TECHNICAL COMMENTARY

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Basal ganglia

Introduction

The basal ganglia are a group of sub-cortical nuclei thought to be involved in motor control and learning. The nuclei comprising the basal ganglia include the caudate, putamen, globus pallidus, the subthalamic nucleus and the substantia nigra. The caudate and putamen together form the striatum, while the globus pallidus (including the ventral pallidum) and the putamen together form the lenticular (lentiform) nucleus.

The striatum is the principal input centre, receiving afferents primarily from the cortex, but also the substantia nigra, thalamus, and external globus pallidus. There are two primary pathways from the striatum through the basal ganglia ('direct' and 'indirect' pathways) which incorporate different components of the basal ganglia circuitry and play different roles in controlling and planning movements and cognition.

Schizophrenia has been associated with altered structure and function of the basal ganglia. Understanding of brain alterations in people with schizophrenia may provide insight into changes in brain development associated with illness onset or progression. Reviews contained in this technical summary reflect structural imaging investigations (MRI), functional imaging investigations (fMRI, PET, SPECT) as well as metabolic imaging (MRS) of basal ganglia function 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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found 19 systematic reviews that met our inclusion criteria[3-21].

Structural changes

- Moderate to high quality evidence found increased globus pallidus volume in medicated patients compared to controls. In mediation-naïve patients, the caudate nucleus was reduced compared to controls.
- Moderate quality evidence found grey matter increases in the left caudate head of people with schizophrenia but decreases in the left caudate head of people with persistent negative symptoms.
- In people with first-episode schizophrenia, there was decreased grey matter in bilateral caudate head (but not nucleus) and increased grey matter in the left putamen compared to controls**.** There was also increased grey matter in the left putamen of people with schizophrenia (not necessarily first-episode) compared to relatives of people with schizophrenia.
- Moderate to low quality evidence found greater reductions in the bilateral caudate in first-episode treatment-naïve patients (vs. controls) than in first episode treated patients (vs. controls).
- Moderate to high quality evidence suggests increased antipsychotic use was associated with increased basal ganglia volume over time (>2 years).
- Moderate to low quality evidence found similar grey matter volume decreases in the right putamen in people with schizophrenia and people with an autistic spectrum disorder compared to controls.

Functional changes

- Moderate quality evidence found reduced activity in the right putamen during executive functioning and timing tasks in people with schizophrenia compared to controls, with no differences during cognitive control, memory (long-term and working memory), or language processing.
- Moderate quality evidence found increased activation in the left putamen of people with schizophrenia compared to controls during emotionally neutral tasks.
- Moderate to low quality evidence finds increased activation in the right caudate of relatives of people with schizophrenia (compared to controls) during cognitive tasks, and the left lentiform nucleus during emotion tasks.
- Moderate quality evidence finds unmedicated people with schizophrenia have a medium to large increase in choline in the basal ganglia.
- Moderate to low quality evidence found no differences in D2/D3 receptor availability in the substantia nigra of unmedicated people with schizophrenia compared to controls, and no differences in GABA levels in the striatum of people with schizophrenia.

Structural and functional changes

- Moderate quality evidence suggests decreased grey matter volume and decreased functional activity in the left caudate nucleus in drug-free first-episode patients.

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Basal ganglia

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

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

Schizophrenia Research 2017; 188: 21-32

View online review abstract

Comparison	**Basal ganglia activation during timing tasks in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found during timing tasks, there was decreased activity in the bilateral caudate nuclei and right putamen.**
Basal ganglia activation	
8 studies, N = 395 *Significant, decreased activation in people with schizophrenia was found in;* Bilateral caudate nuclei Right putamen	
Consistency in results‡	Unable to assess; no measure of consistent is reported.
Precision in results§	Unable to assess; no measure of precision is reported.
Directness of results‖	Direct

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

Basal ganglia

Comparison	**Basal ganglia volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds no differences between first-episode schizophrenia and controls in caudate nucleus or putamen volume.**
Basal ganglia volume	
There were no significant differences in; Caudate nucleus: 22 studies, N = 2,096, g = -0.11, 95%CI -0.28 to 0.05, p = 0.23, I^2 = 79% Putamen: 15 studies, N = 1,809, g = -0.31, 95%CI -0.68 to 0.07, p = 0.11, I^2 = 79%	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

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	**Regions of overlapping brain alterations in people with schizophrenia and people with autistic spectrum disorders vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests overlapping grey matter volume decreases in the right putamen between schizophrenia and autism.**
Overlapping brain alterations	
Regions of decreased grey matter volume, reporting the % that is contributed to by schizophrenia and autism studies;	

Right putamen: Talairach coordinates (28, 0, 6), 61.1% SZ, 38.9% ASD Left putamen: Talairach coordinates (-23, 2, 5), 0.2% SZ, 99.8% ASD *Regions of increased grey matter volume, reporting the % that is contributed to by schizophrenia and autism studies;* Left putamen: Talairach coordinates (-22, 0, 12), 94.4% SZ, 5.6% ASD	
Consistency in results	No measure of consistency is reported.
Precision in results	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 activations in the left putamen of people with schizophrenia during emotionally neutral tasks.**
Limbic activity	
23 studies, N = 946 *Schizophrenia was characterised by;* Increased activations in the left putamen.	
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

Egerton A, Modinos G, Ferrera D, McGuire P

Neuroimaging studies of GABA in schizophrenia: a systematic review with meta-analysis

Translational Psychiatry 2017; 7: e1147

View review abstract online

Comparison	**GABA levels in the striatum of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized sample, inconsistent, imprecise, direct) finds no differences in GABA levels.**
GABA levels	
No significant differences between groups; 4 studies, N = 219, g = 0.004, 95%CI -0.70 to 0.70, p = 1.00, I^2 = 82% There were no moderating effects of age, illness duration, symptom severity, %grey matter or publication date.	
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	**Basal ganglia volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess**

	consistency or precision) suggests decreased bilateral caudate head grey matter and increased left putamen grey matter in people with first-episode schizophrenia.
Basal ganglia volume	
27 studies, N = 1,556 First-episode schizophrenia decreases vs. controls Left caudate head: Talairach coordinates (-12, 6, 12), cluster 528mm^3, ALE 0.01, p = 0.0002 Right caudate head: Talairach coordinates (10, 10, 12), cluster 1392mm^3, ALE 0.012, p < 0.0002 First-episode schizophrenia increases vs. controls Left putamen: Talairach coordinates (-22, 0, 12), cluster 1592mm^3, ALE 0.008, *p* < 0.0002	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Ellison-Wright I, Bullmore E

Anatomy of bipolar disorder and schizophrenia: A meta-analysis.

Schizophrenia Research 2010; 117: 1-12

View review abstract online

Comparison	**Basal ganglia volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests grey matter increases were reported in the right globus pallidus and left caudate head in people with schizophrenia.**
Basal ganglia volume	

42 studies, N = 4,189 *Regions of increased grey matter;* Right globus pallidus: Talairach coordinates (16, 0, 4), Sum of ranks = 71.6, *p* = 0.00005 Left caudate head: Talairach coordinates (-6, 8, 4), Sum of ranks = 67.8, *p* = 0.00005	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S

Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies

Neuroscience and Biobehavioural Reviews 2013; 37: 1680-1691

View review abstract online

Comparison	**Longitudinal changes in basal ganglia grey matter volume in medicated people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, precise, direct) suggests no differences between schizophrenia and controls in overall caudate nucleus volume over time.**
Changes in basal ganglia grey matter volume over time (4 - 520 weeks)	
There were no significant changes over time in overall caudate nucleus volume; 13 studies, patients *g* = -0.010, 95%CI -0.183 to 0.164, *p* = 0.913, controls *g* = -0.149, 95%CI -0.357 to 0.059, *p* = 0.160, Q_B = 0.996, *p* = 0.318	
Consistency in results	Authors report heterogeneity in the longitudinal data.
Precision in results	Precise
Directness of results	Direct

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

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

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

View review abstract online

Comparison	**Overlap between regions of functional and structural alteration in drug-free people with first-episode schizophrenia vs. controls.** **Note; most patients were drug naïve.**
Summary of evidence	**Moderate quality evidence (large sample, mostly consistent, direct, unable to assess precision) suggests decreased grey matter volume and decreased functional activity in the left caudate nucleus in drug-free patients.**
Structural and functional alteration	
15 structural MRI studies, N = 971, 16 functional MRI studies, N = 831 *Significant decreased grey matter volume and decreased functional activity in;* Left caudate nucleus: 111 voxels, MNI coordinates (-10, 0, 12), $p < 0.001$	
Consistency in results	Authors report most findings were consistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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

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Comparison	**Basal ganglia grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) found increased globus pallidus in medicated patients compared to controls, with no differences in the caudate nucleus or putamen. In mediation-naïve patients, the caudate nucleus was reduced compared to controls**
Basal ganglia grey matter volume	
Medicated patients *Small, increased globus pallidus in patients, with no differences in caudate nucleus or putamen;* Globus pallidus: 15 studies, N = 1,144, *d* = 0.26, 95%CI 0.02 to 0.50, *p* = 0.034, Q = 53.9, *p* = 1.3 × 10−6, I^2 = 74% Caudate nucleus: 35 studies, N = 2,255, *d* = -0.03, 95%CI -0.14 to 0.07, *p* = 0.50, Q = 47.3, *p* = 0.06, I^2 = 28% Putamen: 28 studies, N = 1,956, *d* = 0.10, 95%CI -0.07 to 0.26, *p* = 0.24, Q = 81.8, *p* = 2.0 × 10−7, I^2 = 67% Antipsychotic-naive patients *Medium-sized decreased caudate nucleus in patients;* Caudate nucleus: 11 studies, N = 721, *d* = -0.38, 95%CI -0.54 to -0.23, *p* = 9.5 × 10−7, Q = 8.3, *p* = 0.60, I^2 = 0%	
Consistency in results	Consistent for caudate nucleus in antipsychotic-naïve patients only.
Precision in results	Precise
Directness of results	Direct

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

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

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

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Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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Comparison	**Association between long-term antipsychotic use and changes in basal ganglia volume over time (>2 years) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) suggests increased antipsychotic use was associated with increased basal ganglia volume over time (>2 years).**
Longitudinal changes in volume	
Small, significant association between long-term antipsychotic use and increased basal ganglia; 4 studies, N = 225, r = 0.10, 95%CI -0.00 to 0.19, p = 0.044, I^2 = 0%	
Consistency in results	Consistent
Precision in results	Precise
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 in unmedicated people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized sample, consistent, imprecise, direct) finds unmedicated people with schizophrenia have a medium to large increase in choline in the basal ganglia.**
Choline levels	
A significant, medium to large increase in choline in the basal ganglia of unmedicated people with schizophrenia;	

3 studies, N = 168, SMD = 0.77, 95%CI 0.24 to 1.31, p = 0.005, I^2 = 48%, p = 0.15	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Kambeitz J, Abi-Dargham A, Kapur S, Howes OD

Alterations in cortical and extrastriatal subcortical dopamine function in schizophrenia: Systematic review and meta-analysis of imaging studies

British Journal of Psychiatry 2014; 204(6): 240-249

View review abstract online

Comparison	**Cortical and extrastriatal D2/D3 receptor availability in unmedicated people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, inconsistent, imprecise, direct) suggests no differences in D2/D3 receptor availability in the substantia nigra.**
D2/D3 receptor availability	
No significant differences between groups; 5 studies, N = 143, d = 0.04, 95%CI -0.92 to 0.99, p = 0.90, I^2 = 85% Meta-regression showed no effect of publication year, gender, or age in any analysis.	
Consistency in results	Some inconsistency.
Precision in results	Some imprecision.
Directness of results	Direct

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

Gray Matter in First-Episode Schizophrenia Before and After Antipsychotic Drug Treatment. Anatomical Likelihood Estimation Meta-

analyses With Sample Size Weighting **Schizophrenia Bulletin 2011; 37(1): 199-211** View review abstract online	
Comparison	**Basal ganglia volume in medication-naïve people with first-episode schizophrenia vs. controls, and treated people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (large sample, indirect, unable to assess consistency or precision) suggests reductions in the bilateral caudate were greater in treatment-naïve than treated patients.**
Basal ganglia volume	
6 studies, N = 327 *Regions where grey matter reductions were larger in magnitude in treatment-naïve patients (vs. controls) than in treated patients (vs. controls);* Right caudate: Talairach coordinates (10, 10, 12), cluster 1992mm^3, ALE 0.0106 Left caudate: Talairach coordinates (0, 12, 4), cluster 360mm^3, ALE 0.0276 Left caudate: Talairach coordinates (-12, 6, 0), cluster 264mm^3, ALE 0.0095	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is provided.
Directness of results	Indirect

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	**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 people with persistent negative symptoms show reductions in the left caudate head.**
Basal ganglia volume	
There was significantly reduced grey matter volume in; Left caudate head: Talairach coordinates (-4, 6, -2)	
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

MacDonald AW, Thermenos HW, Barch DM, Seidman LJ

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

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

View review abstract online

Comparison	**Basal ganglia activation in first-degree relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, direct, unable to assess precision or consistency) suggests no differences in basal ganglia activity during cognitive control tasks, memory tasks (long term and working), or language processing.**
Cognitive control	
7 studies investigated functional activity during cognitive control tasks, N = 308 6 studies investigated the basal ganglia, 2/6 showed reduced activity compared to controls	
Working memory	

4 studies (5 independent samples) investigated functional activity during working memory tasks, N = 239 2 studies investigated the basal ganglia, 1/2 showed increased activity compared to controls	
Long term memory	
3 studies investigated functional activity during episodic long-term memory tasks, N = 195 3 studies investigated the basal ganglia, 3/3 showed no group differences	
1 study investigated functional activity during procedural long-term memory tasks, N = 27 Reduced activity in relatives was shown in basal ganglia	
Language processing	
4 studies investigated functional activity during language processing tasks, N = 164 4/4 showed no task-related response in the basal ganglia	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC

Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia

Archives of General Psychiatry 2009; 66(8): 811-822

View review abstract online

Comparison	**Basal ganglia activation in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests people with schizophrenia showed reduced activity in the right putamen during executive functioning.**
Executive functioning	

41 studies, N = 1,217 *Significantly reduced activity in schizophrenia patients compared to controls;* Right putamen: Talairach centre of mass (20, -4, 14), cluster volume 448mm^3	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Niu Y, Li Z, Cheng R, Peng B, Liu B, Ma Y

Altered gray matter and brain activity in patients with schizophrenia and their unaffected relatives: A multimodal meta-analysis of voxel-based structural MRI and resting-state fMRI studies

International Journal of Clinical and Experimental Medicine 2017; 10: 1866-78

View review abstract online

Comparison	**Basal ganglia volume in relatives of people with schizophrenia vs. people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests relatives had decreased grey matter in the left putamen compared to people with schizophrenia.**
Basal ganglia volume	
7 studies, N = 945 *Compared to people with schizophrenia, relatives had decreased grey matter in;* Left putamen: 358 voxels, MNI coordinates (-26, -2, 8), p = 0.00001	
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

Scognamiglio C, Houenou J

Basal ganglia

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 to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests increased activation in the right caudate of relatives compared to controls during cognitive tasks, and the left lentiform nucleus (lateral globus pallidus) during emotion tasks.**
Cognitive and emotion tasks	
Increased activation in relatives compared to controls during cognitive tasks in; Right caudate (right transverse temporal gyrus, BA41): Talairach coordinates 32, -36, 4, $p < 0.01$ *Increased activation in relatives compared to controls during emotion tasks in;* Left lentiform nucleus (lateral globus pallidus): Talairach coordinates -24, -12, -6, $p < 0.01$	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MNI = Montreal Neurological Institute, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[22].

† 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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[22].

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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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 which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[24].

‖ 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Kambeitz J, Abi-Dargham A, Kapur S, Howes OD (2014): Alterations in cortical and extrastriatal subcortical dopamine function in schizophrenia: Systematic review and meta-analysis of imaging studies. *British Journal of Psychiatry* 204: 420-9.
4. Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E (2008): The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *American Journal of Psychiatry* 165: 1015-23.
5. Minzenberg MJ, Laird AR, S. T, Carter CS, Glahn DC (2009): Meta-analysis of 41 Functional Neuroimaging Studies of Executive Function in Schizophrenia. *Archives of General Psychiatry* 66: 811-22.
6. MacDonald AW, 3rd, Thermenos HW, Barch DM, Seidman LJ (2009): Imaging genetic liability to schizophrenia: systematic review of FMRI studies of patients' nonpsychotic relatives. *Schizophrenia Bulletin* 35: 1142-62.
7. Ellison-Wright I, Bullmore E (2010): Anatomy of bipolar disorder and schizophrenia: A meta-analysis. *Schizophrenia Research* 117: 1-12.
8. Leung M, Cheung C, Yu K, Yip B, Sham P, Li Q*, et al.* (2009): Gray Matter in First-Episode Schizophrenia Before and After Antipsychotic Drug Treatment. Anatomical Likelihood Estimation Meta-analyses With Sample Size Weighting. *Schizophrenia Bulletin*.
9. Iwata Y, Nakajima S, Plitman E, Mihashi Y, Caravaggio F, Chung JK*, et al.* (2018): Neurometabolite levels in antipsychotic-naive/free patients with schizophrenia: A systematic review and meta-analysis of 1H-MRS studies. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 86: 340-52.
10. Egerton A, Modinos G, Ferrera D, McGuire P (2017): Neuroimaging studies of GABA in schizophrenia: a systematic review with meta-analysis. *Translational Psychiatry* 7: e1147.
11. Alustiza I, Radua J, Pla M, Martin R, Ortuno F (2017): Meta-analysis of functional magnetic resonance imaging studies of timing and cognitive control in schizophrenia and bipolar disorder: Evidence of a primary time deficit. *Schizophrenia Research* 56: 179-89.
12. Brugger SP, Howes OD (2017): Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia: A Meta-analysis. *JAMA Psychiatry* 74: 1104-11.
13. Cheung C, Yu K, Fung G, Leung M, Wong C, Li Q*, et al.* (2010): Autistic Disorders and Schizophrenia: Related or Remote? An Anatomical Likelihood Estimation. *PLoS ONE* 5: e12233.
14. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S (2013): Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neuroscience and Biobehavioral Reviews* 37: 1680– 91.
15. Gao X, Zhang W, Yao L, Xiao Y, Liu L, Liu J*, et al.* (2018): Association between structural and functional brain alterations in drug-free patients with schizophrenia: A multimodal meta-analysis. *Journal of Psychiatry and Neuroscience* 43: 131-42.
16. Haijma SV, Van Haren N, Cahn W, Koolschijn PCMP, Hulshoff Pol HE, Kahn RS (2012): Brain Volumes in Schizophrenia: A Meta-Analysis in Over 18 000 Subjects. *Schizophrenia Bulletin* 39: 1129-38.
17. Li Y, Li WX, Xie DJ, Wang Y, Cheung EFC, Chan RCK (2018): Grey matter reduction in the caudate nucleus in patients with persistent negative symptoms: An ALE meta-analysis. *Schizophrenia Research* 192: 9-15.
18. Niu Y, Li Z, Cheng R, Peng B, Liu B, Ma Y (2017): Altered gray matter and brain activity in patients with schizophrenia and their unaffected relatives: A multimodal meta-analysis of voxel-based

structural MRI and resting-state fMRI studies. *International Journal of Clinical and Experimental Medicine* 10: 1866-78.

19. Scognamiglio C, Houenou J (2014): A meta-analysis of fMRI studies in healthy relatives of patients with schizophrenia. *Australian and New Zealand Journal of Psychiatry* 48: 907-16.
20. Huhtaniska S, Jaaskelainen E, Hirvonen N, Remes J, Murray GK, Veijola J*, et al.* (2017): Long-term antipsychotic use and brain changes in schizophrenia - a systematic review and meta-analysis. *Human Psychopharmacology* 32: doi: 10.1002/hup.2574.
21. Dugre JR, Bitar N, Dumais A, Potvin S (2019): Limbic hyperactivity in response to emotionally neutral stimuli in schizophrenia: A neuroimaging meta-analysis of the hypervigilant mind. *American Journal of Psychiatry* 176: 1021-9.
22. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
23. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
24. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*