Reduced activation in in people with schizophrenia 11 studies, N = 298 Left hippocampus: Talairach coordinates (-30, -14, -20) ALE: 0.005559 Voxel probability: 0.000034	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Boos HB, Aleman A, Cahn W, Hulshoff Pol H, Kahn RS

Brain volumes in relatives of patients with schizophrenia: a meta-analysis

Archives of General Psychiatry 2007; 64(3): 297-304

View review abstract online

Comparison 1	**Hippocampal volume in first-degree relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large sample sizes, direct, mostly consistent, precise) suggests first-degree relatives have reduced hippocampal volume compared to healthy controls.**
Grey matter volume	

Hippocampus

Amygdala and hippocampus volume combined *Medium combined effect size for decreased amygdala and hippocampus volume in first-degree relatives compared to healthy controls;* N = 1280, 12 studies, *d* = 0.52 95%CI 0.16 to 0.89, *p* < 0.05, Q = 94.17, *p* < 0.001 Hippocampus volume *Small effect size for decreased total hippocampal volume in first-degree relatives compared to healthy controls;* N = 1024, 9 studies, *d* = 0.31 95%CI 0.13 to 0.49, *p* < 0.05, Q = 13.79, *p* = 0.09, FSN = 18 *Medium effect size for decreased left hippocampal volume in first-degree relatives compared to healthy controls;* N = 943, 9 studies, *d* = 0.47 95%CI 0.34 to 0.61, *p* < 0.05, Q = 6.56, *p* = 0.58 *Small effect size for decreased right hippocampal volume in first-degree relatives compared to healthy controls;* N = 943, 9 studies, *d* = 0.23 95%CI 0.01 to 0.96 *p* < 0.05, Q = 19.43, *p* = 0.01	
Consistency in results	Inconsistent
Precision in results	Precise except for right hippocampal volume.
Directness of results	Direct
Comparison 2	**Hippocampus volume in first-degree relatives vs. people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, precise, direct) suggests people with schizophrenia have reduced hippocampal volume compared to first-degree relatives.**
Grey matter volume	
Medium effect size for decreased hippocampal volume in people with schizophrenia compared to first-degree relatives N = 846, 9 studies, *d* = 0.43, 95%CI 0.17 to 0.68, Q = 22.28, *p* = 0.004	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

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Davidson LL, Heinrichs RW

Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: a meta-analysis

Psychiatry Research 2003; 122(2): 69-87

View review abstract online

Comparison 1	**Grey matter volume in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample, mostly inconsistent, precise, direct) suggests grey matter volume is significantly reduced in the hippocampus in schizophrenia.**
Grey matter volume	
Left hippocampus *Medium effect size suggests reduced volume in schizophrenia;* N = 1919, *d* = -0.55, 95%CI -0.74 to -0.36, *p* not reported, SD = 0.51, FSN = 140 Right hippocampus *Medium effect size suggests reduced volume in schizophrenia;* N = 1814, *d* = -0.58, 95%CI -0.74 to -0.41, *p* not reported, SD = 0.44, FSN = 144 Left hippocampus/amygdala complex *Medium effect size suggests reduced volume in schizophrenia;* N = 1302, *d* = -0.41, 95%CI -0.74 to -0.41, *p* not reported, SD = 0.44, FSN = 71 Right hippocampus/amygdala complex *Small effect size suggests reduced volume in schizophrenia;* N = 1238, *d* = -0.36, 95%CI -0.54 to -0.18, *p* not reported, SD = 0.40, FSN = 57	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Functional activity in people with schizophrenia vs. healthy controls during cognitive tasks.**

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Summary of evidence	**Moderate to low quality evidence (large sample size, inconsistent, imprecise, direct) suggests no differences in hippocampus functional activity during cognitive tasks.**
Functional activity	
Left hippocampus *No effect on activity in schizophrenia;* N = 415, *d* = 0.13, 95%CI -0.69 to 0.43, SD = 0.78, FSN = 3 Right hippocampus *No effect on activity in schizophrenia;* N = 415, d = -0.07, 95%CI -0.60 to 0.46, SD = 0.74, FSN <0.1	
Consistency in results	Inconsistent
Precision in results	Imprecise
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. people with chronic schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess consistency or precision) suggests reduced grey matter in the hippocampus in chronic schizophrenia.**
Grey matter volume	
N = 1556, 27 studies Significant reduction of volume was seen in the hippocampus, *p* = 0.0004	

Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
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 (GMV) and grey matter concentration (GMC, grey matter as a proportion of the whole brain volume) in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests grey matter reductions in the hippocampus of people with schizophrenia.**

Grey matter volume

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

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

37 studies, N = 3336

Clusters where GMC reductions were significantly more frequent than GMV reductions;

Left amygdala/hippocampus: Talairach coordinates (-18.33, -4.63, -15.34), Voxel cluster size 1592mm^3, ALE 0.98 x 10^{-3}

Left hippocampal formation: Talairach coordinates (-30.51, -34.78, -12.2), Voxel cluster size 240mm^3, ALE 0.65 x 10^{-3}

As GMC had fewer foci available for comparison, a random subset was initially selected for comparison with GMV. To increase validity of this comparison, four additional GMC/GMV contrasts were performed with different GMC subsets, and demonstrated high consistency between randomisations.

Both cluster size and ALE statistic were larger for comparisons using concentration measures

compared to volume measures; Cluster size t = 2.54, *p* = 0.02 ALE statistic t = 2.82, p = 0.01	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are provided.
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	**Metabolite levels (measured by ^{1}H-MRS) in first-degree relatives of people with schizophrenia vs. healthy controls (NAA and Cr are reported as a ratio, NAA/Cr).**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess precision and inconsistency) suggests reduced NAA/Cr in the hippocampus of relatives when compared to controls.**
NAA/Cr	
4 studies, N = 268 Reduced NAA/Cr in relatives	
Consistency in results	No measured of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL, Bullmore

E, Fox PT

Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis

Biological Psychiatry 2008; 64(9): 774-781

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Comparison	**Grey matter volume in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests schizophrenia is associated with significant grey matter reductions in the parahippocampal gyrus.**

Grey matter volume

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

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

13 studies, N = 2457

Clusters where schizophrenia patient density reductions were significantly more frequent than control reductions;

Left parahippocampal gyrus: Talairach coordinates (-18, -2, -16), Voxel cluster size 2504mm^3, $p < 0.01$, ALE = 0.018

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

Honea R, Crow TJ, Passingham D, Mackay CE

Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies

American Journal of Psychiatry 2005; 162(12): 2233-2245

View review abstract online	
Comparison	**Grey matter volume in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests schizophrenia is associated with significant reductions in the grey matter density of the parahippocampal gyrus.**
Grey matter volume	
15 studies, N = 754, varying FWHM smoothing kernel (range 4-12mm) *Regions showing reduced grey matter density in people with schizophrenia;* Left parahippocampal gyrus: reduced in around 50% of studies	
Consistency in results	No measure of heterogeneity is reported, appears inconsistent.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

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

Diffusion tensor imaging in schizophrenia

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

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Comparison	**White matter fractional anisotropy (FA) in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to fully assess precision and consistency) suggests decreased FA in the parahippocampal gyrus in people with schizophrenia.**
White matter volume	
19 studies, N = 640 Parahippocampal gyrus illustrated decreased FA in at least one study between people with schizophrenia and controls.	

Hippocampus did not show reduced FA, no significant difference between people with schizophrenia and controls	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct comparison of white matter integrity between people with schizophrenia and controls

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	**White matter integrity in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (sample size unclear, direct, unable to assess precision and consistency) suggests reduced white matter integrity in the hippocampus and the entorhinal gyrus in people with schizophrenia.**
White matter volume	
17 studies, N = unclear 8 studies report decreases in the hippocampus and entorhinal gyrus in schizophrenia.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Li H, Chan R, McAlonan G, Gong Q-Y

Facial emotion processing in schizophrenia: A meta-analysis of functional neuroimaging data

Schizophrenia Bulletin 2010; 36(5): 1029-1039

View review abstract online

Comparison	**Functional activation in people with schizophrenia vs. controls during a facial emotion processing task.**
Summary of evidence	**Moderate to low quality evidence (unclear samples, direct, unable to assess consistency or precision) suggests decreased activation during emotion processing tasks in the parahippocampus of people with schizophrenia.**

Activation during a facial emotion processing task

Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis.

13 studies reported reduced activation in people with schizophrenia compared to controls during an emotion perception task ;

Right parahippocampal gyrus/amygdala: Talairach coordinates (26, -8, -12), 4 foci, 368mm^3, 0.052 ALE

Left parahippocampal gyrus/amygdala: Talairach coordinates (-26, -10, -13), 3 foci, 272mm^3, 0.060 ALE

Subtraction meta-analysis of activation during an implicit emotional task suggests decreased activation in people with schizophrenia;

Left parahippocampal gyrus/amygdala: Talairach coordinates (-26, -10, -14), 3 foci, 280mm^3, 0.060 ALE

Right left parahippocampal gyrus/amygdala: Talairach coordinates (24, -8, -12), 3 foci, 280mm^3, 0.051 ALE

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

Navari S, Dazzan P

Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings

Psychological Medicine 2009; 39(11): 1763-1777

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Comparison	**Brain volume in medicated, drug-free, and drug-naïve people with schizophrenia vs. healthy controls.**
Summary of evidence	**Low quality evidence (sample sizes unclear, indirect, unable to assess consistency or precision) is unclear as the effect of antipsychotic medications on brain structure.**
Grey matter volume	
Patients medicated for less than 12 weeks compared to drug naïve and controls 1 study, N unclear Medicated patients (type unspecified) showed reduced hippocampus volume compared to controls, which was not related to antipsychotic dose Follow up at 2.5 years No longitudinal change in hippocampal volume in patients, compared to reduced volume in controls. Patients mediated for more than 12 weeks compared to drug naïve and controls 2 studies, N unclear Two studies reported reduced hippocampal volume in medicated patients, one of these studies reported a larger effect for patients treated with first generation antipsychotics.	
Consistency in results	No measure of heterogeneity is reported, results appear inconsistent for long-term medication.
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 whole brain grey matter volume in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large sample sizes, inconsistent, precise, direct) suggests no significant change in hippocampus volume over time in people with schizophrenia compared to controls.**

Grey matter volume

Progressive changes in grey matter volume reported across longitudinal MRI scans over 1-10 years.

Significantly greater decreases over time in schizophrenia compared to controls in;

Right hippocampus/amygdala complex: N = 153, 5 studies, d = -0.060, 95%CI -0.38 to 0.26, p = 0.716, I^2 = 0%

Significantly greater increases over time in schizophrenia compared to controls in;

Left hippocampus/amygdala complex: N = 153, 5 studies, d = 0.107, 95%CI -0.22 to 0.43, p = 0.518, I^2 = 0%

Left Hippocampus: N = 524, 8 studies, d = 0.089, 95%CI -0.16 to 0.34, p = 0.490, I^2 = 42.9%

Right Hippocampus: N = 524, 8 studies, d = 0.145, 95%CI -0.15 to 0.44, p = 0.337, I^2 = 57.2%

Consistency in results	Consistent for hippocampus/amygdala complex only
Precision in results	Precise
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

View review abstract online

Comparison	**Grey matter volume changes 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) suggests increased hippocampal volume after treatment with second generation antipsychotics.**
Grey matter volume	
13 studies assessed structural changes following administration of antipsychotics and found people with chronic schizophrenia treated with second generation antipsychotics showed increased hippocampus volume over time compared to controls. In one study of first-episode psychosis patients (N = unclear) treated with second generation antipsychotics also showed increased hippocampal volume.	
Consistency in results	No measure of heterogeneity is reported, results appear inconsistent
Precision in results	No confidence intervals are reported.
Directness of results	Direct

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	**Metabolic NAA activity (measured by ^{1}H-MRS) in the hippocampus of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (large samples, direct, inconsistent, unable to assess precision) suggests NAA and NAA/Cr is decreased in the hippocampus of people with schizophrenia.**
NAA and NAA/Cr	

5 studies, N = 248 Patient average hippocampus NAA: 85.8% of control levels, SD = 6.1; $p < 0.0001$ 8 studies, N = 305 Patient average hippocampus NAA/Cr: 88.8% of control levels, SD = 8.7; $p < 0.0001$	
Consistency in results	Significant heterogeneity reported, $p < 0.0001$.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Steen RG, Mull C, McClure R, Hame, RM, Lieberman JA

Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies

British Journal of Psychiatry, 2006. 188(6): 510-8

View review abstract online

Comparison	**Brain 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 hippocampal volume is significantly decreased in people with first-episode schizophrenia compared to healthy controls.**
Grey matter volume	
Significant reduction in hippocampal volume in people with first-episode schizophrenia; N = 587, 11 studies The average schizophrenia patient's left hippocampus volume was 8.2% smaller than controls. The average schizophrenia patient's right hippocampus volume was 8.3% smaller than controls.	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Hippocampus

Vita A, De Peri L, Silenzi C, Dieci M

Brain morphology in first-episode schizophrenia: A meta-analysis of quantitative magnetic resonance imaging studies

Schizophrenia Research 2006; 82(1): 75-88

View review abstract online

Comparison	**Brain volume in people with first-episode schizophrenia vs. healthy controls.**
Summary of evidence	**High quality evidence (large sample sizes, precise, consistent, direct) suggests significant medium-sized reductions in hippocampal volume of people with first-episode schizophrenia.**
Grey matter volume	
Right hippocampus 6 studies, N = 455 *Medium effect size suggests reduced right hippocampal volume in people with schizophrenia;* *d* = 0.473, 95%CI 0.268 to 0.677, *p* < 0.000, Q = 3.63, *p* = 0.6 Left hippocampus 6 studies, N = 455 *Medium effect size suggesting significantly reduced right hippocampal volume in people with schizophrenia;* *d* = 0.659, 95%CI 0.452 to 0.866, *p* < 0.000, Q = 9.57, *p* = 0.08	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET

Meta-analysis of regional brain volumes in schizophrenia

Hippocampus

American Journal of Psychiatry 2000; 157(1): 16-25 View review abstract online	
Comparison	**Hippocampal-Amygdala volume in people with schizophrenia vs. healthy controls.**
Summary of evidence	**High quality evidence (large sample size, consistent, precise, direct) suggests small reductions in hippocampus and parahippocampal volume in people with schizophrenia.**
Grey matter volume	
Left hippocampus-amygdala *Small effect size – average volume of schizophrenia hippocampus-amygdala 95% of control volume, 95%CI 92% to 99%;* 15 studies, N =731, *d* = -0.24, no CIs reported , *p* = 0.10 Right hippocampus-amygdala *Small effect size – average volume of schizophrenia hippocampus-amygdala 94% of control volume, 95%CI 92% to 97%;* 15 studies, N = 731, *d* = -0.28, no CIs reported, *p* = 0.50 Left hippocampus *Small effect size – average volume of schizophrenia hippocampus 93% of control volume, 95%CI 90% to 97%;* 24 studies, N = 1298, *d* = -0.42, no CIs reported, *p* < 0.01 Right hippocampus *Small effect size - volume of schizophrenia hippocampus 94% of control volume, 95%CI 91% to 96%;* 24 studies, N = 1298, *d* = -0.38, no CIs reported, *p* < 0.01 Left parahippocampus *Medium effect size – average volume of schizophrenia parahippocampus 89% of control volume, 95%CI 83% to 95%;* 8 studies, N = 353, *d* = -0.69, CIs reported, *p* < 0.01 Right parahippocampus *Small effect size – average volume of schizophrenia parahippocampus 92% of control volume, 95%CI 86% to 98%;* 8 studies, N = 353, *d* = -0.40, no CIs reported, *p* = 0.03	
Consistency in results	Consistent

Hippocampus

Precision in results	Precise – CI %s do not exceed 10% in either direction.
Directness of results	Direct

Explanation of acronyms

ALE = activation likelihood estimation, CI = Confidence Interval, Cr = creatine, *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, FSN = fail-safe N, FWHM = full-width at half maximum smoothing kernel, Gln = glutamine, Glu = glutamate, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MNI = Montreal Neurological Institute, MRS = magnetic resonance spectroscopy, N = number of participants, NAA = N-acetyl aspartate, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PET = positron emission tomography, SD = standard deviation, Q = Q statistic (chi-square) for the test of heterogeneity, vs = versus, $\chi 2$ = chi-squared.

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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[21].

† 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[21].

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. 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) which 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[22, 23].

‖ 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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