TECHNICAL COMMENTARY

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Functioning

Introduction

Functional outcomes refer to aspects of general life and day-to-day function that may be impacted as a consequence of illness-related impairments. For example, symptom severity has been significantly associated with community functioning, including social functioning, work performance, and social skills. Impaired social cognition may impact on functional outcome in terms of maintaining efficient social interactions and independent living skills. Interventions to improve symptom severity or cognitive impairments may have additional benefit for general functional outcomes.

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 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 (RCT) 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 four systematic reviews that met our inclusion criteria[3-6].

- Moderate quality evidence found only around 16% of people with bipolar disorder are estimated to function at a high level. There is less autonomy, poorer occupational, cognitive, financial, and interpersonal functioning, and fewer leisure activities reported in patients compared to people without the disorder.
- High quality evidence finds poor cognitive ability across multiple domains is associated with poor general functioning.

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- Moderate to low quality evidence finds a relationship between poor emotion identification and regulation and poor general functioning, particularly in people with more severe depressive symptoms.

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Akers N, Lobban F, Hilton C, Panagaki K, Jones SH

Measuring social and occupational functioning of people with bipolar disorder: A systematic review

Clinical Psychology Review 2019; 74: 101782

View review abstract online

Comparison	**Functioning in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests around 16% of individuals with bipolar disorder can be estimated to function at a high level.**
General functioning	
Around 16% of individuals with bipolar disorder can be estimated to function at a high level, defined as those falling within two standard deviations of the mean score on each measure; 379 studies, N = 12,392 Scales were; the Global Assessment of Functioning (GAF), Functioning Assessment Short Test (FAST), Social and Occupational Functioning Scale (SOFAS), Social Adjustment Scale (SAS), Social Functioning Scale (SFS) and LIFE-Range of Impaired Functioning (LIFE-RIFT).	
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

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

View review abstract online

Comparison	**Associations between cognition and functioning in people with bipolar disorder.**

Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests poor cognitive ability across multiple domains is associated with poor general functioning.**
General functioning	
Significant, small associations between poor cognitive ability and poor general functioning; Global cognition: 22 studies, N = 1344, *r* = 0.27, 95%CI 0.22 to 0.32, *p* < 0.001, Q*p* = 0.582 Verbal learning and memory: 17 studies, *r* = 0.23, 95%CI 0.14 to 0.31, *p* < 0.0045, Q*p* = 0.088 Processing speed: 12 studies, *r* = 0.23, 95%CI 0.16 to 0.30, *p* < 0.0045, Q*p* = 0.710 Executive control: 11 studies, *r* = 0.26, 95%CI 0.19 to 0.33, *p* < 0.0045, Q*p* = 0.545 Verbal fluency: 10 studies, *r* = 0.22, 95%CI 0.13 to 0.30, *p* < 0.0045, 5.0, Q*p* = 0.833 Reasoning & problem solving: 10 studies, *r* = 0.23, 95%CI 0.14 to 0.32, *p* < 0.0045, Q*p* = 0.686 Working memory: 9 studies, *r* = 0.29, 95%CI 0.20 to 0.38, *p* < 0.0045, Q*p* = 0.177 Attention & vigilance: 9 studies, *r* = 0.22, 95%CI 0.13 to 0.30, *p* < 0.0045, Q*p* = 0.833 General verbal ability: 8 studies, *r* = 0.24, 95%CI 0.14 to 0.33, *p* < 0.0045, Q*p* = 0.762 Global cognitive ability: 6 studies, *r* = 0.34, 95%CI 0.20 to 0.47, *p* < 0.0045, Q*p* = 0.057 Visual learning and memory: 5 studies, *r* = 0.26, 95%CI 0.16 to 0.35, *p* < 0.0045, Q*p* = 0.597 Visuospatial ability: 4 studies, *r* = 0.26, 95%CI 0.12 to 0.39, *p* < 0.0045, Q*p* = 0.656	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Leda-Rego G, Bezerra-Filho S, Miranda-Scippa A

Functioning in euthymic patients with bipolar disorder: A systematic review and meta-analysis using the Functioning Assessment Short Test

Bipolar Disorders 2020; 22: 569-81

View review abstract online

Comparison	**Functioning in people with bipolar disorder during euthymia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, unable to assess precision, direct) finds poorer functioning in people with**

	bipolar disorder than controls without the disorder. There was less autonomy, poorer occupational, cognitive, financial, and interpersonal functioning, and fewer leisure activities reported in patients.
Functional impairment **Functioning Assessment Short Test (FAST)**	
People with bipolar disorder showed poorer functioning on the following FAST scales; Global: 9 studies, N = 1,249, MD = 12.13, 95%CI 11.11 to 13.16, $p < 0.00001$, $I^2 = 83\%$ Autonomy: 9 studies, N = 1,249, MD = 1.51, 95%CI 1.31 to 1.70, $p < 0.00001$, $I^2 = 65\%$ Occupational: 9 studies, N = 1,249, MD = 4.01, 95%CI 3.54 to 4.47, $p < 0.00001$, $I^2 = 90\%$ Cognitive: 9 studies, N = 1,249, MD = 1.28, 95%CI 1.09 to 1.47, $p < 0.00001$, $I^2 = 90\%$ Financial: 9 studies, N = 1,249, MD = 0.53, 95%CI 0.40 to 0.66, $p < 0.00001$, $I^2 = 65\%$ Interpersonal: 9 studies, N = 1,249, MD = 1.03, 95%CI 0.88 to 1.19, $p < 0.00001$, $I^2 = 79\%$ Leisure: 9 studies, N = 1,249, MD = 2.63, 95%CI 2.33 to 2.94, $p < 0.00001$, $I^2 = 67\%$	
Consistency in results	Inconsistent
Precision in results	Unable to assess; MDs not standardized.
Directness of results	Direct

Vlad M, Raucher-Chene D, Henry A, Kaladjian A

Functional outcome and social cognition in bipolar disorder: Is there a connection?

European Psychiatry 2018; 52: 116-25

View review abstract online

Comparison	**Associations between social cognition and functioning in people with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, appears consistent, unable to assess precision, direct) suggests a relationship between poor emotion processing (identification and regulation) and poor general functioning, particularly in people with more severe depressive symptoms.**
General functioning	

Functioning

12 of 13 studies reported a correlation between poor functioning and poor emotion processing (identification of specific emotions, and emotion regulation). 3 of 11 studies reported a correlation between poor functioning and poor Theory of Mind ability. 6 studies found a significant effect of worse depressive symptoms and worse emotion processing, with no associations between manic symptoms and emotion processing.	
Consistency in results	Appears consistent for emotion processing and depression symptoms.
Precision in results	Unable to assess; no confidence intervals are reported.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, *p* = probability of rejecting a null hypothesis of no differences between groups, Q = test for heterogeneity

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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[7].

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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[7].

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[8]. 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.

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[7];

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

§ 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[9].

‖ 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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