TECHNICAL COMMENTARY

IQ and general cognition

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Introduction

Cognitive dysfunction is a common feature of bipolar disorder that exists across a number of cognitive domains and usually persists in remission. It is unclear whether cognitive deficits are apparent prior to the onset of bipolar disorder or whether they develop during the course of the illness.

Intelligence quotient (IQ) is derived from standardised tests used to measure general cognitive functioning. IQ is most commonly measured using the Wechsler Adult Intelligence Scale (WAIS). The WAIS is designed to measure all aspects of cognitive functioning, and is divided into subtests measuring verbal IQ (verbal comprehension and working memory) and non-verbal IQ (perceptual organisation and processing speed).

Other tests used to assess IQ include the Mini-Mental State Examination (MMSE), which assesses cognitive impairment; the National Adult Reading Test (NART), which assesses premorbid intelligence; the Wide Range Achievement Test (WRAT), which assesses both verbal and mathematic ability; and the Raven's Progressive Matrices, which assesses general intelligence.

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 or related disorders. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. 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 reviews assessing the same topic were found, only the most recent and/or comprehensive review was included.

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 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 11 systematic reviews that met our inclusion criteria[3-13].

- Moderate to high quality evidence suggests a small, significant effect of poorer premorbid general cognitive functioning in people with bipolar disorder compared to controls when assessments were conducted retrospectively, but not prospectively. After illness onset, there was a significant, medium-sized effect of poorer general cognitive functioning in people with bipolar disorder compared to controls. The effect was smaller in people with first-episode patients than in chronic patients.
- High quality evidence shows a medium-sized effect of poorer global cognition, and a small effect of poorer premorbid IQ in people with first-episode bipolar disorder compared to controls. Moderate to high quality evidence also suggests a medium-sized effect of poorer current IQ in first-episode patients.
- Moderate quality evidence suggests a large impairment in global cognition in youth with bipolar disorder aged ~13 years who were matched to controls for age and IQ, but no differences in elderly people with bipolar disorder and controls matched for age and education. Similarly, there was no deterioration in IQ or global cognition in patients over time (3-7 years).
- High quality evidence suggests a small effect of poorer global cognition in people with bipolar disorder and a history of psychotic symptoms compared to people with bipolar disorder and no history of psychotic symptoms, and in people with bipolar I disorder compared to people with bipolar II disorder. There was also poorer global cognition in overweight patients compared to normal weight patients.
- Moderate to high quality evidence suggests no differences in IQ between first-degree relatives of people with bipolar disorder and controls. However, in young relatives aged 10 to 25 years, high quality evidence shows a small effect of lower IQ compared to controls.
- Moderate to high quality evidence suggests a small to medium-sized effect of higher IQ in relatives of people with bipolar disorder compared to relatives of people with schizophrenia.

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Bora E, Pantelis C

Meta-analysis of Cognitive Impairment in First-Episode Bipolar Disorder: Comparison With First-Episode Schizophrenia and Healthy Controls

Schizophrenia Bulletin 2015; 41(5): 1095-1104

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Comparison	**Global cognition and IQ in people with first-episode bipolar disorder vs. controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) shows a medium-sized effect of poorer global cognition and a small effect of poorer premorbid IQ in people with first-episode bipolar disorder. Moderate to high quality evidence (inconsistent) suggests a medium-sized effect of poorer current IQ.**

Global cognition

A significant, medium-sized effect of poorer global cognition in people with first-episode bipolar disorder;

15 studies, N = 1,950, d = 0.54, 95%CI 0.41 to 0.66, $p < 0.001$, I^2 = 19.8%, p = 0.23

There were no changes in the effect size according to gender, education, age, state (euthymic vs non-euthymic), and exclusion of people with drug use.

Authors report no evidence of publication bias.

IQ

A significant, small to medium-sized effects of lower premorbid and current IQ in people with first-episode bipolar disorder;

Premorbid IQ: 7 studies, N = 707, d = 0.26, 95%CI 0.10 to 0.42, $p < 0.001$, I^2 = 0%, p = 0.73

Current IQ: 8 studies, N = 890, d = 0.45, 95%CI 0.19 to 0.71, $p < 0.001$, I^2 = 63.6%, p = 0.007

Authors report no evidence of publication bias.

Consistency in results‡	Consistent, apart from current IQ.
Precision in results§	Precise
Directness of results‖	Direct

Bora E, McIntyre RS, Ozerdem A

Neurococognitive and neuroimaging correlates of obesity and components of metabolic syndrome in bipolar disorder: a systematic review

Psychological medicine 2019; 49: 738-49

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Comparison	**Global cognition in overweight people with bipolar disorder vs. normal weight people with bipolar disorder.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) shows a medium-sized effect of poorer global cognition in overweight patients compared to normal weight patients.**
Global cognition	
A medium-sized effect showed overweight/obese patients were significantly associated with impaired global cognition; 7 studies, N = 711, *d* = 0.36, 95%CI 0.19 to 0.52, *p* < 0.001, I^2 = 0%	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

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	**IQ in first-degree relatives of people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests no differences in IQ between first-degree**

	relatives of people with bipolar disorder and controls.
IQ	
There were no differences in IQ scores; 13 studies, N = 1,110, *d* = 0.16, 95%CI -0.04 to 0.35, *p* = 0.11, I^2 = 60%, *p* = 0.003 There was no evidence of publication bias.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct
Comparison 2	**IQ in first-degree relatives of people with bipolar disorder vs. first-degree relatives of people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, precise, some inconsistency, direct) suggests a small to medium-sized effect of higher IQ in relatives of people with bipolar disorder.**
IQ	
Significant, small to medium-sized effect of better performance in relatives of bipolar patients; 13 studies, N = 1,263, *d* = 0.38, 95%CI 0.14 to 0.62, *p* < 0.001, I^2 = 72%, *p* < 0.01	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Bora E, Ozerdem A

A meta-analysis of neurocognition in youth with familial high risk for bipolar disorder

European Psychiatry 2017; 44: 17-23

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Comparison	**IQ in first-degree relatives aged 10 to 25 years of a person with bipolar disorder vs. controls.**

Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small effect of lower IQ in young relatives.**
IQ	
Significant, small effect of poorer IQ in relatives; 15 studies, N = 1,286, *d* = 0.29, 95%CI 0.15 to 0.44, *p* < 0.001, I^2 = 41%, *p* = 0.05	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Bora E

Neurocognitive features in clinical subgroups of bipolar disorder: A meta-analysis

Journal of Affective Disorders 2018; 229: 125-34

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Comparison 1	**Global cognition in people with bipolar I disorder vs. people with bipolar II disorder.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small significant effect of poorer global cognition in people with bipolar I disorder.**
Global cognition	
Small, significant effect of poorer global cognition in people with bipolar I disorder; Global cognition: 19 studies, N = 1,914, *d* = 0.17, 95%CI 0.07 to 0.27, *p* < 0.001, I^2 = 7%, *p* = 0.38	
Comparison 2	**Global cognition in people with bipolar disorder and a history of psychotic symptoms vs. people with bipolar disorder and no history of psychotic symptoms.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests small significant effects of greater cognitive impairment in global cognition in people with bipolar disorder and a history of psychotic symptoms.**

Global cognition	
Small, significant effect of poorer global cognition in people with a history of psychosis; 21 studies, N = 1,708, *d* = 0.19, 95%CI 0.09 to 0.29, *p* < 0.001, I^2 = 0%, *p* = 0.96	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Depp CA, Mausbach BT, Harmell AL, Savla GN, Bowie CR, Harvey PD, Patterson TL

Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder

Bipolar Disorders 2012; 14: 217-26

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Comparison	**Association between global cognition and functioning in people with bipolar disorder.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests poor global cognition is associated with poor general functioning (small effect).**
Global cognition	
Significant, small association between poor global cognition and poor general functioning; 22 studies, N = 1,344, *r* = 0.27, 95%CI 0.22 to 0.32, *p* < 0.001, Q*p* = 0.582	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Elias LR, Miskowiak KW, Vale AM, Kohler CA, Kjaerstad HL, Stubbs B, Kessing LV,

Vieta E, Maes M, Goldstein BI, Carvalho AF

Cognitive Impairment in Euthymic Pediatric Bipolar Disorder: A Systematic Review and Meta-Analysis

Journal of the American Academy of Child & Adolescent Psychiatry 2017; 56: 286-96

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Comparison	**Global cognition in euthymic youth with bipolar disorder vs. controls of similar age (mean 13 years) and IQ (mean 104).**
Summary of evidence	**Moderate quality evidence (medium to large sample, inconsistent, imprecise, direct) suggests a large impairment in global cognition in youth with bipolar disorder.**
Global cognition	
Large, significant effects of more impairment in euthymic youth with bipolar disorder in; Global cognition: 7 studies, N = 342, g = 0.78, 95%CI 0.16 to 1.41, p = 0.014, I^2 = 85%, $p < 0.05$	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Samame C, Martino DJ, Strejilevich SA

A quantitative review of neurocognition in euthymic late-life bipolar disorder

Bipolar Disorders 2013; 15: 633-44

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Comparison	**Global cognition in older people with bipolar disorder vs. controls matched for age and years of education.**
Summary of evidence	**Moderate to low quality evidence (medium to large samples, inconsistent, imprecise, direct) suggests no significant differences between groups.**
Global cognition	

No significant differences were found between patients and controls; Mini-mental state examination: 4 studies, N = 418, g = 0.52, 95%CI -0.09 to 1.12, p = 0.09, I^2 = 87%, p < 0.001 Clock drawing test: 3 studies, N = 327, g = 0.20, 95%CI -0.02 to 0.42, p = 0.08, I^2 = 0%, p = 0.80 Subgroup analyses showed no changes in the effect size according to age or years of education.	
Consistency in results	Inconsistent for mini-mental state examination.
Precision in results	Imprecise for mini-mental state examination.
Directness of results	Direct

Samame C, Martino DJ, Strejilevich SA

Longitudinal course of cognitive deficits in bipolar disorder: a meta-analytic study

Journal of Affective Disorders 2014; 164: 130-8

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Comparison	**Changes in IQ and global cognition over time in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, consistent, precise, direct) suggests no changes in measures of IQ or global cognition over time (~3-7 years).**
IQ and global cognition	
There were no significant changes over time; IQ: 4 studies, N = 109, follow up = 6.70 years, d = 0.13, 95%CI -0.13 to 0.38, p = 0.33, I^2 = 0%, p = 0.50 Global cognition: 7 studies, N = 279, follow up = 3.44 years, d = 0.00, 95%CI -0.16 to 0.17, p = 0.96, I^2 = 0%, p = 0.64	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

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Szmulewicz A, Valerio MP, Martino DJ

Longitudinal analysis of cognitive performances in recent-onset and late-life Bipolar Disorder: A systematic review and meta-analysis

Bipolar Disorders 2020; 22(1): 28-37

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Comparison	**Changes in global cognition over time in recent-onset (within 2 years of diagnosis) and later-life patients (>50 years old) vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, some inconsistency and imprecision, direct) suggests no significant differences between groups over time.**
Global cognition	
No differences in neurocognitive functioning over time in both recent-onset and later-life patients; Recent-onset patients vs. controls (change scores over mean follow-up 17 months) 6 studies, N = 549, d = 0.11, 95%CI -0.09 to 0.31, p = 0.28, I^2 = 0% Later-life patients vs. controls (change scores over mean follow-up 33 months) 4 studies, N = 269, d = -0.35, 95%CI -0.84 to 0.15, p = 0.17, I^2 = 81%	
Consistency in results	Consistent for recent-onset patient analysis only.
Precision in results	Precise for recent-onset patient analysis only.
Directness of results	Direct

Trotta A, Murray RM, MacCabe JH

Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis

Psychological Medicine 2015; 45: 381-94

View review abstract online

Comparison	**General cognitive functioning in people with first-episode bipolar disorder compared to controls vs. general cognitive**

	functioning in people with chronic bipolar disorder compared to controls.
Summary of evidence	**Moderate to high quality evidence (large sample, some inconsistency, precise, direct) suggests a small, significant effect of poorer premorbid general cognitive functioning in people with bipolar disorder compared to controls when assessments were conducted retrospectively, but not prospectively. After illness onset, there was a significant, medium-sized effect of poorer general cognitive functioning in people with bipolar disorder compared to controls. The effect was smaller in people with first-episode bipolar disorder than in chronic patients.**
General cognition	
Small, significant effect of poorer premorbid general cognitive functioning in people with bipolar disorder compared to controls when assessments were conducted retrospectively, but not prospectively; All studies: 17 studies, N = 773,408, SMD = -0.113, 95%CI -0.202 to -0.024, $p = 0.013$, $I^2 = 34.5\%$, $p = 0.066$ Retrospective studies: 13 studies, N = 2,922, SMD = -0.147, 95%CI -0.238 to -0.056, $p < 0.001$, $I^2 = 9.8\%$, $p = 0.341$ Prospective studies: 4 studies, N = 770,816, SMD = -0.029, 95%CI -0.199 to 0.142, $p = 0.744$, $I^2 = 46.8\%$, $p = 0.131$ *After illness onset, there was a significant, medium-sized effect of poorer general cognitive functioning in people with bipolar disorder;* 17 studies, N = 2,211, SMD = -0.623, 95%CI -0.717 to -0.529, $p < 0.0001$, $I^2 = 81.6\%$, $p < 0.0001$ *Small, significant effect of more general cognitive impairment in people with first-episode bipolar disorder than in controls;* First episode: 3 studies, N = 390, SMD = -0.277, 95%CI -0.510 to -0.044, $p = 0.020$, $I^2 = 15.1\%$, $p = 0.308$ *The effect was medium-sized in chronic patients;* Chronic patients: 16 studies, N = 1,789, SMD = -0.691, 95%CI -0.793 to -0.588, $p < 0.0001$, $I^2 = 82.4\%$, $p < 0.0001$ Authors report no effects of medications, age, duration of illness, clinical status, source population, year of publication, and cognitive test used.	
Consistency in results	Consistent for premorbid assessments and first-episode bipolar disorder. Inconsistent for post-onset assessment and chronic patients.

IQ and general cognition

Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, *d* = Cohen's *d* and *g* = Hedges's *g* standardised mean difference, 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 = test for heterogeneity, *r* = correlation coefficient, SMD = standardised mean difference

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IQ and general cognition

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 tath 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[14].

† Different effect measures are reported by different reviews.

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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[14].

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, an 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. An 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[15]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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).

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of

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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 dependent 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 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[14];

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

§ 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[16].

‖ 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 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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