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 38 systematic reviews that met our inclusion criteria[3-40].

Structural changes

- High quality evidence found bilateral hippocampal grey matter reductions in people with schizophrenia compared to controls. There are also grey matter reductions in the parahippocampus.
- Moderate quality evidence found common decreases in grey matter in the left hippocampus in medicated and medication-naïve first-episode patients. Grey matter in the right hippocampus was increased in medicated but decreased in antipsychotic-naive patients.
- Moderate quality evidence found reductions in white matter integrity in the hippocampus, entorhinal gyrus, and parahippocampal gyrus in people with schizophrenia.
- Moderate to high quality evidence found a small association between increased hippocampal volume and better verbal learning in people with schizophrenia. There was also a small association between increased left hippocampal volume and better immediate recall in people at genetic risk of schizophrenia, with no associations with the right hemisphere or the left hemisphere and delayed recall.
- Moderate quality evidence found decreases in bilateral parahippocampal/hippocampal regions in people at high-risk for psychosis (clinical or genetic) compared to controls. People at high clinical risk showed decreases in the left hippocampus and the right parahippocampus compared to controls. People at high genetic risk showed increases in the right hippocampus and decreases in bilateral parahippocampus compared to controls. There were decreases in the left parahippocampus in people at high genetic risk compared to people at high clinical risk.
- Moderate to high quality evidence shows small reductions in left cornu ammonis (CA)1, left CA2/3, left CA4/dentate gyrus, right presubiculum, and right subiculum in people with schizophrenia compared to people with bipolar disorder, with no differences in left presubiculum or subiculum, or right CA1, CA2/3, or CA4/dentate gyrus.

Functional changes

- Moderate quality found decreased activation in the left hippocampus of people with schizophrenia at rest compared to controls at rest.
- Moderate quality evidence found increased activation in the hippocampus during auditory hallucinations, and decreased activation in the retrosplenial/hippocampus during external auditory stimulation in people with schizophrenia.
- Moderate quality evidence found decreased activation in the hippocampus during memory encoding and retrieval tasks in people with schizophrenia.
- Moderate to low quality evidence found increased activation in the left parahippocampal gyrus during episodic memory encoding, and increased activation in the right parahippocampal gyrus during episodic memory retrieval in people with schizophrenia.
- Moderate to low quality evidence found increased activation in the left hippocampus and decreased activation in the parahippocampus of people with schizophrenia compared to controls during emotion processing tasks.
- During implicit, but not explicit, threat processing, there was decreased activity in bilateral amygdala extending into putamen, hippocampus and parahippocampal gyrus. There was increased activity in the parahippocampus and hippocampus during emotionally neutral tasks.

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- Moderate quality evidence found over-activation in the left parahippocampal gyrus during emotion tasks of first-degree relatives of people with schizophrenia compared to controls.
- Moderate quality evidence found reduced hippocampal N-acetyl aspartate/creatine (NAA/Cr) and choline/creatine (Cho/Cr) ratios in people with schizophrenia. NAA/Cr was also reduced in first-degree relatives. Moderate quality evidence found no differences in NAA, Glx, Cho, Cr or myoinositol levels.
- Moderate quality evidence finds reduced translocator protein in the hippocampus of people with schizophrenia compared to controls.

Structural and functional changes

- Moderate quality evidence found increased activation in the left parahippocampus during facial emotion recognition tasks in people with schizophrenia compared to people with autism. Moderate to low quality evidence found similar overlapping grey matter volume decreases in the right parahippocampus of people with schizophrenia and people with autism.

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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. controls during episodic memory tasks.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, unable to assess precision and consistency, direct) 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

Adriano F, Caltagirone C, Spalletta G

Hippocampal volume reduction in first episode and chronic schizophrenia:

a review and meta-analysis

The Neuroscientist 2012; 18(2): 180-200

View review abstract online

Comparison	**Hippocampal grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, mostly inconsistent, precise, direct) suggests reduced hippocampal grey matter volume bilaterally in both first episode and chronic schizophrenia.**

Hippocampal grey matter volume

All patients

Medium effect size shows significantly reduced hippocampus;

Right hippocampus: 51 studies, N = 3,799, *d* = -0.53, 95%CI -0.65 to -0.41, $p < 0.00001$, Q = 140.64, $p < 0.00001$, $I^2 = 64\%$

Left hippocampus: 51 studies, N = 3,799, *d* = -0.48, 95%CI -0.65 to -0.32, $p < 0.00001$, Q = 287.62, $p < 0.00001$, $I^2 = 83\%$

Subgroup analysis showed similar effects in male-only groups;

Right: N = 1,031, *d* = -0.63, 95%CI -0.82 to -0.44, $p < 0.00001$, Q not reported, $p = 0.003$

Left: N = 1,031, *d* = -0.43, 95%CI -0.80 to -0.07, $p = 0.02$, Q not reported, $p < 0.00001$

First-episode schizophrenia

Medium effect size shows significantly reduced hippocampus;

Right hippocampus: 13 studies, N = 950, *d* = -0.56 95%CI -0.72 to -0.40, $p < 0.00001$, Q = 14.36, $p = 0.28$, $I^2 = 16\%$

Left hippocampus: 13 studies, N = 950, *d* = -0.60, 95%CI -0.83 to -0.38, $p < 0.00001$, Q = 27.24, $p = 0.007$, $I^2 = 56\%$

Chronic schizophrenia

Medium effect size shows significantly reduced hippocampus;

Right hippocampus: 22 studies, N = 1,635, *d* = -0.65, 95%CI -0.87 to -0.43, $p < 0.00001$, Q = 90.26, $p < 0.00001$, $I^2 = 77\%$

Left hippocampus: 22 studies, N = 1,635, *d* = -0.58, 95%CI -0.94 to -0.22, $p = 0.002$, Q = 229.32, $p < 0.00001$, $I^2 = 91\%$

Consistency in results	Mostly inconsistent.

Precision in results	Precise for all outcomes.
Directness of results	Direct

Antoniades M, Schoeler T, Radua J, Valli I, Allen P, Kempton MJ, McGuire P

Verbal learning and hippocampal dysfunction in schizophrenia: A meta-analysis

Neuroscience and Biobehavioral Reviews 2018; 86: 166-75

View review abstract online

Comparison 1	**Association between verbal learning and hippocampal volume in people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, consistent, precise, direct) suggests a small association between increased hippocampal volume and better verbal learning in people with schizophrenia, with no associations in control samples.**

Hippocampal volume

Total hippocampal volume

Small, significant association between increased volume and better delayed recall;

3 studies, N = 293, r = 0.228, 95%CI 0.047 to 0.394, p = 0.0138, I^2 = 14%

Left hippocampal volume

Small, significant association between increased volume and better immediate recall;

5 studies, N = 162, r = 0.256, 95%CI 0.089 to 0.409, p = 0.0029

Small, significant association between increased volume and better delayed recall;

11 studies, N = 431, r = 0.131, 95%CI 0.042 to 0.218, p = 0.0038

Right hippocampal volume

Small, significant association between increased volume and better immediate recall;

5 studies, N = 162, r = 0.230, 95%CI 0.094 to 0.358, p = 0.001

Small, significant association between increased volume and better delayed recall;

8 studies, N = 311, r = 0.234, 95%CI 0.135 to 0.329, p < 0.0001

There were no significant associations in the analyses of control subjects.

Hippocampus

Consistency in results	Consistent for total hippocampal volume, unable to assess hemispheres (I^2 not reported).
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Association between verbal learning and hippocampal volume in people at genetic risk of schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (small samples, consistent, precise, direct) suggests a small association between increased left hippocampal volume and better immediate recall in people at genetic risk of schizophrenia, with no associations with the right hemisphere or the left hemisphere and delayed recall.**
Hippocampal volume	
Left hippocampal volume *Small, significant association between increased volume and better immediate recall;* 2 studies, N = 89, *r* = -0.356, 95%CI 0.153 to 0.531, *p* = 0.0009, I^2 = 0% *There was no association between volume and delayed recall;* N = 228, *r* = -0.031, 95%CI -0.223 to 0.163, *p* > 0.05, I^2 = 32% Right hippocampal volume *There was no association between volume and immediate recall;* N = 89, *r* = 0.160, 95%CI -0.075 to 0.379, *p* > 0.05, I^2 = 11% *There was no association between volume and delayed recall;* N = 170, *r* = -0.034, 95%CI -0.237 to 0.171, *p* > 0.05, I^2 = 4%	
Consistency in results	Consistent
Precision in results	Precise
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

Hippocampus

View review abstract online	
Comparison 1	**Hippocampal volume in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) suggests first-degree relatives have reduced hippocampal volume compared to controls.**
Hippocampal volume	
Small effect size for decreased total hippocampal volume in first-degree relatives; 9 studies, N = 1,024, *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;* 9 studies, N = 943, *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;* 9 studies, N = 943, *d* = 0.23 95%CI 0.01 to 0.96 *p* < 0.05, Q = 19.43, *p* = 0.01	
Consistency in results	Mostly inconsistent
Precision in results	Precise except for right hippocampal volume.
Directness of results	Direct
Comparison 2	**Hippocampal 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.**
Hippocampal volume	
Medium effect size for decreased hippocampal volume in people with schizophrenia; 9 studies, N = 846, *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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Brugger SP, Howes OD

Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia: A Meta-analysis

JAMA Psychiatry 2017; 74: 1104-11

View review abstract online

Comparison	**Hippocampal volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, direct, mostly inconsistent, precise) finds a medium-sized reduction in the hippocampus of people with first-episode schizophrenia.**
Hippocampal volume	
Significant, medium-sized reduction in first-episode schizophrenia in; Hippocampus: 36 studies, N = 3,298, g = -0.66, 95%CI -0.84 to -0.47, $p < 0.001$, I^2 = 74%	
Consistency in results	Inconsistent, apart from frontal lobe and the third ventricle.
Precision in results	Precise
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	**Hippocampal volume in people with chronic schizophrenia vs. controls.**

Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests people with chronic schizophrenia have grey matter reductions in the right parahippocampus.**
Hippocampal grey matter volume	
19 studies, N = 1,664 *Significant reductions in schizophrenia in;* Right parahippocampal gyrus: Talairach coordinates (12, -36, 0), cluster 160mm^3, ALE 0.0132	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct, apart from subtraction analyses.

Cheung C, Yu K, Fung G, Leung M, Wong C, Li Q, Sham P, Chua S, McAlonan G

Autistic disorders and schizophrenia: related or remote? An anatomical likelihood estimation

PLOS One 2010; 5(8): e12233

View review abstract online

Comparison	**Overlapping brain volume alterations in people with schizophrenia and people with autistic spectrum disorders (ASD) vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests similar overlapping grey matter volume decreases in the right parahippocampus.**
Overlapping brain alterations	
Regions of decreased grey matter volume, reporting the % that is contributed to by schizophrenia and autism studies; Right parahippocampal gyrus: Talairach coordinates (28, -14, -15), 57.1% SZ, 42.9% ASD	

Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Crossley NA, Mechelli A, Ginestet C, Rubinov M, Bullmore ET, McGuire P

Altered Hub Functioning and Compensatory Activations in the Connectome: A Meta-Analysis of Functional Neuroimaging Studies in Schizophrenia

Schizophrenia Bulletin 2016; 42: 434-42

View review abstract online

Comparison	**Functional activity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests during episodic memory tasks, there were under-activations in the left hippocampus. During emotion tasks, there were over-activations in left hippocampus.**
Functional activation	
314 studies, N = 10,942 Episodic memory tasks Under-activations in the left hippocampus. Emotion tasks Over-activations in left hippocampus.	
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

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	**Hippocampal grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent, precise, direct) suggests grey matter volume is significantly reduced in the hippocampus in schizophrenia.**
Hippocampal grey matter volume	
Left hippocampus *Medium effect size suggests reduced volume in schizophrenia;* N = 1,919, *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 = 1,814, *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 = 1,238, *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. controls during cognitive tasks.**
Summary of evidence	**Moderate quality evidence (large sample, 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

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) found decreased activity in bilateral amygdala extending into putamen, hippocampus and parahippocampal gyrus during implicit threat processing, with no differences during explicit threat processing.**
Functional activity	
19 studies, N = 728 Implicit threat processing *Decreased activity in;*	

Bilateral amygdala extending into putamen, hippocampus and parahippocampal gyrus: 3,953 voxels, MNI coordinates (-30, -6, -8), $p < 0.001$ No differences during explicit threat processing.	
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

Dugre JR, Bitar N, Dumais A, Potvin S

Limbic hyperactivity in response to emotionally neutral stimuli in schizophrenia: A neuroimaging meta-analysis of the hypervigilant mind

American Journal of Psychiatry 2019; 176: 1021-9

View review abstract online

Comparison	**Limbic functional activity during emotionally neutral stimuli in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found increased activity in the parahippocampus and hippocampus during emotionally neutral tasks.**
Limbic activity	
23 studies, N = 946 *Schizophrenia was characterised by;* Increased activations in the parahippocampus and hippocampus.	
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

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	**Hippocampal grey matter volume (GMV) and grey matter concentration (GMC, grey matter as a proportion of the whole brain volume) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests grey matter reductions in the hippocampus of people with schizophrenia.**

Hippocampal grey matter volume

37 studies, N = 3,336

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. controls (NAA and Cr are reported as a ratio, NAA/Cr).**
Summary of evidence	**Moderate quality evidence (medium-sized sample, unable to assess precision and inconsistency, direct) 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

Fusar-Poli P, Borgwardt S, Crescini A, Deste G, Kempton MJ, Lawrie S, McGuire P, Sacchetti E

Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis

Neuroscience and Biobehavioural Reviews 2011; 35: 1175-1185

View review abstract online

Comparison	**Hippocampus grey matter volume in people at high-risk of schizophrenia (both clinical high-risk and genetic high-risk) vs. controls and vs. people with psychosis.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests decreases in the bilateral parahippocampal/hippocampal region in people at high-risk**

	(clinical or genetic) compared to controls. People at high clinical risk showed decreases in the left hippocampus compared to controls. People at high genetic risk showed decreases in the left parahippocampus compared to controls and compared to people at high clinical risk.
Hippocampus grey matter volume	
19 studies, N = 1,601 All - clinical and genetic high-risk of psychosis vs. controls Decreases were reported in bilateral parahippocampal/hippocampal regions. Genetic high-risk of psychosis vs. controls Decreases were reported in the left parahippocampal gyrus. Clinical high-risk of psychosis vs. controls Decreases were reported in the left hippocampus. Genetic high-risk of psychosis vs. clinical high-risk of psychosis People at high genetic risk showed decreases in the left parahippocampus.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Fusar-Poli P, Radua J, McGuire P, Borgwardt S

Neuroanatomical maps of psychosis onset: voxel-wise meta-analysis of antipsychotic-naive VBM studies

Schizophrenia Bulletin 2012; 38(6): 1297-1307

View review abstract online

Comparison	**Hippocampal grey matter density in people at high clinical risk of psychosis vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests people at clinical high-risk show reductions in the right parahippocampal gyrus.**

Hippocampal grey matter volume	
Reductions of grey matter volume in people at high risk of psychosis in; Right parahippocampal gyrus: Talairach coordinates (30, -10, -20) Kc = 63mm^3	
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

Fusar-Poli P, Smieskova R, Serafini G, Politi P, Borgwardt S

Neuroanatomical markers of genetic liability to psychosis and first episode psychosis: A voxelwise meta-analytical comparison.

World Journal of Biological Psychiatry 2014; 15(3): 219-28

View review abstract online

Comparison	**Hippocampal grey matter in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision and consistency) suggests grey matter reductions in the left parahippocampal gyrus of relatives.**
Hippocampal grey matter volume	
N = 870 *Grey matter reductions in relatives in;* Left parahippocampal gyrus: Talairach coordinates (-28, -4, -12), $p < 0.0002$	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
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

View review abstract online

Comparison	**Hippocampal grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sampleunable to assess consistency or precision, direct,) suggests schizophrenia is associated with significant grey matter reductions in the parahippocampal gyrus.**
Hippocampal grey matter volume	
13 studies, N = 2,457 *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

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

Schizophrenia Bulletin 2012; 39(5): 1129-1138

View review abstract online

Comparison	**Hippocampal grey matter volume in people with schizophrenia vs.**

	controls.
Summary of evidence	**Moderate to high quality evidence (large samples, precise, mostly inconsistent, direct) suggests people with schizophrenia who are medicated or antipsychotic-naïve show reductions in hippocampal grey matter volume. Medicated patients also show reductions in parahippocampal regions.**
Hippocampal grey matter volume	
Decreased in medicated patients; Hippocampus: 87 studies, N = 5,141, *d* = -0.52, 95%CI -0.60 to -0.44, $p < 1 \times 10{-}9$, Q = 169.5, $p < 1 \times 10{-}9$, $I^2 = 49\%$ Parahippocampal gyrus: 20 studies, N = 1,129, *d* = -0.24, 95%CI -0.39 to -0.09, $p = 2.1 \times 10{-}3$, Q = 28.8, *p* = 0.07, $I^2 = 34\%$ *Decreased in antipsychotic-naïve patients;* Hippocampus: 8 studies, N = 445, *d* = -0.43, 95%CI -0.63 to -0.24, $p = 7.6 \times 10{-}6$, Q = 2.4, *p* = 0.93, $I^2 = 0\%$	
Consistency in results	Inconsistent for hippocampus in medicated patients.
Precision in results	Precise
Directness of results	Direct

Haukvik UK, Tamnes CK, Soderman E, Agartz I

Neuroimaging hippocampal subfields in schizophrenia and bipolar disorder: A systematic review and meta-analysis

Journal of Psychiatric Research 2018; 104: 217-26

View online review abstract

Comparison 1	**Hippocampal changes in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, some inconsistency, precise, direct) shows small reductions in all hippocampal subfields in people with schizophrenia.**
Hippocampal subfields	

Hippocampus

6 studies, N = 1,789 *Small, significant reductions in all hippocampal subfields in people with schizophrenia;* <u>Left hemisphere</u> Cornu ammonis 1: *d* = -0.304, 95%CI -0.504 to -0.104, *p* = 0.003, Q*p* = *p* < 0.001 Cornu ammonis 2/3: *d* = -0.450, 95%CI -0.624 to -0.275, *p* < 0.00001, Q*p* = 0.253 Cornu ammonis 4 / dentate gyrus: *d* = -0.493, 95%CI -0.708 to -0.279, *p* < 0.00001, Q*p* < 0.000001 Presubiculum: *d* = -0.286, 95%CI -0.405 to -0.167, *p* < 0.00001, Q*p* = 0.300 Subiculum: *d* = -0.394, 95%CI -0.485 to -0.303, *p* < 0.000001, Q*p* = 0.428 <u>Right hemisphere</u> Cornu ammonis 1: *d* = -0.282, 95%CI -0.391 to -0.173, *p* < 0.000001, Q*p* = 0.279 Cornu ammonis 2/3: *d* = -0.328, 95%CI -0.455 to -0.201, *p* < 0.000001, Q*p* = 0.058 Cornu ammonis 4 / dentate gyrus: *d* = -0.364, 95%CI -0.474 to -0.253, *p* < 0.000001, Q*p* = 0.201 Presubiculum: *d* = -0.349, 95%CI -0.468 to -0.231, *p* < 0.000001, Q*p* = 0.306 Subiculum: *d* = -0.375, 95%CI -0.466 to -0.284, *p* < 0.000001, Q*p* = 0.592	
Consistency in results	Consistent, apart from CA1 and CA4/dentate gyrus.
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Hippocampal changes in people with schizophrenia vs. people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) shows small reductions in left cornu ammonis (CA)1, left CA2/3, left CA4/dentate gyrus, right presubiculum, and right subiculum in people with schizophrenia, with no differences in left presubiculum or subiculum, or right CA1, CA2/3, or CA4/dentate gyrus.**
Hippocampal subfields	
2 studies, N = 809 *Small, significant reductions in the following hippocampal subfields in people with schizophrenia;* <u>Left hemisphere</u> Cornu ammonis 1: *d* = -0.105, 95%CI -0.197 to -0.012, *p* = 0.028, Q*p* = 0.027 Cornu ammonis 2/3: *d* = -0.145, 95%CI -0.254 to -0.037, *p* = 0.0086, Q*p* = 0.009	

Cornu ammonis 4 / dentate gyrus: *d* = -0.153, 95%CI -0.274 to -0.032, *p* = 0.013, Q*p* = 0.013 Right hemisphere Presubiculum: *d* = -0.130, 95%CI -0.210 to -0.050, *p* = 0.0014, Q*p* = 0.001 Subiculum: *d* = -0.091, 95%CI -0.166 to -0.015, *p* = 0.018, Q*p* = 0.018 *No significant differences in;* Left hemisphere Presubiculum: *d* = -0.001, 95%CI -0.085 to 0.084, *p* > 0.05, Q*p* = 0.987 Subiculum: *d* = -0.040, 95%CI -0.122 to 0.042, *p* > 0.05, Q*p* = 0.339 Right hemisphere Cornu ammonis 1: *d* = -0.039, 95%CI -0.115 to 0.037, *p* > 0.05, Q*p* = 0.314 Cornu ammonis 2/3: *d* = 0.021, 95%CI -0.066 to 0.108, *p* > 0.05, Q*p* = 0.633 Cornu ammonis 4 / dentate gyrus: *d* = -0.035, 95%CI -0.111 to 0.041, *p* > 0.05, Q*p* = 0.367

Consistency in results	Consistent, apart from the presubiculum, subiculum, CA 1, 2/3 and 4/dentate gyrus.
Precision in results	Precise
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	**Hippocampal grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests schizophrenia is associated with significant reductions in the grey matter density of the parahippocampal gyrus.**
Hippocampal 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

Iwata Y, Nakajima S, Plitman E, Mihashi Y, Caravaggio F, Chung JK, Kim J, Gerretsen P, Mimura M, Remington G, Graff-Guerrero A

Neurometabolite levels in antipsychotic-naive/free patients with schizophrenia: A systematic review and meta-analysis of ^{1}H-MRS studies

Progress in Neuro-Psychopharmacology & Biological Psychiatry 2018; 86: 340-52

View review abstract online

Comparison	**Neurometabolite levels measured by ^{1}H-MRS in unmedicated people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, some inconsistency, precise, direct) found no differences in neurometabolite levels (NAA, Glx, Cho or myoinositol) in unmedicated people with schizophrenia.**
NAA	
There were no significant differences in NAA in the hippocampus/medial temporal lobe; 6 studies, N = 283, SMD = -0.46, 95%CI -0.95 to 0.03, p = 0.07, I^2 = 68%, p = 0.009	
Glx	
There were no significant differences in Glx in the hippocampus/medial temporal lobe; 3 studies, N = 109, SMD = -0.25, 95%CI -0.23 to 0.72, p = 0.31, I^2 = 33%, p = 0.23	
Choline	
There were no significant differences in choline in the hippocampus/medial temporal lobe;	

6 studies, N = 281, SMD = -0.26, 95%CI -0.70 to 0.19, p = 0.26, I^2 = 61%, p = 0.02	
Myo-inositol	
There were no significant differences in myo-inositol in the hippocampus/medial temporal lobe; 3 studies, N = 182, SMD = -0.09, 95%CI -0.53 to 0.57, p = 0.68, I^2 = 51%, p = 0.10	
Consistency in results	Consistent for Glx and myo-inositol only.
Precision in results	Precise
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

View review abstract online

Comparison	**White matter fractional anisotropy (FA) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess precision and consistency, direct) 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

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 and during auditory stimulation tasks.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, direct, unable to assess precision or consistency) suggests increased activation in the hippocampus during auditory hallucinations, and decreased activation in the retrosplenial/hippocampus during external auditory stimulation.**
During hallucinations (endogenously evoked)	
12 studies, N = 103, showed increased activation during hallucinations in; Hippocampus: (-24 -32 -4) 1064mm^3	
Auditory tasks	
11 studies, N = 384, showed reduced activation during auditory stimulation tasks in people with schizophrenia in; Retrosplenial/hippocampus: (-12 -38 10) 392mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Kraguljac NV, Reid M, White D, Jones R, den Hollander J, Lowman D, Lahti AC

Neurometabolites in schizophrenia and bipolar disorder – a systematic review and meta-analysis

Psychiatry Research: Neuroimaging 2012; 203: 111-25 View review abstract online	
Comparison	**Metabolite levels (measured by ^{1}H-MRS) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (unclear sample sizes, some inconsistency and imprecision, direct) suggests reduced NAA/Cr and Cho/Cr in the hippocampus, with no differences in NAA, Cr or Cho levels.**
NAA/Cr or Cho/Cr	
Significant, medium to large reduction in NAA/Cr ratio; 8 studies, d = -0.72, 95%CI -1.20 to -0.25, $p < 0.01$, I^2 = 74% *Significant, small reduction in Cho/Cr ratio;* 5 studies, d = -0.28, 95%CI -0.54 to -0.02, p = 0.03, I^2 = 0% *There were no differences in:* NAA levels: 7 studies, d = -0.82, 95%CI -1.69 to 0.05, p = 0.06, I^2 = 92% Cr levels: 7 studies, d = -0.12, 95%CI -1.22 to 0.99, p = 0.84, I^2 = 95% Cho levels: 7 studies, d = -0.19, 95%CI -1.09 to 0.71, p = 0.68, I^2 = 93%	
Consistency in results	Consistent for Cho/Cr only.
Precision in results	Precise for NAA/CR and Cho/Cr only.
Directness of results	Direct

Kühn S, Gallinat J

Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis

Schizophrenia Bulletin 2013; 39(2): 358-365 View review abstract online	
Comparison	**Resting-state functional activation in people with schizophrenia vs. controls and in people with major depression vs. controls.**

Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests decreased activation in the left hippocampus of people with schizophrenia at rest.**
Resting state activity	
11 studies, N = 567 *The following clusters showed decreased activity in people with schizophrenia compared to controls;* Left hippocampus: Talairach coordinates (-21, -10, -24), cluster volume 264mm^3	
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	**White matter integrity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess precision and consistency, direct) 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 sample size, unable to assess consistency or precision, direct) 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

Li Y, Li WX, Xie DJ, Wang Y, Cheung EFC, Chan RCK

Grey matter reduction in the caudate nucleus in patients with persistent negative symptoms: An ALE meta-analysis

Schizophrenia Research 2018; 192: 9-15

View review abstract online

Comparison	**Hippocampal grey matter volume in people with persistent negative symptoms of schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests patients with persistent negative symptoms show significant reductions in the bilateral parahippocampal gyri.**
Hippocampal grey matter volume	
12 studies, N = unclear *There was significantly reduced grey matter volume in;* Left parahippocampal gyrus: Talairach coordinates (-20, -10, -14) Left parahippocampal gyrus (BA30): Talairach coordinates (-16, 38, -4) Right parahippocampal gyrus: Talairach coordinates (18, -4, -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

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 hippocampal grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, inconsistent, precise, direct) suggests no significant change in hippocampus volume over time in people with schizophrenia compared to controls.**
Hippocampal 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

Plaven-Sigray P, Matheson GJ, Collste K, Ashok AH, Coughlin JM, Howes OD, Mizrahi R, Pomper MG, Rusjan P, Veronese M, Wang Y, Cervenka S

Positron Emission Tomography Studies of the Glial Cell Marker Translocator Protein in Patients With Psychosis: A Meta-analysis Using Individual Participant Data

Biological Psychiatry 2018; 84: 433-42

View review abstract online

Comparison	**Translocator protein (measured by PET) in people with schizophrenia vs. controls.**

Summary of evidence	**Moderate quality evidence (small sample, consistent, imprecise, direct) finds reduced translocator protein in the hippocampus of people with schizophrenia.**
Translocator protein	
A significant decrease in translocator protein in the hippocampus of people with schizophrenia; 5 studies, N = 152, total distribution volume = -0.64, 95%CredInt -1.02 to -0.27, $p < 0.05$ There were no moderating effects of medication (drug free vs. medicated).	
Consistency in results	Authors report results were consistent.
Precision in results	Appears imprecise.
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 during episodic memory tasks in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) suggests functional activity is increased in the left parahippocampal gyrus during episodic encoding and increased in the right parahippocampal gyrus during episodic retrieval.**
Episodic encoding	
Significantly greater activity in people with schizophrenia in; Left parahippocampal gyrus: cluster volume 304mm^3, Talairach centre of mass (-28, -50, -4)	
Episodic retrieval	
Significantly greater activity in people with schizophrenia;	

Right parahippocampal gyrus: cluster volume not reported, Talairach centre of mass (20, -36, -4)	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Scognamiglio C, Houenou J

A meta-analysis of fMRI studies in healthy relatives of patients with schizophrenia

Australian and New Zealand Journal of Psychiatry 2014; 48(10): 907-16

View review abstract online

Comparison	**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 over-activation in the left parahippocampal gyrus of relatives during emotion tasks.**
Cognitive and emotion tasks	
Emotion tasks: 4 studies *The following areas showed increased activation in relatives compared to controls;* Left parahippocampal gyrus (BA28): Talairach coordinates (-20, -14, -20), $p < 0.01$ There were no differences during cognitive tasks.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Shah C, Zhang W, Xiao Y, Yao L, Zhao Y, Gao X, Liu L, Liu J, Li S, Tao B, Yan Z, Fu Y, Gong Q, Lui S

Common pattern of gray-matter abnormalities in drug-naive and medicated first-episode schizophrenia: a multimodal meta-analysis

Psychological Medicine 2017; 47: 401-13

View review abstract online

Comparison	**Hippocampal grey matter volume in first-episode schizophrenia (treated and medication naïve) vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests common decreases in grey matter in the left hippocampus between medicated and medication-naïve first-episode patients. Grey matter in the right hippocampus was increased in medicated but decreased in antipsychotic-naive patients.**
Hippocampal grey matter volume	
24 studies, N = 1,358 *Grey matter decreased in both medicated and medication-naïve first-episode patients in;* Left hippocampus, BA 20: MNI coordinates (-26, -16, -22) *Grey matter increased in medicated but decreased in medication-naïve first-episode patients in;* Right hippocampus, BA 20: MNI coordinates (34, -28, -6)	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is 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

View review abstract online

Comparison	**Hippocampal grey matter volume changes in treated and untreated people with schizophrenia compared to controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess consistency or precision, direct) suggests increased hippocampal volume after treatment with second generation antipsychotics.**
Hippocampal 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, 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	**Hippocampal grey matter volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests hippocampal volume is significantly decreased in people with first-episode schizophrenia compared to controls.**
Hippocampal 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

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 samples, direct, unable to assess precision or consistency) suggests increased activation in schizophrenia in the left parahippocampus 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 parahippocampus: Talairach coordinates (-22, -22, -10), cluster volume 392mm^3	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

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	**Hippocampal grey matter volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests significant medium-sized reductions in hippocampal volume of people with first-episode schizophrenia.**
Hippocampal 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

American Journal of Psychiatry 2000; 157(1): 16-25

View review abstract online

Hippocampus

Comparison	**Hippocampal-amygdala volume in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests small reductions in hippocampus and parahippocampal volume in people with schizophrenia.**
Hippocampal-amygdala 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
Precision in results	Precise
Directness of results	Direct

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Xiao Y, Zhang W, Lui S, Yao L, Gong Q

Similar and different gray matter deficits in schizophrenia patients and their unaffected biological relatives

Frontiers in Psychiatry 2013; 4: 150

View review abstract online

Comparison	**Hippocampal grey matter volume in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests increased grey matter volume in the right hippocampus and decreased bilateral parahippocampal volume of relatives.**
Grey matter volume	
Regions of increased grey matter volume in relatives; Right hippocampus: Talairach coordinates (24, -20, -20), $p < 0.0001$ *Regions of decreased grey matter volume in relatives;* Right parahippocampus: Talairach coordinates (26, -48, -4), $p < 0.0001$ Left parahippocampus: Talairach coordinates (-26, -54, -6), $p < 0.01$	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

ALE = activation likelihood estimation, Cho = choline, CI = confidence interval, Cr = creatine, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, 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, Glx = Gln+Glu, 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.

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[41].

† 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[41].

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[42, 43].

‖ 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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