TECHNICAL COMMENTARY

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Cognition in family members

Introduction

Cognitive deficits have been reported in people with bipolar disorder that are present early in the course of the disorder and may be stable over time. Relatives may show attenuated signs of cognitive deficits. If cognitive deficits found in people with bipolar disorder are also found in their relatives, this may be suggestive of an underlying genetic basis.

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 2010 that report results separately for people with a diagnosis of bipolar and related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent and/or comprehensive review 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 that 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 or if there is a dose dependent response. We have also taken into account sample size and whether results are 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 two reviews that met inclusion criteria[3, 4].

- High quality evidence suggests small to medium-sized effects of poorer processing speed, verbal fluency, executive functioning (speed tasks) and social cognition in relatives, with no differences in executive functioning (accuracy), IQ, verbal memory, visual memory, working memory or sustained attention compared to controls.
- Moderate to high quality evidence suggests small to medium-sized effects of better IQ, verbal memory, working memory, processing speed, verbal fluency and accuracy of executive functioning in relatives of people with bipolar disorder compared to relatives of people with schizophrenia, with no differences in executive functioning (speed tasks), visual memory or sustained attention.

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Bora E

A comparative meta-analysis of neurocognition in first-degree relatives of patients with schizophrenia and bipolar disorder

European Psychiatry: the Journal of the Association of European Psychiatrists 2017; 45: 121-8

View review abstract online

Comparison 1	**Cognition in first-degree relatives of people with bipolar disorder vs. healthy controls.**
Summary of evidence	**High quality evidence (large samples, precise, consistent, direct) suggests small to medium-sized effects of poorer performance on processing speed, verbal fluency and speeded executive functioning tasks in relatives. There were no differences in executive functioning - accuracy, IQ, verbal memory, visual memory, working memory and sustained attention.**
Cognition	
Significant, small to medium-sized effects of poorer performance in relatives on; Processing speed: 8 studies, N = 778, d = 0.41, 95%CI 0.23 to 0.60, $p < 0.001$, I^2 = 33%, p = 0.16 Verbal fluency: 7 studies, N = 509, d = 0.33, 95%CI 0.15 to 0.50, $p < 0.001$, I^2 = 0%, p = 0.66 Executive functioning - speed: 7 studies, N = 715, d = 0.35, 95%CI 0.15 to 0.55, $p < 0.001$, I^2 = 31%, p = 0.19 There were no differences in executive functioning - accuracy, IQ, verbal memory, visual memory, working memory and sustained attention. There was no evidence of publication bias.	
Consistency‡	Consistent
Precision§	Precise
Directness‖	Direct
Comparison 2	**Cognition in first-degree relatives of people with bipolar disorder vs. first-degree relatives of people with schizophrenia.**

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Summary of evidence	**Moderate to high quality evidence (large samples, precise, some inconsistency, direct) suggests small to medium-sized effects of better performance on IQ, verbal memory, working memory, processing speed, verbal fluency and accuracy of executive functioning in relatives of people with bipolar disorder. There were no differences in speeded executive functioning tasks, IQ, visual memory, and sustained attention.**
Cognition	
Significant, small to medium-sized effects of better performance in relatives of bipolar patients on; IQ: 13 studies, N = 1,263, d = 0.38, 95%CI 0.14 to 0.62, $p < 0.001$, I^2 = 72%, $p < 0.01$ Verbal memory: 8 studies, N = 815, d = 0.28, 95%CI 0.04 to 0.53, p = 0.02, I^2 = 49%, p = 0.06 Working memory: 10 studies, N = 589, d = 0.42, 95%CI 0.18 to 0.66, $p < 0.001$, I^2 = 59%, p = 0.009 Processing speed: 9 studies, N = 699, d = 0.30, 95%CI 0.06 to 0.53, p = 0.01, I^2 = 56%, p = 0.02 Executive functioning - accuracy: 10 studies, N = 753, d = 0.27, 95%CI 0.12 to 0.42, $p < 0.001$, I^2 = 4%, p = 0.40 Verbal fluency: 7 studies, N = 431, d = 0.24, 95%CI 0 to 0.47, p = 0.05, I^2 = 33%, p = 0.18 There were no differences in visual memory, sustained attention, or executive functioning – speed. Younger age in the relatives of people with schizophrenia was associated with greater between-group differences in working memory. Shorter duration of education in the relatives of people with schizophrenia was associated with greater between-group differences in global cognition.	
Consistency	Inconsistent for IQ, verbal memory, working memory and processing speed.
Precision	Precise
Directness	Direct

Bora E, Ozerdem A

Social cognition in first-degree relatives of patients with bipolar disorder: A meta-analysis

European Neuropsychopharmacology 2017; 27: 293-300

View review abstract online

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Comparison	**Social cognition in first-degree relatives of people with bipolar disorder vs. healthy controls.**
Summary of evidence	**High quality evidence (large samples, precise, consistent, direct) suggests small effects of poorer social cognition in relatives of people with bipolar disorder.**
Social cognition	
Significant, small effects of poorer social cognition in relatives of people with bipolar disorder; Overall social cognition: 16 studies, N = 1,593, *d* = 0.25, 95%CI 0.14 to 0.36, *p* < 0.001, I^2 = 9%, *p* = 0.35 Theory of Mind: 9 studies, N = 485, *d* = 0.34, 95%CI 0.16 to 0.52, *p* < 0.001, I^2 = 6%, *p* = 0.39 Facial emotion recognition: 8 studies, N = 1,147, *d* = 0.17, 95%CI 0.16 to 0.29, *p* = 0.004, I^2 = 0%, *p* = 0.56 Authors report that the facial emotion recognition analysis may be non-significant after possible publication bias was taken into account. Subgroup analysis showed only facial expressions of anger and fear were significant, but not happy and sad. Meta-regression showed no effects of age or gender.	
Consistency	Consistent
Precision	Precise
Directness	Direct

Explanation of acronyms

CI = Confidence Interval, *d* = Cohen's standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IQ = intelligence quotient, 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.[5]

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† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

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).

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) that 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.[5]

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[6]. 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 can provide an indirect 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.

‡ Inconsistency refers to differing estimates of 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 considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[5];

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

§ 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, these criteria should be relaxed.[7]

‖ 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 that allows indirect comparisons 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 and is therefore 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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