TECHNICAL COMMENTARY

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Thalamus

Introduction

The thalamus is a midline structure located directly on top of the brainstem, surrounding the third ventricle. It is thought to be primarily involved in relaying information from the brainstem and subcortex into the cortex, particularly sensation, special sense and motor signals. Every sensory system except olfaction utilises a thalamic relay to the associated cortical region. The thalamus has also been implicated in autonomic functions such as the regulation of consciousness, sleep and wakefulness. The thalamus may also have higher cognitive functions, being implicated in some emotional processing as well as memory propagation.

Schizophrenia has been associated with altered structure and function of the thalamus. Understanding of any brain alterations in people with schizophrenia may provide insight into changes in brain development associated with the illness onset or progression. Reviews contained in this technical summary reflect both structural (MRI) and functional imaging investigations (fMRI, PET), as well as metabolic concentrations (MRS) of the thalamus 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 people with people with 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 31 systematic reviews that met our inclusion criteria[3-33].

Structural changes

- High quality evidence found bilateral reductions in grey matter in the thalamus (particularly mediodorsal nucleus) in people with schizophrenia, which is of slightly larger magnitude in people with first-episode schizophrenia than in people with chronic schizophrenia. There were greater reductions in first-episode patients than relatives of people with schizophrenia.
- Moderate to high quality evidence found increased grey matter volume in the right thalamus of people at clinical high-risk for psychosis compared to controls.

Functional changes

- Moderate quality evidence found reduced connectivity at rest within the thalamus network, and between the thalamus network and the ventral/attention and frontoparietal networks. Moderate to low quality evidence found increased activity in the thalamus after cognitive remediation.
- Moderate quality evidence showed decreased activation in the left mediodorsal thalamus of people with schizophrenia compared to controls during executive function tasks. During episodic retrieval, clusters of reduced activity were found in bilateral thalamus along with a cluster of increased activity in right thalamus. There was decreased activation in the right thalamus during cognitive control tasks. There was decreased activity in the thalamus during explicit threat processing and auditory stimulation, with no differences during implicit threat processing. There was decreased activation in the left thalamus during reward anticipation tasks.
- Moderate quality evidence found people with schizophrenia showed less activation in the left thalamus than people with bipolar disorder during facial emotion processing.
- Moderate quality evidence suggests increased activation in the right thalamus and decreased activation in the left thalamus of first-degree relatives of people with schizophrenia compared to controls during executive functioning tasks. There was increased activity in bilateral thalamus of relatives during working memory tasks.
- Moderate to high quality evidence found decreased NAA levels in the thalamus of people with first-episode or chronic schizophrenia and in people at high-risk of schizophrenia. Moderate to low quality evidence suggests decreased N-acetyl aspartate/creatine ratio in the thalamus of people with chronic schizophrenia. There were no differences in creatine or choline levels.
- Moderate to high quality evidence finds a medium-sized decrease in glutamate in the thalamus of people at clinical high risk for psychosis. Moderate to low evidence suggests increased glutamate/glutamine ratio in the thalamus of people with first-episode schizophrenia.

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Abbott C, Bustillo J

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

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

View review abstract online

Comparison	**Thalamus metabolic activity (measured by 1H-MRS) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small samples, direct, unable to assess precision or consistency) suggests decreased N-acetyl aspartate/creatine (NAA/Cr) ratio and increased glutamine (Gln) levels in the thalamus of people with schizophrenia.**
Thalamic metabolic activity	
NAA/Cr 1 study, N = 44 NAA/Cr levels were decreased in people with chronic schizophrenia. Gln 2 studies, N = 102 Gln levels were increased in the thalamus in antipsychotic-naive people with schizophrenia (mean illness duration 1.7 years) and in people with chronic schizophrenia.	
Consistency in results‡	No measure of consistency is reported.
Precision in results§	No confidence intervals are reported.
Directness of results‖	Direct

Adriano F, Spoletini I, Caltagirone C, Spalletta G

Updated meta-analyses reveal thalamus volume reduction in patients with first-episode and chronic schizophrenia

Schizophrenia Research 2010; 123(1): 1-4

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View review abstract online	
Comparison	**Thalamic grey matter volume in people with schizophrenia (both chronic and first-episode) vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests reduced thalamic grey matter volume bilaterally in schizophrenia, of slightly larger magnitude in first-episode schizophrenia than in chronic schizophrenia.**
Thalamic volume	
All patients vs. controls *Small to medium effect sizes show reduced bilateral thalamus volume in schizophrenia;* Right thalamus: 15 studies, N = 957, *d* = -0.38, 95%CI -0.52 to -0.25, *p* = 0.00001; Q = 13.16, *p* = 0.51, I^2 = 0% Left thalamus: 15 studies, N = 957, *d* = -0.40, 95%CI -0.53 to -0.26, *p* = 0.00001; Q = 8.94, *p* = 0.84, I^2 = 0% First-episode of schizophrenia vs. controls *Medium effect sizes show reduced bilateral thalamus volume in schizophrenia;* Right thalamus: 15 studies, N = 384, *d* = -0.45, 95%CI -0.66 to -0.23, *p* = 0.00001; Q = 2.83, *p* = 0.73, I^2 = 0% Left thalamus: 15 studies, N = 384, *d* = -0.48, 95%CI -0.70 to -0.26, *p* = 0.00001; Q = 2.71, *p* = 0.74, I^2 = 0% Chronic schizophrenia vs. controls *Small effect sizes show reduced bilateral thalamus volume in schizophrenia;* Right thalamus: 15 studies, N = 488, *d* = -0.32, 95%CI -0.50 to -0.14, *p* = 0.0005; Q = 7.92, *p* = 0.24, I^2 = 24% Left thalamus: 15 studies, N = 488, *d* = -0.33, 95%CI -0.51 to -0.15, *p* = 0.0003; Q = 3.41, *p* = 0.76, I^2 = 0%	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

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

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

Schizophrenia Research 2017; 188: 21-32

View online review abstract

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

Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, Yücel M, Velakoulis D, Pantelis C

Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis

Schizophrenia Research 2011; 127: 46-57

View review abstract online	
Comparison	**Grey and white matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample size, direct, unable to assess consistency or precision) suggests people with schizophrenia show bilateral thalamus reductions.**
Thalamic volume	
49 studies, N = 4,179 Bilateral thalamus: Talairach coordinates (-2, -16, 4), cluster 544mm^3, $p < 0.000001$	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Brugger S, Davis JM, Leucht S, Stone JM

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

Biological Psychiatry 2011; 69: 495-503

View review abstract online

Comparison	**N-acetyl aspartate (NAA) in people at high risk of schizophrenia (clinical and genetic), first-episode schizophrenia, and chronic schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, mostly consistent, precise where applicable, direct) found decreased NAA levels in the thalamus of people with first-episode or chronic schizophrenia, and in people at high-risk of schizophrenia.**
NAA	
Significant, small to medium-sized reduction of NAA in people with chronic schizophrenia; 12 studies, N = 546, d = -0.32, 95%CI -0.53 to -0.10, p = 0.004, Q = 25.67, p = 0.14, I^2 = 26%	

Significant, medium-sized reduction of NAA in people with first-episode schizophrenia; 5 studies, N = 190, *d* = -0.40, 95%CI -0.70 to -0.06, *p* = 0.02, Q = 9.05, *p* = 0.25, I^2 = 23% *Significant, medium to large reduction of NAA in people at high-risk of psychosis;* 2 studies, N = 98, *d* = -0.72, 95%CI not reported, *p* = 0.0006, Q = 1.83, *p* = 0.39, I^2 = 0%	
Consistency in results	Consistent apart from frontal lobe and temporal lobe data.
Precision in results	Precise where confidence intervals are reported.
Directness of results	Direct

Chan RCK, Di X, McAlonan GM, Gong Q

Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and People with chronic schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression

Schizophrenia Bulletin 2011; 37(1) 177-188

View review abstract online

Comparison	**Grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests people with schizophrenia have grey matter reductions in the thalamus. There were greater reductions in first-episode patients compared to relatives.**
Thalamic volume	
19 studies, N = 1,664 All patients vs. controls *Areas of reduced grey matter in schizophrenia vs. controls;* Left thalamus: Talairach coordinates (-2, -18, 6), cluster 1648mm^3, ALE 0.0281 First-episode schizophrenia vs. first-degree relatives *Greater grey matter reduction was found in people with first-episode schizophrenia;* Left thalamus: Talairach coordinates (-2, -14, 4), cluster 192mm^3, ALE 0.0095	
Consistency in results	No measure of consistency is reported.

Precision in results	No confidence intervals are reported.
Directness of results	Direct

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

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

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

View review abstract online

Comparison	**Comparison of functional activity in relatives of people with schizophrenia vs. controls during various tasks.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) suggest relatives show decreased activity in the left thalamus of relatives. A combined analysis of structural and functional anomalies demonstrated decreased grey matter with decreased activation in the left thalamus.**
Functional activation	
13 studies, N = 561 *Relatives showed decreased activation in;* Left thalamus: Talairach coordinates (-6, -12, 16), p = 0.00008 Authors report decreased grey matter and decreased activation in the left thalamus.	
Consistency in results	Authors report the results are consistent.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Delvecchio G, Sugranyes G, Frangou S

Evidence of diagnostic specificity in the neural correlates of facial affect processing in bipolar disorder and schizophrenia: a meta-analysis of

functional imaging studies	
Psychological Medicine 2013; 43(3): 553-69 View review abstract online	
Comparison	**Comparison of functional activation during facial emotion processing in people with schizophrenia vs. people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests people with schizophrenia show less activation in the left thalamus than people with bipolar disorder during facial emotion processing.**
Functional activation	
29 studies, 1,018 *People with schizophrenia were less likely to activate the left pulvinar thalamus;* Left thalamus pulvinar: Talairach coordinates (-5, -26, 6), cluster volume 336mm^3	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

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

Brain structural abnormalities as potential markers for detecting individuals with ultra-high risk for psychosis: A systematic review and meta-analysis

Schizophrenia Research 2019; 209: 22-31

View review abstract online

Comparison	**Grey matter volume in people at clinical high risk of psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) found increased grey matter**

	volume in the right thalamus of high-risk individuals.
Grey matter volume	
14 VBM studies, N = 1,331 *Increased grey matter volumes were found in people at high risk in;* Right thalamus (Z = 1.039)	
Consistency in results	Authors report consistent results.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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

Abnormal brain activation during threatening face processing in schizophrenia: A meta-analysis of functional neuroimaging studies

Schizophrenia Research 2018; 197: 200-208

View review abstract online

Comparison	**Functional activity during threatening face processing in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests during explicit threat processing, there was decreased activity in the thalamus, with no differences during implicit threat processing.**
Functional activation	
19 studies, N = 728 *Decreased activity during explicit threat processing;* Thalamus extending into right amygdala: 819 voxels, MNI coordinates (-4, -6, 2), $p < 0.001$ There were no differences during implicit 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

Dong D, Wang Y, Chang X, Luo C, Yao D

Dysfunction of Large-Scale Brain Networks in Schizophrenia: A Meta-analysis of Resting-State Functional Connectivity

Schizophrenia Bulletin 2018; 44: 168-81

View review abstract online

Comparison	**Functional connectivity during rest in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found reduced connectivity within the thalamus network, and between the thalamus network and the ventral/attention and the frontoparietal networks.**
Functional connectivity	
52 studies, N = 4,412 *Schizophrenia was characterised by;* Reduced connectivity was found within the thalamus network (gating information), and between the thalamus network and the ventral attention and the frontoparietal networks.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Ellison-Wright I, Bullmore E

Anatomy of bipolar disorder and schizophrenia: A meta-analysis

Schizophrenia Research 2010; 117:1-12

View review abstract online

Comparison	**Grey matter volume in schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests reduced grey matter in the mediodorsal thalamic nucleus of people with schizophrenia.**
Thalamic volume	
42 studies, N = 4,189 *Regions of decreased grey matter in schizophrenia;* Left mediodorsal thalamus: Talairach coordinates (-4, -14, 4), Sum of ranks = 181.3, p = 0.00005	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

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

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

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

View review abstract online

Comparison	**Grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample sizes, direct, unable to assess consistency or precision) suggests bilateral reductions in grey matter volume in the thalamus of people with schizophrenia.**
Thalamic volume	
37 studies, N = 3,336 Decreased grey matter was found bilaterally in the thalamus of people with schizophrenia. *Clusters where grey matter concentration reductions were significantly more frequent than grey matter volume reductions;* Left thalamus: Talairach coordinates (-0.83, -20.22, 7.67), Voxel cluster size 2048mm^3, ALE 1.44 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 consistency is reported.
Precision in results	No confidence intervals are 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	**Grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests schizophrenia is associated with significant reductions in grey matter in the thalamus.**
Thalamic volume	
13 studies, N = 2,457 *Areas where density reductions were significantly more frequent in schizophrenia;* Thalamus: Talairach coordinates (0, -20, 6), Voxel cluster size 2296mm^3, p < 0.01, ALE = 0.020	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Goghari MV

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

Psychological Medicine 2001; 41: 1239-1252

View review abstract online

Comparison	**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 increased activity in the right thalamus and decreased activity in the left thalamus during executive functioning and working memory tasks in relatives of people with schizophrenia.**
Functional activation	
17 studies, N = 456 Executive functioning task *Increased activity in relatives of people with schizophrenia compared to controls;* Right thalamus: Talairach coordinates (4, -10, 10), cluster volume 344 mm^3 *Decreased activity in relatives of people with schizophrenia compared to controls;* Left thalamus: Talairach coordinates (-14/-10/-6, -6/-12/-8, 10/12/12), cluster volume 304 mm^3 Subgroup analysis: only those studies that assessed whole-brain voxel-based activation. *Decreased activity in relatives of people with schizophrenia compared to controls;* Left thalamus: Talairach coordinates (-10/-14/-6, -12/-6/-8, 12/10/12), cluster volume 368 mm^3 Working memory task *Increased activity in relatives of people with schizophrenia compared to controls;* Right thalamus: Talairach coordinates (4, -10, 10), cluster volume 408 mm^3 *Decreased activity in relatives of people with schizophrenia compared to controls;* Left thalamus: Talairach coordinates (-14/-6/-10, -6/-8/-12, 10/12/12), cluster volume 312 mm^3	
Consistency in results	No measure of consistency is reported.

Precision in results	No confidence intervals are reported.
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	**N-acetylaspartate in unmedicated people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized sample, consistent, precise, direct) finds unmedicated people with schizophrenia have a medium-sized decrease in N-acetylaspartate in the thalamus.**
NAA	
Significant, medium-sized decrease in NAA in the thalamus of unmedicated people with schizophrenia; 3 studies, N = 174, SMD = -0.56, 95%CI -0.87 to -0.25, p = 0.0005, I^2 = 0%, p = 0.37	
Consistency in results	Consistent
Precision in results	Precise
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	**D2/D3 receptor availability in unmedicated people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, some inconsistency precise, direct) suggests no differences in D2/D3 receptor availability in the thalamus of people with schizophrenia.**
D2/D3 receptor availability **Binding potential relative to the non-displaceable compartment**	
Thalamus *No significant differences between groups in D_2/D_3 receptor availability;* 8 studies, N = 264, *d* = -0.32, 95%CI -0.68 to 0.03, *p* = 0.07, I^2 = 49% Authors report that the effect became significant when the only 2 studies with positive effect sizes were excluded from the analysis. Subgroup analysis of 5 studies of participants with previous exposure to antipsychotic medication showed a non-significant effect size (*d* = -0.34). There were too few studies of drug-naïve patients for meta-analysis (k = 3), and effect sizes from these studies ranged from -0.77 to 0.35. Meta-regression showed no effect of publication year, gender, or age. There was no evidence of publication bias.	
Consistency in results	Some inconsistency.
Precision in results	Precise
Directness of results	Direct

Kompus K, Westerhausan R, Hugdahl K

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

Neuropsychologia 2011; 49: 3361-9

View review abstract online

Comparison	**Functional activation during auditory stimulation tasks in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, direct, unable to assess precision or consistency) suggests decreased activation in the thalamus during auditory stimulation in people with schizophrenia.**
Functional activation	
11 studies, N = 384, showed reduced activation during auditory stimulation tasks in; Thalamus: Talairach coordinates 12, -22, 18, cluster volume 520mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Konick LC, Friedman L

Meta-analysis of thalamic size in schizophrenia

Biological Psychiatry 2001; 49(1): 28-38

View review abstract online

Comparison	**Thalamic volume in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests that people with schizophrenia show significant reductions in thalamic volume.**
Thalamic volume	
Small effect size suggesting significant volumetric reductions; 8 studies, N = 689, *d* = -0.22 95%CI -0.37 to -0.07, *p* = 0.0043, Q = 14.62, *p* = 0.041 *Similar results with one study outlier removed;* 7 studies, N= 657, *d* = -0.18, 95%CI -0.33 to -0.02, *p* = 0.024, Q = 7.96, *p* = 0.24	
Relative thalamic volume (adjusted for brain size)	

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Small effect size suggesting significant volumetric reductions; 11 studies N = 622, *d* = -0.32, 95%CI -0.49 to -0.15, *p* < 0.0001, Q = 16.37, *p* = 0.02 *Similar results with one study outlier removed;* 10 studies, N= 590, *d* = -0.25 95%CI -0.43 to -0.07, *p* = 0.003, Q = 8.13, *p* = 0.229

Consistency in results	Consistent
Precision in results	Precise
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	**Whole brain comparison of metabolite levels (measured by ^{1}H-MRS) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (unclear sample size, some inconsistency, precise, direct) suggests reduced NAA and NAA/Cr in the thalamus, with no differences in Cr or Cho.**

NAA/Cr or Cho/Cr

Significant, medium-sized reduction in NAA levels;

8 studies, *d* = -0.62, 95%CI -1.12 to -0.13, *p* = 0.01, Q not reported, *p* = 0.001, I^2 = 73%

When first-episode patients (unmedicated) and chronic schizophrenia patients (medicated) were analysed separately, reduced NAA levels were found only for chronic schizophrenia (*d* = -0.77, *p* < 0.01), and not first-episode patients (*d* = -0.13, *p* = 0.86).

Significant, medium-sized reduction in NAA/Cr ratio;

9 studies, *d* = -0.37, 95%CI -0.58 to -0.17, *p* < 0.01, I^2 = 6%

There were no differences in;

Cr levels: 8 studies, *d* = -0.03, 95%CI -0.29 to 0.23, *p* = 0.81, I^2 = 0%

Cho levels: 8 studies, *d* = -0.13, 95%CI -0.41 to 0.16, *p* = 0.38, I^2 = 18%

Cho/Cr ratio: 6 studies, d = -0.02, 95%CI -0.34 to 0.30, p = 0.91, I^2 = 42%	
Consistency in results	Inconsistent for NAA and Cho/Cr levels.
Precision in results	Precise
Directness of results	Direct

Lahuis B, Kemner C, Van Engeland H

Magnetic resonance imaging studies on autism and childhood-onset schizophrenia in children and adolescents – a review

Acta Neuropsychiatrica 2003; 15(3): 140-147

View review abstract online

Comparison	**Brain volume in children with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests children with schizophrenia have volume reductions in the thalamus.**
Thalamic volume	
12 studies, N unclear Reduced volume was observed in the thalamus of children with schizophrenia.	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

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

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

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

View review abstract online	
Comparison	**Functional activity during reward anticipation in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found reduced activation in the left thalamus of people with schizophrenia during reward anticipation tasks.**
Functional activation	
11 studies, N = 488 *Schizophrenia was characterised by;* Reduced activation in the left thalamus	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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

Gray Matter in People with 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

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Comparison	**Grey matter volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample sizes, indirect, unable to assess consistency or precision) suggests decreases in the right thalamus of treated first-episode patients.**
Grey matter volume	

9 studies, N = 820 *Areas of reduced volume in schizophrenia;* Right thalamus: Talairach coordinates (2, -14, 4), cluster 352mm^3, ALE 0.0048	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

MacDonald AW, Thermenos HW, Barch DM, Seidman LJ

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

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

View review abstract online

Comparison	**Functional activation in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision or consistency) suggests abnormal functional activation during cognitive control tasks in the thalamus of relatives. No significant alterations were seen with memory or language tasks.**

Functional activation

Cognitive control tasks

6 studies investigated functional activation during cognitive control tasks, N = 308.

3/6 showed increased activity. Activity (hyper- and hypo-) was abnormal in 86% of reports.

Working memory tasks

4 studies investigated functional activation during working memory tasks, N = 239.

2/4 showed no group differences.

Long-term memory tasks

3 studies investigated functional activation during episodic long-term memory tasks, N = 195.

3/3 showed no group differences

1 study investigated functional activation during procedural long-term memory tasks, N = 27. Reduced activity in relatives was shown in thalamus. <u>Language processing tasks</u> 4 studies investigated functional activation during language processing tasks, N = 164. 3/4 showed no task-related response in the thalamus, 1/4 showed reduced bilateral activity.

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

Marsman A, van den Heuvel MP, Klomp DWJ, Kahn RS, Luijten PR, Hulshoff Pol HE

Glutamate in schizophrenia: a focused review and meta-analysis of ^{1}H-MRS studies

Schizophrenia Bulletin 2013; 39(1): 120-9

View review abstract online

Comparison	**Glutamate levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small sample, direct, unable to assess precision or consistency) suggests no differences in glutamate levels in the thalamus.**
Glutamate	
No significant difference; 3 studies, N = 128, *d* = -0.286, *p* = 0.20	
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

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	**Functional 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 show reduced activity in the left mediodorsal thalamus during executive function tasks.**
Functional activation	
41 studies, N = 1,217 *Significantly reduced activity in people with schizophrenia in;* Left mediodorsal thalamus: Talairach centre of mass (-4, -14, 10), cluster volume 1736mm^3	
Consistency in results	No measure of heterogeneity is provided
Precision in results	No confidence intervals are reported.
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 retrieval in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests reduced activity in the bilateral thalamus and increased activity in right thalamus of people with schizophrenia during episodic memory retrieval.**

Functional activation	
Decreased activity in people with schizophrenia in; Left thalamus: cluster volume 1496mm^3, Talairach centre of mass (-4, -8, 18) Right thalamus: cluster volume 1448mm^3, Talairach centre of mass (8, -24, 10) *Increased activity in people with schizophrenia in;* Right thalamus: cluster volume 792mm^3, Talairach centre of mass (26, -30, 6) ALE analysis excluding those studies which did not control for performance differences, all foci showed similar activation patterns.	
Consistency in results	No measure of consistency is reported
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Ramsay IS, Macdonald AW

Brain Correlates of Cognitive Remediation in Schizophrenia: Activation Likelihood Analysis Shows Preliminary Evidence of Neural Target Engagement

Schizophrenia Bulletin 2015; 41(6): 1276-84

View review abstract online

Comparison	**Functional activation changes in response to cognitive remediation in people with schizophrenia vs. various control conditions. Training duration was an average of 10 weeks comprising 40 sessions.**
Summary of evidence	**Moderate to low quality evidence (small sample, direct, unable to assess precision or consistency) suggests increased activity in the thalamus after cognitive remediation.**
Changes in activation	
9 studies, N = 128 *There were increases in activation after cognitive remediation in;* Thalamus, lentiform nucleus, caudate: Talairach coordinates -10, -2, 0, cluster volume 312mm^3	

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

Wenneberg C, Glenthoj BY, Hjorthoj C, Buchardt Zingenberg FJ, Glenthoj LB, Rostrup E, Broberg BV, Nordentoft M

Cerebral glutamate and GABA levels in high-risk of psychosis states: A focused review and meta-analysis of ^{1}H-MRS studies

Schizophrenia Research Jan: doi: 10.1016/j.schres.2019.10.050

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Comparison	**Cerebral glutamate measured by ^{1}H-MRS in people at high risk of psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized samples, consistent, precise, direct) finds a medium-sized decrease in glutamate in the thalamus of people at clinical high risk for psychosis.**
Glutamate	
Thalamus *A medium-sized effect showed significantly lower glutamate levels in the thalamus of people at clinical high risk;* 3 studies, N = 218, SMD = 0.50, 95%CI 0.23 to 0.78, p = 0.0003, I^2 = 0%	
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

Comparison	**Thalamic volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, consistent, precise, direct) shows decreased thalamus volume in people with schizophrenia.**
Thalamic volume	
Left thalamus *Small effect size – average volume of schizophrenia thalamus 96% of control volume, 95%CI 90% to 101%;* 3 studies, N = 210, *d* = -0.35, no CIs reported, *p* = 0.07 Right thalamus *Small effect size – average volume of schizophrenia thalamus 96% of control volume, 95%CI 92% to 102%* 3 studies, N = 210, *d* = -0.31, no CIs reported, *p* = 0.10	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Zhang R, Picchioni M, Allen P, Toulopoulou T

Working memory in unaffected relatives of patients with schizophrenia: A meta-analysis of functional magnetic resonance imaging studies

Schizophrenia Bulletin 2016; 42: 1068-77

View review abstract online

Comparison	**Functional activity during working memory tasks in relatives of people with schizophrenia vs. controls.**

Thalamus

Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests increased activity in bilateral thalamus of relatives during working memory tasks.**
Functional activity	
15 studies, N = 547 *Increased activity in relatives in;* Right thalamus: Talairach coordinates (4, -10, 10) Left thalamus: Talairach coordinates (-10, -20, 4)	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

ALE = activation likelihood estimate, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardized mean differences (see below for interpretation of effect size), Cr = creatine, fMRI = functional magnetic resonance imaging, Gln = glutamine, Glu = glutamate, GMC = grey matter concentration, GMV = grey matter volume, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), 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, Q = Q statistic (chi-square) for the test of heterogeneity, 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[34].

† 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 and over represents a large effect[34].

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

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measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, *r*) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An *r* of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

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

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

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[36].

‖ 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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