TECHNICAL COMMENTARY

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Amygdala

Introduction

The amygdala is located deep in the medial temporal lobe and has reciprocal connections with many regions of the cortex, such as prefrontal and cingulate cortex, as well as sub-cortical regions such as the brainstem and hippocampus. The amygdala is implicated in the processing and memory of emotional responses, particularly emotional learning, as well as mediating the autonomic expression of emotion.

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

Results

We found 13 systematic reviews that met our inclusion criteria[3-15].

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Structural changes

- Moderate to high quality evidence found reduced grey matter volume in the amygdala and amygdala/hippocampus of people with schizophrenia compared to controls. There were also reductions in the amygdala of first-episode patients.
- Moderate to low quality evidence suggests a medium-sized effect of reduced amygdala volume in people with schizophrenia compared to people with bipolar disorder.
- Moderate to high quality evidence found first-degree relatives of people with schizophrenia have reduced amygdala/hippocampus volume, and those at genetic or clinical high risk have reduced left amygdala volume.

Functional changes

- Moderate quality evidence suggests people with schizophrenia show increased activity in the amygdala during executive function tasks.
- Moderate quality evidence suggests people with schizophrenia have decreased or increased activation in the amygdala during emotion processing tasks. During explicit threat processing, there was decreased activity in the thalamus extending to the amygdala, and during implicit threat processing, there was decreased activity in bilateral amygdala extending into putamen, hippocampus and parahippocampal gyrus.

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Anticevic A, Van Snellenburg JX, Cohen RE, Repovs G, Dowd EC, Barch DM

Amygdala recruitment in schizophrenia in response to aversive emotional material: a meta-analysis of neuroimaging studies

Schizophrenia Bulletin 2012; 38(3): 608-21

View review abstract online

Comparison	**Functional activation of the amygdala in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (unclear sample size, precise, direct, unable to assess consistency) suggests decreased activation in the amygdala in people with schizophrenia during aversive emotional tasks.**
Amygdala functional activity	
35 studies (N not reported) found small decreases in activation of bilateral amygdala, particularly the right side, in people with schizophrenia; Bilateral: *d* = -0.22, 95%CI -0.37 to -0.08 *p* = 0.002 Right: *d* = -0.17, 95%CI -0.37 to -0.03 *p* = 0.01 Left: *d* = -0.13, 95%CI -0.31 to 0.04 *p* = 0.136	
Consistency in results‡	No measured of heterogeneity is provided.
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

View review abstract online

Comparison	**Amygdala/hippocampus volume in first-degree relatives of**

	people with schizophrenia vs. controls.
Summary of evidence	**Moderate to high quality evidence (large sample size, direct, inconsistent, precise) suggests first-degree relatives have decreased amygdala/hippocampus volume.**
Amygdala/hippocampus volume	
Medium-sized effect of decreased amygdala/hippocampus volume in first-degree relatives; 12 studies, N = 1,280, *d* = 0.52, 95%CI 0.16 to 0.89, $p < 0.05$, Q = 94.17, $p < 0.001$	
Consistency in results	Inconsistent
Precision in results	Precise
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

Comparison	**Amygdala volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds medium-sized reductions in the amygdala in people with first-episode schizophrenia.**
Amygdala volume	
Significant, medium-sized reductions in the amygdala of first-episode patients; 23 studies, N = 2,315, *g* = -0.46, 95%CI -0.65 to -0.26, $p < 0.001$, $I^2 = 78\%$	
Consistency in results	Inconsistent
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

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Comparison 1	**Amygdala volume in people at genetic or clinical high risk of schizophrenia vs. controls and first-episode patients.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests high-risk individuals have grey matter reductions in left amygdala.**
Amygdala volume	
8 studies, N = 1,031 *Compared to controls, high-risk subjects showed greater grey matter reductions in;* Left amygdala: Talairach coordinates (-28, -8, -12), cluster 800mm^3, ALE 0.0112 *Compared to first-episode patients, high-risk subjects showed greater grey matter reductions in;* Left amygdala: Talairach coordinates (-30, -8, -12), cluster 128mm^3, ALE -0.0097	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct
Comparison 2	**Grey matter changes 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 bilateral amygdala.**

Amygdala

Amygdala volume	
19 studies, N = 1,664 *Compared to controls, patients showed greater grey matter reduction in;* Left amygdala: Talairach coordinates (-16, -6, -12), cluster 840mm^3, ALE 0.0247 Right amygdala: Talairach coordinates (18, -4, -12), cluster 584mm^3, ALE 0.0195	
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

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Comparison	**Amygdala 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 emotion tasks, there were under-activations in thalamic and occipito-temporal regions, and over-activations in left amygdala and hippocampus, left medial frontal region, left cuneus, and bilateral parietal cortex.**
Amygdala functional activation	
314 studies, N = 10,942 Emotion tasks Under-activations in thalamic and occipito-temporal regions; over-activations in left amygdala and hippocampus, left medial frontal region, left cuneus, and bilateral parietal cortex.	
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

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Comparison	**Amygdala volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests grey matter volume is significantly reduced in the amygdala and hippocampus/amygdala of people with schizophrenia.**
Amygdala volume	
Small to medium-sized effect finds reduced amygdala volume in schizophrenia; Left amygdala: N = 970, *d* = -0.39, 95%CI -0.68 to -0.10, *p* not reported SD = 0.53, FSN = 44 Right amygdala: N = 1,109, *d* = -0.38, 95%CI -0.72 to -0.04, *p* not reported SD = 0.67, FSN = 48	
Amygdala/hippocampus complex volume	
Small to medium-sized effects of reduced amygdala/hippocampus volume in schizophrenia Left hippocampus/amygdala complex: N = 1,302, *d* = -0.41, 95%CI -0.74 to -0.41, *p* not reported SD = 0.44, FSN = 71 Right hippocampus/amygdala complex: N = 1,238, *d* = -0.36, 95%CI -0.54 to -0.18, *p* not reported SD = 0.40, FSN = 57	
Consistency in results	Significant heterogeneity reported in all outcomes.
Precision in results	Precise for all outcomes.
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

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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 across explicit and implicit threat processing tasks, people with schizophrenia showed decreased activity in the right amygdala and the left fusiform gyrus. During explicit threat processing, there was decreased activity in the thalamus extending to the amygdala, and during implicit threat processing, there was decreased activity in bilateral amygdala extending into putamen, hippocampus and parahippocampal gyrus.**
Functional activity	
19 studies, N = 728 Explicit threat processing *Decreased activity in;* Thalamus extending into right amygdala: 819 voxels, MNI coordinates -4, -6, 2, $p < 0.001$ Implicit threat processing *Decreased activity in;* Bilateral amygdala extending into putamen, hippocampus and parahippocampal gyrus: 3,953 voxels, MNI coordinates -30, -6, -8, $p < 0.001$ Across tasks, people with schizophrenia showed decreased activity in the right amygdala and left fusiform gyrus.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E

The anatomy of first episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis

American Journal of Psychiatry 2008; 165(8): 1015-23

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Comparison	**Amygdala 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 reductions in bilateral uncus/amygdala grey matter in first-episode schizophrenia.**
Amygdala volume	
27 studies, N = 1,556 *Significant reductions of volume observed in the amygdala in first-episode schizophrenia;* Left uncus/amygdala: Talairach coordinates (-18, -2, -22), cluster 2760mm^3, ALE 0.018, p < 0.0002 Right uncus/amygdala: Talairach coordinates (20, -4, -22), cluster 688mm^3, ALE 0.012, 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

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	**Amygdala grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, precise,**

	inconsistent, direct) reduced amygdala grey matter volume in medicated patients with schizophrenia.
Amygdala grey matter density	
Small effect of reduced amygdala grey matter density in medicated patients; 40 studies, N = 2,205, *d* = -0.31, 95%CI -0.43 to -0.19, *p* = 5.5 × 10−7, Q = 72.1, *p* = 9.9 × 10−4, I^2 = 46% There were no reductions in antipsychotic-naïve patients.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Ho NF, Chong PLH, Lee DR, Chew QH, Chen G, Sim K

The Amygdala in Schizophrenia and Bipolar Disorder: A Synthesis of Structural MRI, Diffusion Tensor Imaging, and Resting-State Functional Connectivity Findings

Harvard Review of Psychiatry 2019; 27: 150-64

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Comparison	**Amygdala volume in people with schizophrenia vs. controls or people with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, inconsistent, some imprecision, direct) suggests a large effect of reduced amygdala volume in people with schizophrenia compared to controls, and a medium-sized effect when compared to people with bipolar disorder.**
Amygdala volume	
A large effect of reduced amygdala volume in people with schizophrenia vs. controls; 20 studies, N not reported, *g* = -0.90, 95%CI -1.62 to -0.18, *p* = 0.014, I^2 = 98% *A medium-sized effect of reduced amygdala volume in people with schizophrenia vs. bipolar disorder;*	

6 studies, N not reported, g = -0.47, 95%CI -0.91 to -0.03, p = 0.04, I^2 = 78% Smaller, but significant effects were found in subgroup analysis of people in the early stages of illness.	
Consistency in results	Inconsistent
Precision in results	Imprecise for controlled analysis, precise for bipolar disorder analysis.
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 during facial emotion processing tasks in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests people with schizophrenia show decreased activation during emotion processing tasks in the amygdala.**
Amygdala activation during facial emotion processing tasks	
13 studies *Reduced activation in people with schizophrenia in;* 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 found decreased activation in implicit and explicit tasks.	
Consistency in results	No measure of consistency is reported.
Precision in results	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

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Comparison	**Functional activation during executive functioning tasks 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 increased activity in the amygdala during executive function tasks.**
Amygdala activation during executive functioning tasks	
41 studies, N = 1,217 *Increased activity in people with schizophrenia;* Right amygdala: Talairach centre of mass (18, -4, -12), cluster volume 592mm^3	
Consistency in results	No measure of consistency is reported.
Precision in results	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

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Comparison	**Amygdala changes over time in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, mostly inconsistent, precise, direct) suggests no changes in amygdala volume over time in people with schizophrenia compared to controls.**
Grey matter volume	
No differences between patients and controls; Right hippocampal/amygdala: 5 studies, N = 153, *d* = -0.060, 95%CI -0.38 to 0.26, *p* = 0.716, I^2 = 0% Right amygdala: 5 studies, N = 235, *d* = -0.138, 95%CI -0.43 to 0.16, *p* = 0.362, I^2 = 12.5% Left hippocampal/amygdala: 5 studies, N = 153, *d* = 0.107, 95%CI -0.22 to 0.43, *p* = 0.518, I^2 = 0% Left amygdala: 5 studies, N = 235, *d* = 0.019, 95%CI -0.24 to 0.28, *p* = 0.887, I^2 = 0%	
Consistency in results	Consistent for hippocampal/amygdala complex only.
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

ALE = activation/anatomical likelihood estimate, CI = confidence interval, *d* = Cohen's *d* = standardised mean differences, FSN = fail-safe N, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square), SD = standard deviation, 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[16].

† 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[16].

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[17]. 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 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[18].

‖ 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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