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Review article

Prevalence and correlates of cognitive impairment in euthymic adults with bipolar disorder: A systematic review

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ABSTRACT

Background: Previous reviews have identified medium-large group differences in cognitive performance in adults with bipolar disorder (BD) compared to healthy peers, but the proportion with clinically relevant cognitive impairment has not yet been established. This review aimed to quantify the prevalence of cognitive impairment in euthymic adults with BD, and to describe sociodemographic, clinical and other factors that are significantly associated with cognitive impairment.
Methods: Systematic literature review. The population was euthymic community-dwelling adults with BD, aged 18–70 years, and recruited consecutively or randomly. The outcome was cognitive impairment, relative to healthy population norms. Electronic databases and reference lists of relevant articles were searched, and authors were contacted. Original cross-sectional studies published in peer-reviewed English-language journals from January 1994 to February 2015 were included. Methodological bias and reporting bias were assessed using standard tools. A narrative synthesis is presented together with tables and forest plots.
Results: Thirty articles were included, of which 15 contributed prevalence data. At the 5th percentile impairment threshold, prevalence ranges were: executive function 5.3–57.7%; attention/working memory 9.6–51.9%; speed/reaction time 23.3–44.2%; verbal memory 8.2–42.1%; visual memory 11.5–32.9%. More severe or longstanding illness and antipsychotic medication were associated with greater cognitive impairment.
Limitations: The synthesis was limited by heterogeneity in cognitive measures and impairment thresholds, precluding meta-analysis.
Conclusions: Cognitive impairment affects a substantial proportion of euthymic adults with BD. Future research with more consistent measurement and reporting will facilitate an improved understanding of cognitive impairment burden in BD.

Contents

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1. Introduction

Bipolar disorder (BD) is known to be associated with cognitive impairment, which persists between illness episodes and contributes to functional disability. Impairment is typically found on tests of attention, working and episodic memory, processing speed and executive function, with significant group differences of medium to large effect size compared to healthy comparison groups (Arts et al., 2008; Bourne et al., 2013; Mann-Wrobel et al., 2011; Robinson et al., 2006). Although such group-level differences have been consistently reported, the proportion of adults with BD who have clinically relevant levels of cognitive impairment has not yet been clearly established. It is likely that there is marked within-group variation, ranging from normal performance through to severe multi-domain impairment. It has been argued that if overall group differences are being driven by a subgroup of patients with marked levels of impairment, this serves to obscure the true picture of cognitive impairment in the BD population, which in fact may be severe for some and absent for many others (Iverson et al., 2011).

There are a number of reasons why it would be beneficial to establish the prevalence of cognitive impairment in the BD population. From a clinical point of view, cognitive impairment is a major contributor to the overall burden of disability in mood disorders, and is a target in its own right for therapeutic intervention. Service planning would be helped by clearer information about numbers and characteristics of those who are likely to need more clinical or social care input to manage the disabling effects of cognitive impairment. From a research perspective, shifting our focus to identifying subgroups with cognitive impairment will facilitate efforts to understand why some people with BD experience significant problems with cognition while others remain unimpaired. This, in turn, may help to identify particular risk factors for clinically significant cognitive impairment.

1.1. Objectives

1. To determine the prevalence of cognitive impairment in euthymic adults with a history of BD.
2. To describe sociodemographic, clinical and other factors that are associated with cognitive impairment in BD.

1.2. Scope of review

The population of interest was community-dwelling adults with a history of BD (the exposure), who were euthymic at the time of assessment. The outcome of interest was cognitive impairment, measured using standardised tests; presence or absence of impairment was defined with reference to healthy population norms. Since the aim was to determine prevalence, only cross-sectional results were considered (cross-sectional studies or baseline results from cohort studies or trials).

2. Materials and methods

The review was conducted according to a structured protocol which followed PRISMA-P guidance (Moher et al., 2015). The protocol was registered on the PROSPERO database on 16 March 2015 (reference number CRD42015017558; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015017558). Reporting is in accordance with PRISMA and MOOSE guidelines (Moher et al., 2009; Stroup et al., 2000).

2.1. Eligibility criteria

The following inclusion criteria were applied during the search and screening process: original research published in peer-

reviewed journals from 1994 onwards (the year that DSM-IV and ICD-10 diagnostic classifications came into use); articles published in English; studies of community-dwelling adults (not hospital inpatients) aged 18-70 years inclusive (to minimise the additional contribution of age-related cognitive decline); cross-sectional studies or baseline results from cohort studies or trials; clinical samples must have been recruited consecutively from clinics or via a method that ensured eligible individuals in the target population had an equal chance of being approached (so that prevalence estimates would be based on representative samples); primary diagnosis of BD; euthymic at time of assessment; assessed using at least one direct, standardised, objective cognitive measure. Articles were excluded if samples were selected on the basis of presence/absence of cognitive impairment (known or suspected).

2.2. Concepts and definitions

2.2.1. Bipolar disorder

History of bipolar disorder type I, II or not otherwise specified, meeting defined criteria (e.g. DSM or ICD).

2.2.2. Euthymia

Not meeting defined criteria for a depressive or manic episode at time of cognitive assessment; or as otherwise defined by the study authors based on an appropriate clinical measure.

2.2.3. Cognitive impairment

Evidence of impaired performance on one or more objective cognitive tests. Impairment was defined as the fail range on a pass/fail test, or as otherwise defined by the study authors with reference to the score distribution of a healthy comparison group (e.g. from published test norms, or an appropriate comparison group recruited to the study). Results based on any threshold that was less strict than 1 standard deviation (SD) below the comparison mean would not be considered.

2.2.4. Prevalence

Assessments must have been conducted at a single time point, yielding a point prevalence estimate of cognitive impairment, reported as the proportion of the sample falling below the cut-off for impairment.

2.2.5. Correlates

Any sociodemographic, clinical or other factor that was reported by the authors to be significantly associated with presence or severity of cognitive impairment.

2.3. Search strategy

2.3.1. Information sources

The following electronic databases were searched on 24 February 2015: Web of Science (Thomson Reuters), including Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index, Current Contents Connect, Data Citation Index, MEDLINE and SciELO Citation Index; PubMed (NCBI), including MEDLINE, PubMed Central and in-process/ahead-of-print citations; EBSCOhost (EBSCO), including CINAHL and PsycINFO. Additional articles published up to the search date were sought via: the 'cited by' function within individual electronic records of relevant articles; hand searching of reference lists of relevant articles and recent review papers; and email contact with authors.

2.3.2. Process for study identification and selection

A detailed search strategy was developed and tailored for each electronic database. Controlled vocabulary and free text variations were used, including synonyms, abbreviations and spelling variants. Appendix 1 shows the search strategy as implemented in Web of Science. Search outputs were managed using EndNote software.

Duplicate records were removed, and study titles and/or abstracts were screened for relevance by B.C. Screening was carried out with reference to a detailed checklist of eligibility criteria; this was piloted by B.C. and J.W. independently against a sample of initial search results, and refined as required (see Appendix 2 for the final checklist). The sensitivity of the search strategy was checked by testing whether key papers that were known to be relevant were detected by the search. Reproducibility was assessed by J.W., who independently ran the search in one electronic database (Web of Science) and screened the first 200 titles and/or abstracts for relevance. Agreement was 93% (100% following consensus discussion). Full text was obtained for all potentially relevant papers that remained. These were assessed by B.C. using the eligibility checklist, with J.W. independently assessing the first 100 papers for comparison. Agreement was 95% (100% following consensus discussion). Reasons for exclusion were documented.

2.4. Data extraction

A spreadsheet template was used for extracting data from included papers, having been piloted by B.C. and J.W. independently. The list of data fields is given in Appendix 3. Data extraction was carried out by B.C., following which J. W. compared four randomly-chosen data extraction records against the source papers to check for accuracy and completeness; no discrepancies were identified. Where authors appeared to have collected data that could be used to report prevalence of impairment, but had not reported prevalence explicitly in the paper (e.g. articles only reporting group mean differences), the authors were contacted via email to request prevalence results using an appropriate cut-off of their choice.

2.5. Assessment of risk of bias

2.5.1. Risk of bias within studies

Each included study was assessed for risk of bias using a critical appraisal tool for systematic reviews addressing questions of prevalence (Munn et al., 2014). Reporting bias was assessed using the STROBE checklist for cross-sectional studies (von Elm et al., 2007). B.C. and N.A.G. independently rated randomly-chosen articles for comparison, followed by consensus discussion. Initial rating concordance was 83–95% across four articles, and 93% when one further article was independently assessed following the consensus discussion exercise. Subsequent ratings were made by B.C. only. These assessments were considered in the synthesis and discussion, in order to comment on the quality of the literature in this field and to aid interpretation of the results.

2.5.2. Risk of bias across studies

Funnel plots were generated using the metafunnel package in Stata v13 (College Station, TX: StataCorp LP), to allow visual inspection of the relationship between magnitude and precision of prevalence estimates. These are scatter plots depicting a measure of study size (e.g. sample size or standard error of the effect estimate) on the vertical axis against the study's effect estimate on the horizontal axis. Larger (more precise) studies are expected to have effect estimates close to the centre on the horizontal axis, and smaller studies are expected to have effect estimates scattered symmetrically about the centre. Asymmetry in this characteristic inverted funnel shape indicates "small study bias", for example resulting from publication bias (Egger et al., 1997).

2.6. Data synthesis

Where one study population was analysed in two or more eligible articles, the article reporting the largest sample was included in the data synthesis. Additional articles were only included if they contributed unique relevant information (e.g. additional cognitive measures). A narrative synthesis is presented, alongside summary tables of extracted data (Tables 1–3 and Supplementary Tables S1–S3), and forest plots of impairment prevalence estimates and 95% confidence intervals (CI) by cognitive domain (Figs. 2–5). Forest plots were generated using the metan package in Stata v13 (College Station, TX: StataCorp LP). Sociodemographic, clinical and other variables that were significantly associated with cognitive impairment were summarised, and consistency in these findings was compared across studies (Supplementary Fig. S4). Only variables that were potential risk factors for impairment were included; variables that were viewed as consequences of that impairment (e.g. occupational status, instrumental functioning) were not considered, on the basis that they are not potential causal, mediating or moderating factors in explaining the association between BD status and cognitive impairment.

3. Results

3.1. Article selection

Fig. 1 shows a PRISMA flow diagram of the article selection process. Titles and/or abstracts of 5412 records were screened for eligibility, followed by full text evaluation of 658 papers. Forty-six articles were deemed eligible. The most common reasons for exclusion were lack of evidence of consecutive sample recruitment, inclusion of in-patients in study samples, and inclusion of non-euthymic participants. Examples of acceptable sample recruitment methods in the eligible articles were systematic invitation of: consecutively attending eligible patients at out-patient clinics; all eligible patients on a database of open records at a specific clinical service; all eligible persons identified via national registers during a specific period. Of the 46 eligible articles, 16 were omitted from the data synthesis (see list in Appendix 4): 11 reported on overlapping samples without contributing relevant additional information, and for a further five, results directly addressing the two research questions of this review were unavailable.

3.2. Characteristics of included studies

Key characteristics of the 30 included articles are summarised in Table 1. The majority included BD-I samples only (Altshuler et al., 2004; Arslan et al., 2014; Cavanagh et al., 2002; Doganavsargil-Baysal et al., 2013; Cheung et al., 2013; Fakhry et al., 2013; Ferrier et al., 1999; Frangou et al., 2005; Goswami et al., 2009; Ibrahim et al., 2009; Jamrozinski et al., 2009; Juselius et al., 2009; Kieseppa et al., 2005; Lopera-Vasquez et al., 2011; Lopez-Jaramillo et al., 2010; Normala et al., 2010; Osher et al., 2011; Pirkola et al., 2005). A further eight articles reported on mixed BD samples (Barrera et al., 2013; Daban et al., 2012; Elshahawi et al., 2011; Martino et al., 2014; Martino et al., 2008; Mur et al., 2007; Sánchez-Morla et al., 2009; van der Werf-Eldering et al., 2010) and four articles included separate BD-I and BD-II samples (Martino et al., 2011a, 2011a, 2011b; Sparding et al., 2015). Three articles reported on samples recruited from population registers of twin births and hospital discharges (Juselius et al., 2009; Kieseppa et al., 2005; Pirkola et al., 2005) and the rest recruited from specialist psychiatry clinics. Definitions of euthymia differed across studies; many used the Hamilton Rating Scale for Depression (HRSD) and the Young Mania Rating Scale (YMRS), but score thresholds varied. Most studies excluded participants with major psychiatric, neurological or medical comorbidity or learning disability, and many also excluded those with recent substance misuse or electroconvulsive therapy.

Ratings of methodological and reporting bias are shown in Supplementary Fig. S1 and S2, respectively. Although all studies aimed to recruit representative participants using consecutive or random methods, nine of 30 articles included samples which were unrepresentative of the BD population with regard to gender balance and two did not report gender composition. Most articles did not report numbers of patients initially considered or deemed eligible, or information about comparability of eligible patients who did and did not participate; there was evidence of adequate coverage of the intended population in only four articles. Sample sizes were generally small, with only seven studies having 50 or more per group. All articles reported on objective cognitive measures, but 13 did not report sufficient information to allow appraisal of measurement reliability (e.g. qualifications and training of assessors; inter-rater reliability data). Most did not report adequate consideration of sources of bias or imprecision in their procedures or interpretation.

3.3. Prevalence of cognitive impairment

Prevalence was available for 15 articles, reporting on 16 BD samples. Tables 2 and 3 show prevalence results in BD-I only and mixed BD samples, respectively. Characteristics of these samples are provided in Supplementary Tables S1 and S2. Prevalence was available for one study with separate BD-I and BD-II samples (Supplementary Table S3).

Studies applied a variety of impairment thresholds: some were simple pass/fail cut-offs, and others were based on score distributions from published test norms or from a healthy comparison group. Distribution-based thresholds ranged from 1 SD to 2 SD below comparison mean, with the most common being 1.5 SD (approximately 7th percentile), 1.64 SD (approximately 5th percentile) and 2 SD (approximately 2nd percentile). At every threshold and on almost all cognitive measures, prevalence of impairment in BD samples was higher than in the comparison group. Heterogeneity in prevalence across studies did not clearly relate to study quality/risk of bias. Studies differed in whether they used comparison group score distributions or published norms as the reference for impairment, but there was no clear relationship between choice of reference and magnitude of impairment prevalence. For example, on the same tests at the same thresholds, Mur et al. (2007) used published norms and reported lower prevalence estimates than Juselius et al. (2009), who used their own comparison group. On the other hand, Cheung et al. (2013) used published norms and reported some of the highest prevalence estimates across several cognitive domains. Prevalence of impairment did not differ consistently between BD-I only (Table 2) and mixed BD samples (Table 3), although direct comparison is difficult owing to the variation in measures and thresholds used. In the only study where BD-I and BD-II samples could be directly compared (Sparding et al., 2015) (Table S3), prevalence was higher in the BD-I participants on several measures, but there was considerable overlap between the two samples.

Prevalence of cognitive impairment was further considered according to cognitive domain. Results within domains are presented graphically using forest plots, but pooled estimates are not reported because of the wide variation in cognitive tests used and in cut-offs applied to define presence of impairment. The classification of tests by domain was guided by the classifications used by the authors of the original articles. Where tests were thought to cross multiple domains, this is indicated in Tables 2 and 3.

Table 1
Characteristics of included articles.

Author year	Country	Sample *n*		BD sample type BD definition	Euthymia definition	Exclusion criteria
		BD	HC			
Altshuler (2004)	USA	40	22	BD-I DSM-III-R	HRSD < 6 and YMRS < 7 for 3 consecutive months	Head injury with LOC > 1 h; learning disability; migraine; liver function abnormalities; alcoholic dementia; abuse of alcohol in past 6 months; history of cocaine abuse/dependence; diabetes; hypertension; seizure disorder; any other neurologic illness; left-handedness; ECT in past 2 years; other current DSM-III-R Axis I disorder
Arslan (2014)	Turkey	30	32	BD-I DSM-IV	HRSD < 7 and MADRS < 12 and YMRS ≤ 12	DSM Axis I comorbidities; mental retardation; hearing/visual loss interfering with clinical interview; alcohol/substance abuse in past 6 months; any disease affecting CNS; head trauma with LOC
Barrera (2013)	Argentina	12	12	BD-I or BD-II Not stated	HRSD (17 items) < 7 and YMRS < 8	Significant medical diseases; neurological disorders; mental deficiency; drug abuse
Cavanagh (2002)	UK	20	20	BD-I DSM-IV	HRSD ≤ 7 and MMS ≤ 2	Significant physical or neurological illness; stroke or head trauma; significant alcohol and/or drug misuse; ECT in past 6 months; comorbid psychiatric disorder; neurodegenerative disorder; learning disability; endocrine abnormalities
Cheung (2013)	China (Hong Kong)	52	52	BD-I ICD-10 and DSM-IV	HRSD (21 items) < 7 and YMRS < 7 on two occasions 4 weeks apart	Mental retardation; change in psychotropic medication in past 4 weeks; DSM-IV alcohol/substance abuse in past 12 months; head injury with LOC; neurological disorder; history of psychiatric illness other than BD-I; significant physical health problem which could affect cognition
Daban (2012)	France	53	60	BD DSM-III-R	MADRS < 6 and BR-MRS < 5	History of severe head trauma; learning difficulties; neurological disorder; current alcohol/drug abuse
Doganavsargil-Baysal (2013)	Turkey	54	18	BD-I DSM-IV-TR	HRSD ≤ 7 and YMRS ≤ 5	Comorbid psychiatric or neurological disorders; IQ score < 80; infectious or autoimmune diseases; on anti-inflammatory or antibiotic medication; biochemical values not within normal range
Elshahawi (2011)	Egypt	50	50	BD-I or BD-II; history of ≥ 3 affective episodes ICD-10	HRSD < 8 and YMRS < 6	Comorbid psychiatric disorder; ECT in past 3 months; neurological disorder; mental retardation; substance abuse; organic cause of cognitive impairment
Fakhry (2013)	UAE	30 (recent manic episode) 30 (recent depressive episode)	30	BD-I; history of ≤ 3 affective episodes; illness duration < 5 years DSM-IV	MES and MAS < 6; free from symptoms for at least 8 weeks and not fulfilling DSM-IV criteria for an affective episode	Comorbid psychiatric disorders; ECT in past 6 months; lithium-receiving patients in a trial
Ferrier (1999)	UK	21 ('good' outcome) 20 ('poor' outcome)	20	BD-I; at least 5 years illness duration DSM-IV	HRSD ≤ 8 and MSS < 20	Dementing disorder; learning disability; history of substance misuse, cerebrovascular disease, neurodegenerative disorders, head injury with concussion, clinical epilepsy, systemic illness with known cerebral consequences, severe hypertension, severe hepatic or renal disorder, or endocrine disorders other than corrected hypothyroidism
Frangou (2005)	UK	44	44	BD-I DSM-IV	Syndromal remission: not meeting DSM-IV criteria for a mood episode for at least 3 months; no change in medication type/dose over the same period. Symptomatic remission: HRSD and MRS-SADS < 10	None
Goswami (2009)	India	22 (On medication) 22 (not on medication)	NA	BD-I DSM-IV	HRSD < 8 and MSS < 20 on two occasions 4 weeks apart	Other DSM Axis I or II diagnoses; cardiorespiratory, gastrointestinal, neurological and endocrine disorders (other

Table 1 (*continued*)

Author year	Country	Sample *n*		BD sample type BD definition	Euthymia definition	Exclusion criteria
		BD	HC			
						than corrected hypothyroidism); substance misuse/dependency disorders; other medications e.g. anticholinergics, hypnotics or steroids
Ibrahim[a] (2009)	Malaysia	40	40	BD-I DSM-IV	No active manic or depressive symptoms as reflected by YMRS and HRSD scores	Overtly disturbed/aggressive; severe mental retardation; dementia; significant CNS disease; head injury; comorbid psychiatric disorders; substance abuse/dependence; use of anticholinergics or benzodiazepines
Jamrozinski (2009)	Germany	40	40	BD-I DSM-IV	MADRS $\leq$ 10 and YMRS $\leq$ 12	Other medical disorders
Juselius[b] (2009)	Finland	26	114	BD-I DSM-IV (past diagnosis using ICD-8 or DSM-III-R)	In remission according to DSM-IV criteria	Other psychotic disorders; neurological disorders; brain injury; current alcohol dependence
Kieseppä[b] (2005)	Finland	26	114	BD-I DSM-IV (past diagnosis using ICD-8 or DSM-III-R)	In full symptom remission according to DSM-IV criteria	Other psychotic disorders; neurological disorders; brain injury; current alcohol dependence
Lopera-Vásquez (2011)	Colombia	40 (on medication) 31 (not on medication)	28	BD-I DSM-IV	ZSDS < 8 and YMRS < 6	Illicit substances or benzodiazepines in past 4 weeks; other psychiatric or neurological disorders; mental retardation; any treatment with ECT
López-Jaramillo (2010)	Colombia	24 (1 manic episode) 27 (2 manic episodes) 47 ($\geq$ 3 manic episodes)	66	BD-I DSM-IV	HRSD < 8 and YMRS < 6	Illicit substances or benzodiazepines in past 4 weeks; other psychiatric or neurological disorders that could affect cognition; mental retardation; any treatment with ECT; physical/sensory limitations that could affect performance
Martino[c] (2008)	Argentina	50	30	BD-I or BD-II DSM-IV	HRSD $\leq$ 8 and YMRS $\leq$ 6 for at least 6 weeks	Substance abuse; mental retardation; neurological disease; any clinical condition that could affect cognitive performance
Martino[c] (2011a)	Argentina	48 (BD-I) 39 (BD-II)	39	BD-I; BD-II DSM-IV	HRSD $\leq$ 8 and YMRS $\leq$ 6 for at least 8 weeks	Substance abuse; mental retardation; neurological disease; any clinical condition that could affect cognitive performance
Martino[c] (2011b)	Argentina	45 (BD-I) 36 (BD-II)	34	BD-I; BD-II DSM-IV	HRSD $\leq$ 8 and YMRS $\leq$ 6 for at least 8 weeks	Substance abuse; mental retardation; neurological disease; any clinical condition that could affect cognitive performance
Martino[c] (2011c)	Argentina	48 (BD-I) 37 (BD-II)	34	BD-I; BD-II DSM-IV	HRSD $\leq$ 8 and YMRS $\leq$ 6 for at least 8 weeks	Substance abuse; mental retardation; neurological disease; any clinical condition that could affect cognitive performance
Martino[c] (2014)	Argentina	100	40	BD-I or BD-II DSM-IV	HRSD $\leq$ 9 and YMRS $\leq$ 8 for at least 8 weeks	Substance abuse; mental retardation; neurological disease; any clinical condition that could affect cognitive performance
Mur (2007)	Spain	44	46	BD-I or BD-II DSM-IV	HRSD (17-item) < 8 and YMRS < 6 for at least 3 months; on same treatment regimen and clinically stable for 3 months	Significant physical or neurologic illness; substance abuse/dependence in the past year; ECT in the past year; any mood-stabilising medication other than lithium
Normala[a] (2010)	Malaysia	40	40	BD-I DSM-IV	No active manic or depressive symptoms as reflected by YMRS and HRSD scores	Overtly disturbed/aggressive; severe mental retardation; dementia; significant CNS disease; head injury; comorbid psychiatric disorders; substance abuse/dependence; use of anticholinergics or benzodiazepines
Osher (2011)	Israel	51	495	BD-I	Consensus judgement by two clinicians based on full	Serious physical illness or substance abuse

				DSM-IV	history and evidence of stability for at least three months[d]		
Pirkola[b] (2005)	Finland	22	100	BD-I DSM-III-R or DSM-IV	Not stated		Schizoaffective disorder; psychotic disorder other than BD-I; neurological disease; clinically significant head injury; mental retardation
Sánchez-Morla (2009)	Spain	73	67	BD DSM-IV	HRSD < 7 and YMRS < 6 for 3 consecutive monthly evaluations		Neurological or medical diseases that can affect cognition; mental retardation; history of alcohol or other substance abuse/dependence in past 2 years; ECT in past 2 years; history of head injury with LOC
Sparding (2015)	Sweden	64 (BD-I) 44 (BD-II)	86	BD-I; BD-II DSM-IV	MADRS and YMRS < 14		None stated
van der Werf-Eldering (2010)	The Netherlands	46	75	BD-I, BD-II or BD-NOS DSM-IV	IDS-SR < 14 and YMRS < 8		Mental retardation; systemic or neurological disease which could affect cognition; alcohol use disorder currently needing treatment in a specialised setting

BD, bipolar disorder; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; BD-NOS, bipolar disorder not otherwise specified; BR-MRS, Bech–Rafaelsen Mania Rating Scale; CNS, central nervous system; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders third edition revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders fourth edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders fourth edition text revision; ECT, electroconvulsive therapy; HC, healthy comparison; HRSD, Hamilton Rating Scale for Depression; ICD-8, International Classification of Diseases eighth revision; ICD-10, International Classification of Diseases tenth revision; IDS-SR, Inventory of Depressive Symptomatology – Self Rating; IQ, intelligence quotient; LOC, loss of consciousness; MADRS, Montgomery–Åsberg Depression Rating Scale; MAS, Bech–Rafaelsen Mania Scale; MES, Bech–Rafaelsen Melancholia Scale; MRS-SADS, Mania Rating Scale from the Schedule for Affective Disorders and Schizophrenia (Change Version); MSS, Bech's modification of Beigel's Mania State Rating Scale; NA, not applicable; YMRS, Young Mania Rating Scale; ZSDS, Zung Self-Rated Depression Scale.

[a] Studies contain overlapping samples.
[b] Studies contain overlapping samples.
[c] Studies contain overlapping samples.
[d] Information provided by author.

3.3.1. Executive function, reasoning and social cognition

Fig. 2 shows prevalence of impairment in studies which used a normative distribution-based threshold for impairment. Additional score-based threshold results from three studies (Altshuler et al., 2004; Barrera et al., 2013; Normala et al., 2010) are reported in Tables 2 and 3. Measures which are significantly influenced by performance speed are considered separately from those that are not, to minimise the overlap between underlying processing speed ability and instrumental executive function. The former category included timed fluency measures, Stroop test, Trailmaking test, and composite scores primarily influenced by these. The latter category included Tower tests, non-time-dependent aspects of fluency tasks (e.g. category switching accuracy), reasoning tests, Wisconsin Card Sorting test, BADS Six Elements task, and composite scores primarily influenced by these.

Fig. 2 shows that impairment prevalence tended to be slightly higher on speed-sensitive tasks (panel B) than on those that depend less on speed (panel A), though this pattern was not evident in all studies. The estimates did not follow a clear gradient according to the different threshold strata: for example, the estimates from Cavanagh et al. (2002) were the same at the 5th and 2nd percentile levels. This may be a consequence of small sample size, or may indicate that impaired individuals were strongly clustered at the extreme low end of the score distribution, such that less strict thresholds made little difference to the absolute numbers considered impaired. The estimates from Juselius et al. (2009) were somewhat higher than expected in the context of the other studies. This may be related to study size and quality, but it should also be noted that this study included several twin pairs who were concordant for BD. BD-II-only results are not shown in Fig. 2, but Supplementary Table S3 indicates that fewer BD-II participants were impaired, in comparison with BD-I participants, on most executive function measures in Sparding et al. (2015). Only one study provided prevalence data for social cognition tasks (Barrera et al., 2013): in a small mixed BD sample (n = 12), prevalence of impairment on emotional and cognitive theory of mind measures was higher compared to the healthy comparison sample (Table 3).

3.3.2. Attention and working memory

Fig. 3 shows the prevalence of impairment in five studies (of similar quality) that reported attention/working memory measures. Estimates were generally higher than in the healthy comparison population, and this was most striking on the CNS-VS complex attention score reported by Cheung et al. (2013) and the Mindstreams attention score from Osher et al. (2011). These scores are composites of several demanding tasks, more akin to the executive measures presented in Fig. 2. Additional measures from Normala et al. (2010) are reported in Table 2, showing a slightly elevated percentage of BD participants with reduced forward and backward digit span. The study by Sparding et al. (2015) allows comparison between BD-I and BD-II samples on two attention/working memory measures, indicating that proportions impaired were similar (Supplementary Table S3).

3.3.3. Speed and reaction time

Fig. 4 shows that prevalence of impairment on speed and reaction time measures was similar across different impairment thresholds. However, Daban et al. (2012) reported that 30.2% were impaired on the WAIS-III Digit Symbol Coding task at the 5th percentile threshold, whereas Sparding et al. (2015) reported 19% impairment prevalence on the same task at the less strict threshold of 11th percentile. Daban et al. assessed a mixed BD sample but did not report subtypes or illness characteristics, making it difficult to infer reasons for the disparity with Sparding et al.'s BD-I sample. It was also evident from the Sparding et al.

Table 2
Prevalence of cognitive impairment in BD-I samples.[a]

Author year	Sample *n*		Cognitive measure	Impairment definition	Impairment prevalence *n* (%)		*d*
	BD	HC			BD	HC	
Altshuler (2004)	40	22	WCST categories (executive)	Score 0-3	(42%)	(0%)	−0.98
			CVLT total recall 1–5 (verbal memory)	1.75 SD from published normative mean[b]	(22%)	(0%)	−0.99
Cavanagh (2002)[c]	20	20	Stroop Color-Word Test (executive)	1.64 SD from HC mean	7 (36.8%)	(5%)[d]	−0.61
			Letter fluency (executive)		2 (10%)	(5%)[d]	−0.31
			BADS Six Elements (executive)		1 (5.3%)	(5%)[d]	−0.31
			CVLT trial 1 (verbal memory)		7 (35%)	(5%)[d]	−1.24
			CVLT total recall 1–5 (verbal memory)		5 (25%)	(5%)[d]	−1.06
			CVLT delayed recall (verbal memory)		8 (42.1%)	(5%)[d]	−0.96
			CVLT delayed recognition total (verbal memory)		4 (21.1%)	(5%)[d]	−0.62
			CVLT delayed recognition minus false positives (verbal memory)		4 (21.1%)	(5%)[d]	−0.66
			Stroop Color-Word Test (executive)	2 SD from HC mean	7 (36.8%)	(2.275%)[d]	−0.61
			Letter fluency (executive)		2 (10%)	(2.275%)[d]	−0.31
			BADS Six Elements (executive)		1 (5.3%)	(2.275%)[d]	−0.31
			CVLT trial 1 (verbal memory)		2 (10%)	(2.275%)[d]	−1.24
			CVLT total recall 1–5 (verbal memory)		4 (20%)	(2.275%)[d]	−1.06
			CVLT delayed recall (verbal memory)		5 (26.3%)	(2.275%)[d]	−0.96
			CVLT delayed recognition total (verbal memory)		4 (21.1%)	(2.275%)[d]	−0.62
			CVLT delayed recognition minus false positives (verbal memory)		4 (21.1%)	(2.275%)[d]	−0.66
Cheung (2013)	52	52	CNS-VS neurocognition (overall)	5th percentile of published norm	(46.2%)	(0.0%)	−1.64
			CNS-VS executive function		(53.8%)	(0.0%)	−1.69
			CNS-VS cognitive flexibility		(57.7%)	(0.0%)	−1.66
			CNS-VS complex attention		(51.9%)	(1.9%)	−1.36
			CNS-VS processing speed		(26.9%)	(0.0%)	−1.21
			CNS-VS psychomotor speed		(30.8%)	(1.9%)	−1.15
			CNS-VS reaction time		(44.2%)	(13.5%)	−0.90
			CNS-VS memory composite		(30.8%)	(5.8%)	−0.80
			CNS-VS verbal memory		(28.8%)	(5.8%)	−0.71
			CNS-VS visual memory		(11.5%)	(3.8%)	−0.65
			1 SD from published normative mean on ≥ 2 index scores		(61.5%)	(1.9%)	NA
			2 SD from published normative mean on ≥ 2 index scores		(40.4%)	(0.0%)	NA
Fakhry (2013) S1: recent manic episode	30	30	MMSE (global)	Score < 25	23 (76.7%)	0 (0%)	−4.62
			MTS (global)	Score < 27	18 (60%)	0 (0%)	−2.10
			CDT (executive/visuospatial)	Score < 6	0 (0%)	0 (0%)	−3.31
Fakhry (2013) S2: recent depressive episode	30	30	MMSE (global)	Score < 25	6 (20%)	0 (0%)	−2.74
			MTS (global)	Score < 27	5 (16.7%)	0 (0%)	−0.84
			CDT (executive/visuospatial)	Score < 6	0 (0%)	0 (0%)	−2.89
Ibrahim (2009)[e] and Normala (2010)[e]	40	40	Category fluency (executive/language)	Score ≤ 30	3 (7.5%)	0 (0%)[c]	−1.01
			TMT part A (speed/attention)[c]	$> 40/45/50$ s[f]	19 (47.5%)	11 (27.5%)	−0.52
			TMT part B (executive)[c]	$> 90/100/135$ s[f]	25 (62.5%)	13 (32.5%)	−0.81
			Digit span forward (attention)[c]	Span < 5	3 (7.5%)	1 (2.5%)	−0.97
			Digit span backward (working memory)[c]	Span < 4	18 (15.0%)	5 (12.5%)	−1.10
			RAVLT trial 1 (verbal memory)	Score < 7	31 (77.5%)	13 (32.5%)	NR
			RAVLT trial 5 (verbal memory)	Score < 12	23 (57.5%)	1 (2.5%)	NR
			RAVLT trials 1-5 (verbal memory)	Score increment < 5	16 (40%)	3 (7.5%)	NR
			RAVLT list B (verbal memory)	Score < 7	37 (92.5%)	14 (35%)	NR
Juselius (2009)	26[g]	114	WCST categories (executive)	1.5 SD from HC mean	12 (50%)	(6.68%)[d]	−0.78
			WCST perseverative (executive)		13 (54%)	(6.68%)[d]	−1.74
			Stroop interference (executive)		15 (68%)	(6.68%)[d]	−3.58
			TMT B minus A (executive)		10 (42%)	(6.68%)[d]	−0.33
			Letter fluency (executive/language)		15 (63%)	(6.68%)[d]	−1.75
			Category fluency (executive/language)		18 (78%)	(6.68%)[d]	−3.40
Osher (2011)[c]	51	495	Mindstreams global cognition	1.5 SD from HC mean	25 (49.0%)	(6.68%)[d]	−1.19
			Mindstreams executive function		13 (25.5%)	(6.68%)[d]	−0.83
			Mindstreams attention		20 (39.2%)	(6.68%)[d]	−1.04
			Mindstreams information processing speed		15 (29.4%)	(6.68%)[d]	−0.91
			Mindstreams memory		22 (43.1%)	(6.68%)[d]	−0.96
			Mindstreams verbal function		11 (21.6%)	(6.68%)[d]	−0.51

Table 2 (*continued*)

Author year	Sample *n*		Cognitive measure	Impairment definition	Impairment prevalence *n* (%)		*d*
	BD	HC			BD	HC	
			Mindstreams visual-spatial		16 (31.4%)	(6.68%)[d]	−0.67
			Mindstreams motor skills		12 (23.5%)	(6.68%)[d]	−0.58

BADS, Behavioural Assessment of the Dysexecutive Syndrome; BD, bipolar disorder; BD-I, bipolar disorder type I; CDT, Clock Drawing Test; CNS-VS, Central Nervous System Vital Signs computerised battery; CVLT, California Verbal Learning Test; HC, healthy comparison; MMSE, Mini-mental State Examination; MTS, Mental Test Score; NA, not applicable; NR, unable to calculate as mean and SD not reported in article; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; TMT, Trailmaking Test; WCST, Wisconsin Card Sorting Test.

d is the standardised mean difference between BD and HC groups, calculated from unadjusted results in the article; negative values indicate worse performance in BD group.

[a] Sample characteristics are reported in Supplementary Table S1.

[b] T-score <32; impairment definition not explicit in article but inferred from bar graph of results.

[c] Prevalence data provided by author.

[d] By definition, according to impairment threshold applied.

[e] Same sample; RAVLT reported in Ibrahim (2009) and other tests reported in Normala (2010).

[f] Age groups 18–39, 40–49 and 50–59, respectively.

[g] Sample denominator for prevalence results ranges from 22 to 24.

study that fewer BD-II participants were impaired on these tasks; in the case of WAIS-III Digit-Symbol Coding, the proportion impaired (11%) was in line with the normative score distribution (Supplementary Table S3).

3.3.4. Memory

Fig. 5 shows impairment prevalence results for verbal memory (panel A) and visual memory (panel B). Additional score-based threshold results from Ibrahim et al. (2009) are shown in Table 2. Two studies of similar quality that reported composite verbal and visual measures separately (Cheung et al., 2013; Sánchez-Morla et al., 2009) showed contradictory findings regarding relative prevalence of impairment: both studies reported that 28.8% were impaired on verbal memory at the 5th percentile threshold, but proportions impaired on visual memory were 11.5% in Cheung et al. (2013) versus 32.9% in Sánchez-Morla et al. (2009). The proportions impaired on overall memory composite measures were 43.1% at the 7th percentile threshold (Osher et al., 2011) and 30.8% at the 5th percentile (Cheung et al., 2013).

The California Verbal Learning Test (CVLT) was the most common of the verbal measures, used in four studies with different thresholds. Results from Cavanagh et al. (2002) and Altshuler et al. (2004) indicated a threshold-related gradient, with fewer participants falling below the stricter 2nd percentile level for CVLT learning and recall, though not for recognition performance. Sánchez-Morla et al. (2009) reported lower impairment prevalence than Cavanagh et al. using the same 5th percentile threshold for the same CVLT measures (total trials 1–5, and long delay recall). This may be explained by the larger sample size and mix of BD-I and BD-II participants in the former study. No verbal memory results were available for BD-II separately.

Visual memory results were available from four studies of similar quality. Three (Mur et al., 2007; Sánchez-Morla et al., 2009; Sparding et al., 2015) used the Rey Complex Figure Test (RCFT) at different impairment thresholds; prevalence on this test was lowest in Sparding et al. (2015) despite the less strict threshold and more severe clinical characteristics of their sample. Prevalence of visual memory impairment was similar between BD-I and BD-II samples in that study (Supplementary Table S3).

3.3.5. Visuospatial function

Three studies (Osher et al., 2011; Sánchez-Morla et al., 2009; Sparding et al., 2015) reported visuospatial measures (Tables 2, 3 and S3). Impairment prevalence was lower for visuospatial tasks than for other cognitive domains, though still somewhat higher than would be expected from the normative distribution. Prevalence was highest on the WAIS-III Block Design task—reported as 40% by Sparding et al. (2015) at the 11th percentile threshold—which may reflect the executive and speed components that contribute to success on this task. Prevalence was similarly high among BD-II participants on this task (Sparding et al., 2015).

3.3.6. Any domain, multi-domain and global impairment

Fakhry et al. (2013) used the Mini-mental State Examination (MMSE), Mental Test Score (MTS) and Clock Drawing Test (CDT)—typically used as global measures in dementia settings—to assess BD-I participants, grouped by the polarity of their most recent illness episode. Table 2 shows that the proportions falling below the impairment cut-off were markedly higher in the group whose most recent episode was manic. No BD participant scored below the cut-off on the CDT, however.

Osher et al. (2011) reported that 49% of their BD-I sample fell below the 7th percentile (1.5 SD) on the global cognition measure of the Mindstreams computerised battery. Also in BD-I, 46.2% of the Cheung et al. (2013) sample were below the 5th percentile on the CNS-VS overall measure of neurocognition. Furthermore, 61.5% were at least 1 SD below the normative mean on at least two CNS-VS index scores, and 40.4% met the stricter criterion of being at least 2 SD below the normative mean on at least two index scores.

Two studies reported overall results from mixed BD samples. van der Werf-Eldering et al. (2010) found that 6 of 46 participants (13%) were at least 2 SD above the healthy comparison mean (where higher scores indicated worse performance) in at least one cognitive domain. The sample of 46 was a euthymic sub-group from a larger study, for whom demographic and clinical characteristics were not available. It is therefore unclear why the proportion impaired was relatively low in this study. Martino et al. (2014) assessed a larger sample (n=100), and reported that 70% were impaired using "soft" criteria (1.5 SD below the normative mean in at least one cognitive domain) and 30% were impaired using "hard" criteria (at least 2 SD below the normative mean in at least two domains).

3.3.7. Risk of bias across studies

Supplementary Fig. S3 shows funnel plots of the relationship between prevalence estimates and their precision (standard error), presented separately by cognitive domain, for studies reporting measures at the 5th percentile impairment threshold. Visual inspection suggested a degree of asymmetry for measures of verbal memory, and to a lesser extent for speed-sensitive measures (both within the executive domain and on specific tests of speed/reaction time). Relatively fewer estimates in the lower left quadrant of these plots may indicate publication bias, or reflect other factors such as different sample characteristics or assessment methods in

Table 3
Prevalence of cognitive impairment in mixed BD samples.[a]

Author year	Sample *n*		Cognitive measure	Impairment definition	Impairment prevalence *n* (%)		*d*
	BD	HC			BD	HC	
Barrera (2013)[b]	12	12	Reading the Mind in the Eyes test (theory of mind)	Score < 21	6 (50%)	2 (16.7%)	−0.61
			Faux Pas Recognition Test cognitive items (theory of mind)	Score < 0.75	7 (58.3%)	4 (33.3%)	−0.77
Daban (2012)	53	60	WAIS-III Digit Symbol Coding (processing speed)	1.64 SD from HC mean	(30.2%)	(5%)[c]	−0.89
Martino (2014)	100	40	Various tests (executive, attention/working memory, verbal memory, naming)	1.5 SD from published normative mean in ≥1 cognitive domain	(70%)	(27.5%)	NA
				2 SD from published normative mean in ≥2 cognitive domains	(30%)	(7.5%)	NA
Mur (2007)[b]	44	46	TMT part B (executive)	1.5 SD from published normative mean	0 (0%)	0 (0%)	−0.72
			Letter fluency (executive/language)		6 (13.6%)	0 (0%)	−0.71
			WCST categories (executive)		18 (40.9%)	7 (15.2%)	−0.87
			WCST perseverative (executive)		15 (34.1%)	5 (10.9%)	−0.49
			Stroop inhibition (executive)		11 (25.0%)	1 (2.2%)	−1.30
			Digit span (attention/working memory)		3 (6.8%)	0 (0%)	NR
			TMT part A (speed/attention)		0 (0%)	0 (0%)	−0.28
			CVLT trial 1 (verbal memory)		11 (25.0%)	7 (15.2%)	0.19
			CVLT total words (verbal memory)		17 (38.6%)	6 (13.0%)	0.01
			CVLT immediate recall (verbal memory)		13 (29.5%)	4 (8.7%)	0.12
			CVLT delayed recall (verbal memory)		12 (27.3%)	6 (13.0%)	−0.33
			RCFT immediate (visual memory)		13 (29.5%)	0 (0%)	−0.52
			RCFT delayed (visual memory)		16 (36.4%)	4 (8.7%)	−0.55
Sánchez-Morla (2009)	73	67	Executive composite z-score	1.64 SD from HC mean	33 (45.2%)	(5%)[c]	−1.80
			Sustained attention composite z-score		10 (13.7%)	(5%)[c]	−0.65
			Verbal memory composite z-score		21 (28.8%)	(5%)[c]	−1.18
			Visual memory composite z-score		24 (32.9%)	(5%)[c]	−1.10
			WCST % conceptual level response (executive)		(19.2%)	(5%)[c]	−1.02
			WCST % perseverative errors (executive)		(19.2%)	(5%)[c]	−1.01
			Stroop interference (executive)		(35.6%)	(5%)[c]	−0.98
			TMT part B (executive)		(32.9%)	(5%)[c]	−0.97
			Letter fluency (executive/language)		(16.4%)	(5%)[c]	−1.00
			Animal fluency (executive/language)		(24.7%)	(5%)[c]	−0.89
			Tower of Hanoi no. of movements (executive)		(19.0%)	(5%)[c]	−0.64
			Digit span backward (working memory)		(11.0%)	(5%)[c]	−0.53
			CPT hits (attention)		(9.6%)	(5%)[c]	−0.52
			CPT sensitivity A (attention)		(9.6%)	(5%)[c]	−0.58
			CPT reaction time (attention/speed)		(23.3%)	(5%)[c]	−0.72
			CVLT total recall 1–5 (verbal memory)		(19.2%)	(5%)[c]	−0.97
			CVLT short free-recall (verbal memory)		(27.4%)	(5%)[c]	−0.96
			CVLT long free-recall (verbal memory)		(15.1%)	(5%)[c]	−0.97
			CVLT short cued-recall (verbal memory)		(20.5%)	(5%)[c]	−1.11
			CVLT long cued-recall (verbal memory)		(23.3%)	(5%)[c]	−0.97
			CVLT recognition discriminability (verbal memory)		(8.2%)	(5%)[c]	−0.67
			CVLT semantic strategies trial A (verbal memory)		(41.1%)	(5%)[c]	−0.82
			RCFT copy (visuospatial)		(16.4%)	(5%)[c]	−0.51
			RCFT short-term (visual memory)		(31.5%)	(5%)[c]	−0.98
			RCFT long-term (visual memory)		(32.9%)	(5%)[c]	−1.01
van der Werf-Eldering (2010)	46	75	Various tests (executive, attention/working memory, reaction time, verbal and visual memory)	2 SD from HC mean in ≥1 cognitive domain	6 (13%)	(2.275%)[c]	NA

BD, bipolar disorder; BD-I, bipolar disorder type I; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; HC, healthy comparison; NA, not applicable; NR, unable to calculate as mean and SD not reported in article; RCFT, Rey Complex Figure Test; SD, standard deviation; TMT, Trailmaking Test; WAIS-III, Wechsler Adult Intelligence Scale third edition; WCST, Wisconsin Card Sorting Test.
d is the standardised mean difference between BD and HC groups, calculated from unadjusted results in the article; negative values indicate worse performance in BD group.

[a] Sample characteristics are reported in Supplementary Table S2.
[b] Prevalence data provided by author.
[c] By definition, according to impairment threshold applied.

the smaller/less precise studies. The small number of independent measures meant it was not possible to apply statistical tests of asymmetry.

3.4. Factors associated with cognitive impairment

Twenty-eight articles provided information regarding the association between various sociodemographic, clinical or other variables and presence or severity of cognitive impairment. Articles were not always clear about which associations had been tested statistically, and they varied in the extent to which they adjusted for potential confounders. Supplementary Fig. S4 shows an overview of the types of variables tested, with significant findings highlighted across studies.

Associations with demographic variables and premorbid ability were often not tested. In some cases this was because key background factors had been frequency-matched in a between-group study design, or had been adjusted for when calculating

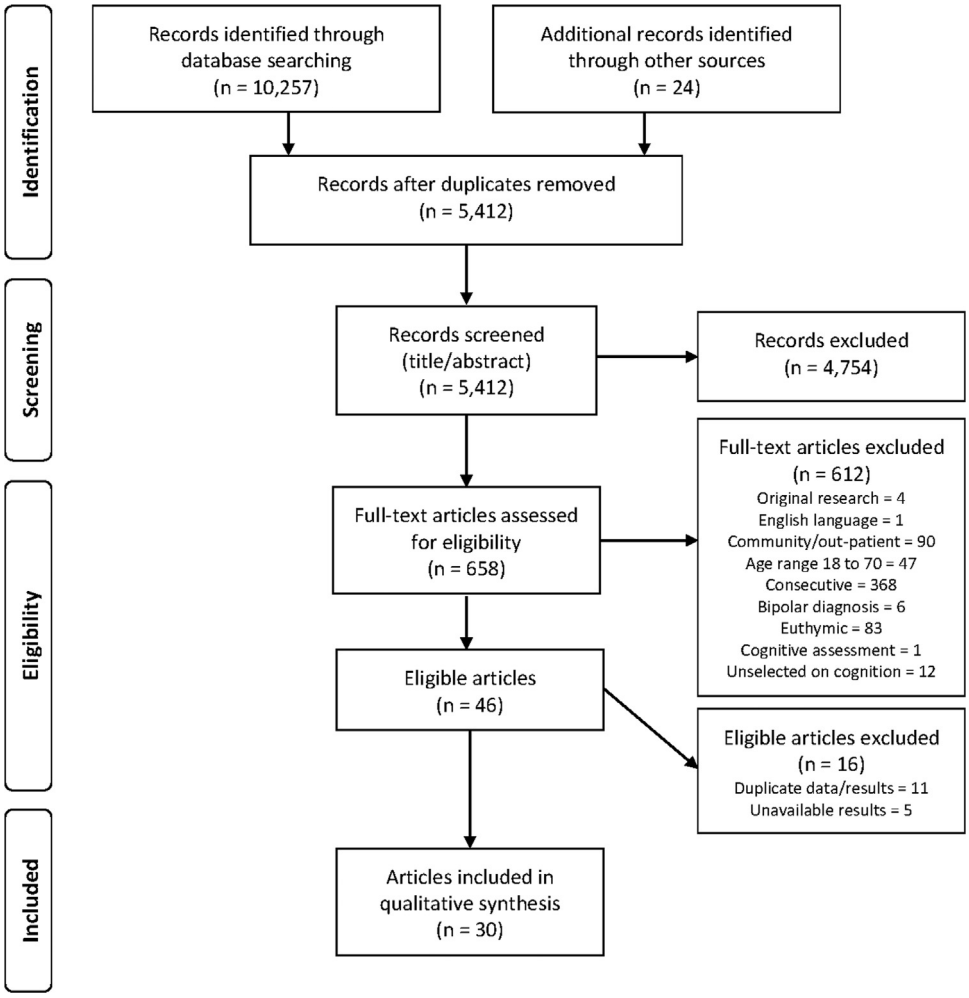

Fig. 1. PRISMA flow diagram showing results of literature search and screening.

standardised cognitive scores. Other analyses included these background factors as covariates (e.g. in multiple regression), without reporting results for these covariates separately. For the remainder, greater cognitive impairment was associated with older age and lower education and premorbid ability in some studies, but others reported no significant findings.

Illness characteristics—such as duration since onset, number of affective episodes and hospitalisations, history of psychotic symptoms, and residual depressive or manic symptoms—were more frequently investigated. Where significant results were reported, they indicated that more severe illness characteristics were associated with worse cognitive function. An exception was history of psychotic symptoms, for which one study reported both positive and negative effects. Several studies investigated associations with psychotropic medication, with mixed findings. The strongest evidence of association was between antipsychotic medication and worse cognition, though some studies reported null findings. By contrast, mood stabilisers (lithium or anticonvulsants) were less frequently associated with impairment.

Although two studies examined history of alcohol/substance use disorder, none investigated the relationship between frequency/amount of alcohol or recreational drug consumption and cognitive impairment. No study examined associations with smoking or other cardiovascular risk factors that may be relevant to cognitive impairment.

4. Discussion

4.1. Summary of findings

The aims of this review were to determine the prevalence of cognitive impairment in euthymic adults with BD, and to ascertain which clinical, sociodemographic or other factors were associated with cognitive impairment in this population. Thirty articles contributed to the findings, of which 15 provided prevalence. Impairment prevalence was similar between BD-I only and mixed BD samples. One study with separate results for BD-I and BD-II participants indicated that impairment was more common in those with BD-I, though considerable overlap was apparent. Examination of impairment proportions across different cognitive domains indicated wide variation both within and between domains. For example, taking the 5th percentile threshold as the reference, impairment prevalence ranges were as follows: non-speed-sensitive executive function 5.3–57.7%; speed-sensitive executive function 10.0–36.8%; attention/working memory 9.6–51.9%; speed/reaction time 23.3–44.2%; verbal memory 8.2–42.1%; visual memory 11.5–32.9%. Generally small sample sizes resulted in wide CIs for most estimates. A recent review of neuropsychological function in BD (Szmulewicz et al., 2015) highlighted impairment prevalence as an issue of particular interest, and reported estimates between 30% and 57% from six studies. Four of these studies were not eligible for the present review, either because participants were not euthymic or because the recruitment method did not meet our

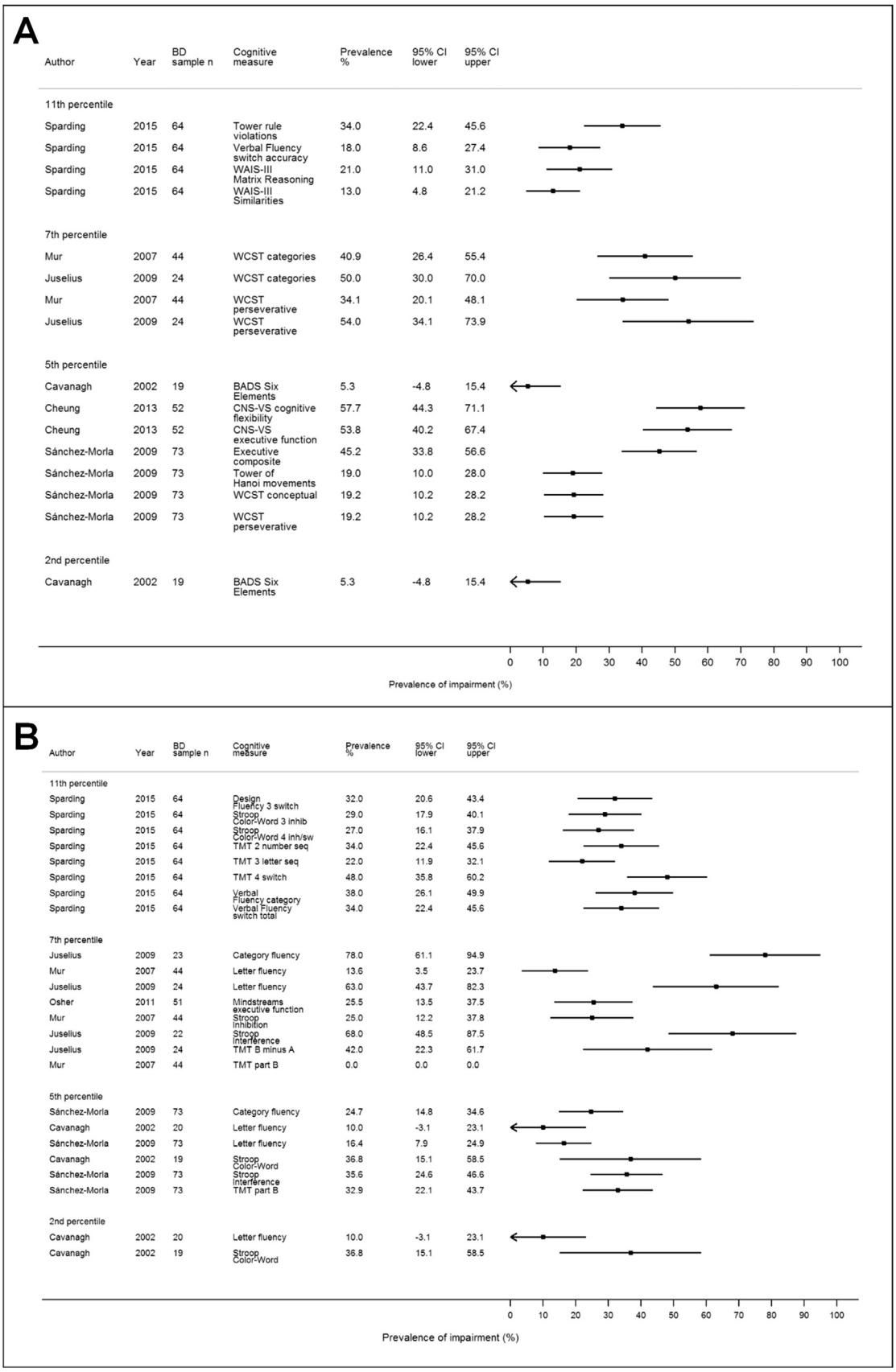

Fig. 2. Executive function impairment prevalence across different thresholds. BADS, Behavioural Assessment of the Dysexecutive Syndrome; BD, bipolar disorder; BD-I, bipolar disorder type I; CI, confidence interval; CNS-VS, Central Nervous System Vital Signs computerised battery; TMT, Trailmaking Test; WAIS-III, Wechsler Adult Intelligence Scale third edition; WCST, Wisconsin Card Sorting Test. Results include mixed BD and BD-I samples. Some studies reported results for several cognitive scores, and so there is sample overlap across rows. CI estimates are based on standard errors calculated as follows: sqrt((prevalence*(100-prevalence))/n). Results are stratified by impairment threshold (percentile), in descending order from least to most strict. Panel A shows executive measures whose scores do not have a prominent timed/speed contribution, and panel B shows executive measures whose scores are influenced by speed.

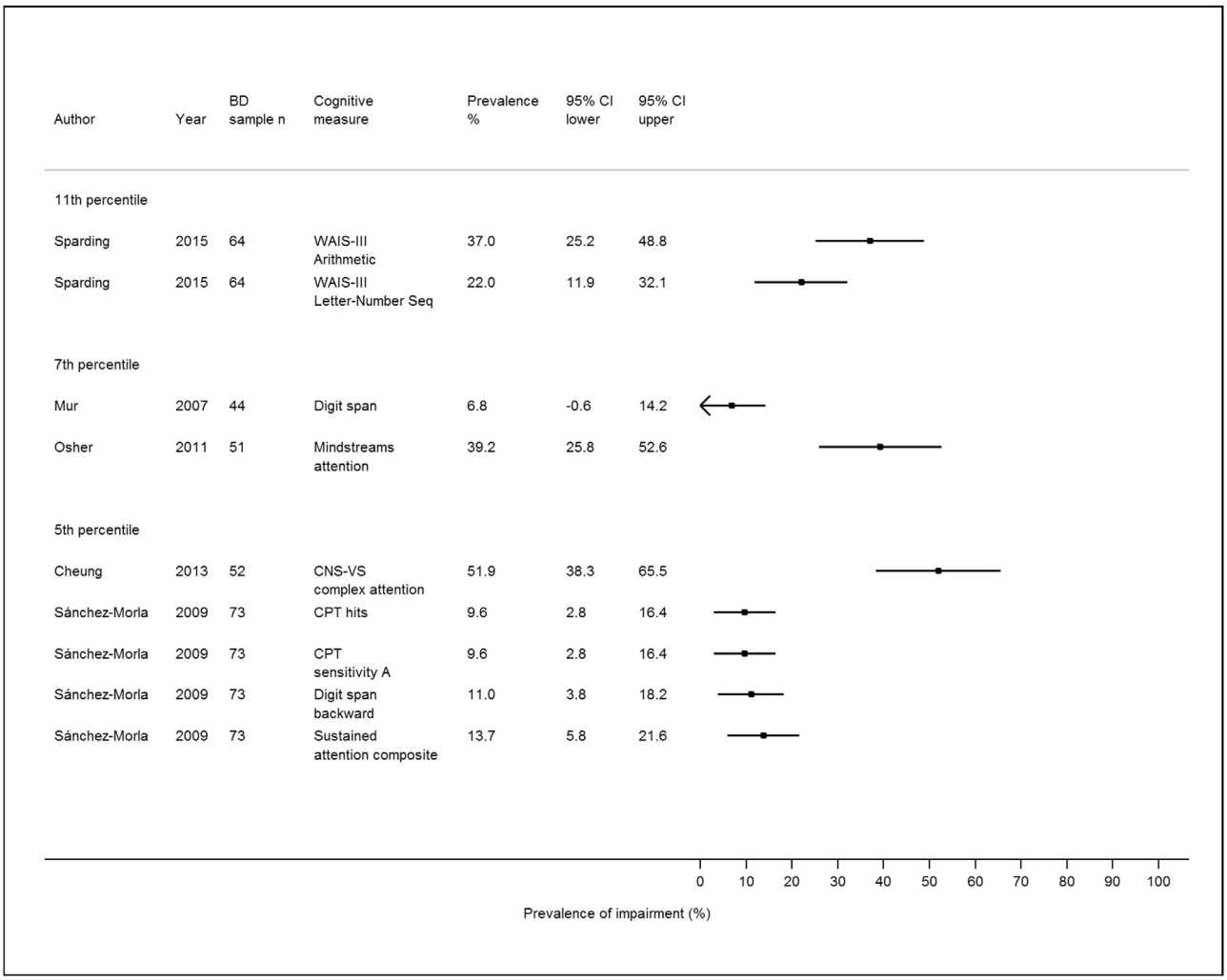

Fig. 3. Attention/working memory impairment prevalence across different thresholds. BD, bipolar disorder; BD-I, bipolar disorder type I; CI, confidence interval; CNS-VS, Central Nervous System Vital Signs computerised battery; CPT, Continuous Performance Test; WAIS-III, Wechsler Adult Intelligence Scale third edition. Results include mixed BD and BD-I samples. Some studies reported results for several cognitive scores, and so there is sample overlap across rows. CI estimates are based on standard errors calculated as follows: sqrt((prevalence*(100-prevalence))/n). Results are stratified by impairment threshold (percentile), in descending order from least to most strict.

criteria. The fact that the lower bounds of the prevalence estimates reported in the present review are below the previous estimate of 30% can be understood in light of our exclusion of non-euthymic participants and samples recruited by convenience, either of which may bias prevalence estimates upwards.

There was some evidence that more severe or longstanding illness was associated with greater cognitive impairment. Several studies reported an association with antipsychotic medication but less so with other types of psychotropic medication; it should be noted, however, that medication associations are likely to be confounded by illness severity as well as treatment adherence and responsiveness. A previous individual participant data meta-analysis of 2876 euthymic patients with BD (Bourne et al., 2013) also reported significant correlations between cognitive impairment and some illness severity indices (number of manic episodes and total hospitalisations), and reported an association for antipsychotic medication only, but not lithium, antidepressants or anticonvulsants.

4.2. Limitations of included studies

Valid prevalence estimates depend on representative samples, but representativeness was questionable in many of the studies included here. Although all appear to have used an appropriate recruitment method (e.g. consecutive or random sampling), details were scant in published papers regarding exact recruitment processes and numbers considered at each stage. Exclusion on the basis of comorbidity such as substance misuse was common, but numbers excluded were rarely reported. Definitions of euthymia varied; even when these were based on common measures (e.g. HRSD and YMRS), cut-off scores differed across studies. Some degree of residual affective symptoms was present in most BD samples, but this was not always considered as a confounding factor in analyses. A wide range of cognitive tests was used, and even within specific tests, many different scores were reported (e.g. CVLT sub-scores). This made direct comparison across studies difficult. The use of different thresholds to define cognitive impairment also limited synthesis at the outcome level. Most studies focused on the cognitive domains of executive function, memory and attention, with other areas of function such as visuospatial ability, language and praxis studied rarely if at all. Articles were sometimes unclear regarding which demographic, clinical or other variables were statistically tested against cognitive measures.

4.3. Limitations of review

We aimed to follow best practice in systematic review methodology, but reproducibility of screening, data extraction and bias

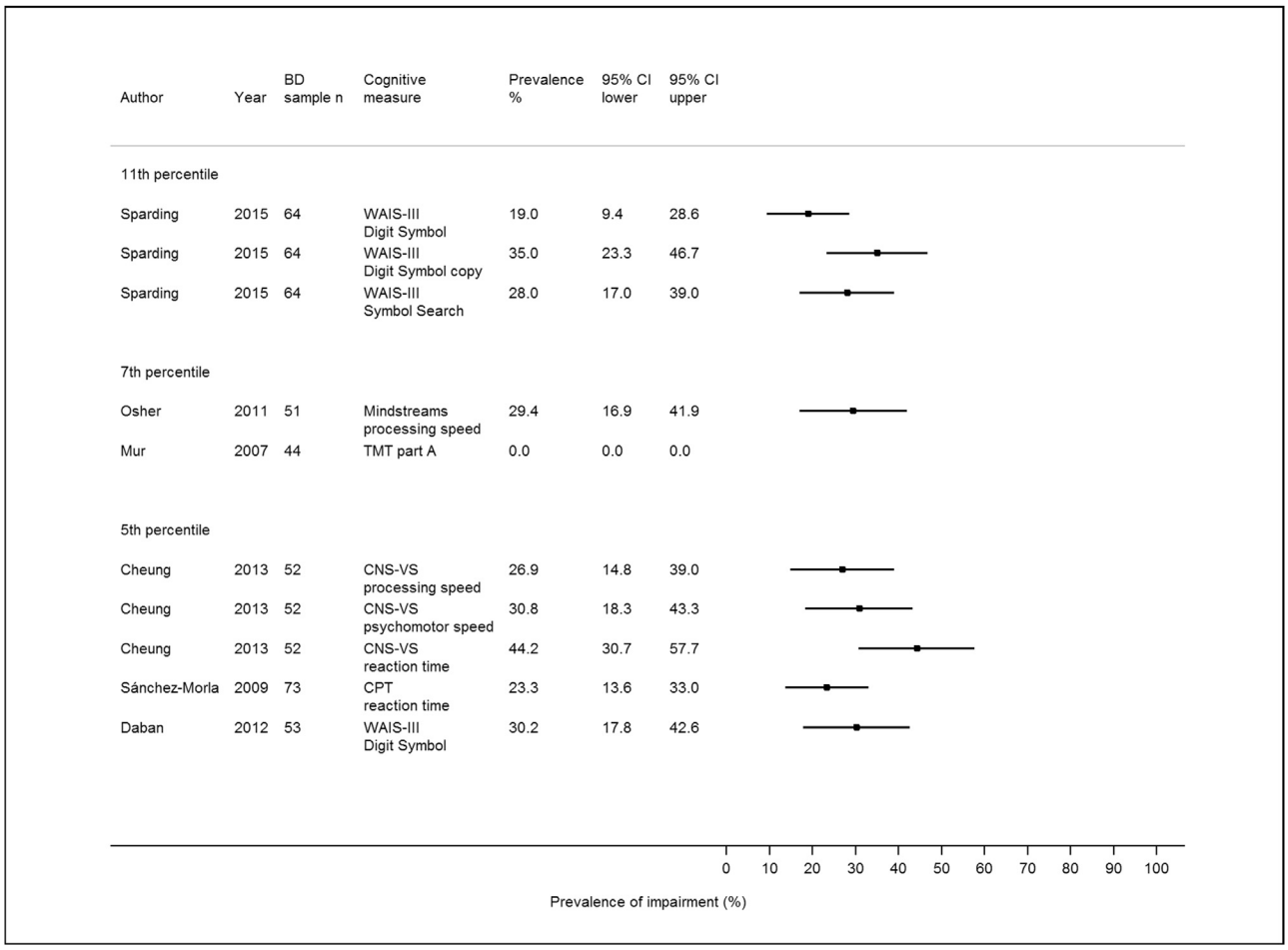

Fig. 4. Speed/reaction time impairment prevalence across different thresholds. BD, bipolar disorder; BD-I, bipolar disorder type I; CI, confidence interval; CNS-VS, Central Nervous System Vital Signs computerised battery; CPT, Continuous Performance Test; TMT, Trailmaking Test; WAIS-III, Wechsler Adult Intelligence Scale third edition. Results include mixed BD and BD-I samples. Some studies reported results for several cognitive scores, and so there is sample overlap across rows. CI estimates are based on standard errors calculated as follows: sqrt((prevalence*(100-prevalence))/n). Results are stratified by impairment threshold (percentile), in descending order from least to most strict.

appraisal processes was checked for only a proportion of records. Judgements about study eligibility relied solely on information contained in the articles, and authors were not contacted to request missing information during the selection process. A large number of articles were excluded on the sample recruitment criterion, in some cases because this information was not contained in the article; it is possible that some of these did in fact employ an appropriate sampling procedure. The requirement for information within the article indicating an acceptable procedure meant that several articles included in previous reviews of cognition in BD are not included here, including some that reported prevalence estimates. Despite repeated attempts to obtain additional prevalence results from authors of eligible articles, prevalence data were available for only 15 articles. In particular, there was little information regarding impairment prevalence in BD-II samples. Heterogeneity of cognitive measures and thresholds meant that it was not feasible to meta-analyse the prevalence estimates obtained, or to conduct statistical tests of funnel plot asymmetry, and so the results are limited to graphical and narrative synthesis only. This was organised by cognitive domain, but we acknowledge that many tests make multiple cognitive demands across domains. Regarding our second research question, variation in the way that correlates were analysed across studies meant it was not possible to comment on the nature of any inter-relationships between the potential risk factors reported here. Risk of bias was considered carefully, but it should be noted that the appraisal tool used was developed for questions of prevalence, whereas many of the studies included here were not originally designed to investigate prevalence. The literature search results were restricted to English-language publications only, although studies from a wide range of international settings were found.

4.4. Conclusions and implications

This review is the first to systematically examine the prevalence of cognitive impairment in euthymic bipolar disorder. It complements and extends the findings of previous reviews, which have focused on magnitude of between-group differences on cognitive measures. Although group differences are important for understanding the nature and extent of cognitive impairment in this population, quantifying the number who have clinically relevant cognitive impairment is essential if we wish to identify risk factors for a cognitively impaired subtype of euthymic BD, and to target clinical resources towards neuropsychological rehabilitation and support for those who need it most. Despite the heterogeneity in the present findings, some tentative conclusions can be drawn. Cognitive impairment affects patients across the BD spectrum; impairment appears to be more common in BD-I but there is considerable overlap with BD-II. It is also evident that even at the lower ends of the prevalence ranges reported here, the proportion of patients whose affective illness is in remission but who continue to show cognitive impairment substantially exceeds the

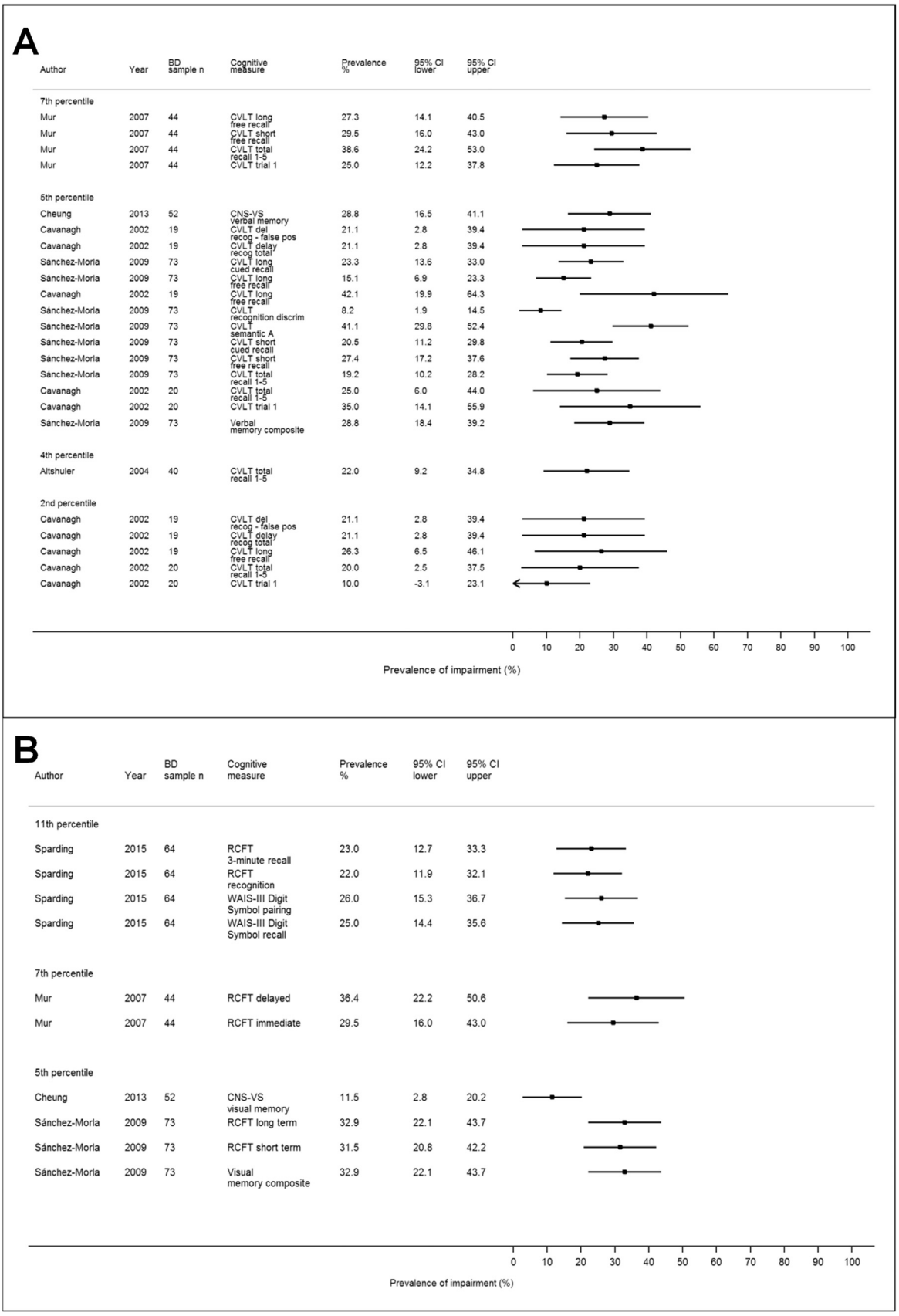

Fig. 5. Verbal and visual memory impairment prevalence across different thresholds. BD, bipolar disorder; BD-I, bipolar disorder type I; CI, confidence interval; CNS-VS, Central Nervous System Vital Signs computerised battery; CVLT, California Verbal Learning Test; RCFT, Rey Complex Figure Test; WAIS-III, Wechsler Adult Intelligence Scale third edition. Results include mixed BD and BD-I samples. Some studies reported results for several cognitive scores, and so there is sample overlap across rows. CI estimates are based on standard errors calculated as follows: sqrt((prevalence*(100-prevalence))/n). Results are stratified by impairment threshold (percentile), in descending order from least to most strict. Panel A shows verbal memory measures and panel B shows visual memory measures.

expected proportion in the general population. With BD diagnosis typically being made in early adulthood, this means that the excess burden of cognitive impairment will affect this population over several decades. There is a great need for effective interventions for cognitive dysfunction in BD, with significant potential to reduce adverse impacts on educational, occupational and domestic functioning over many years.

The wide variation in the prevalence estimates reported here calls attention to the need for greater consistency across studies. This could be achieved by using internationally recommended assessment batteries, such as those based on the MATRICS Consensus Cognitive Battery (Van Rheenen and Rossell, 2014; Yatham et al., 2010). Researchers should consider reporting impairment prevalence at more than one threshold, to facilitate comparison across studies. There is no single consensus threshold to define impairment in clinical practice, since this depends on contextual factors such as premorbid ability, but providing results for several relevant levels would maximise value from data gathered. It would also be very useful to provide graphical summaries of score distributions, to indicate whether cognitive performance in BD samples (both BD-I and BD-II) demonstrates an overall distribution shift compared to healthy comparison groups, or a bimodal picture of distinct impaired versus preserved subgroups. Inspection of standardised mean differences together with proportions impaired does not permit a full appreciation of these issues. This review did not attempt to quantify the proportion of people with BD who are above average on cognitive measures, but this is arguably of equal importance in considering the diverse cognitive phenotype associated with this disorder. Finally, greater efforts should be made to recruit representative samples of adults with BD for cognitive studies. Much of the research in this field is carried out with clinic samples recruited by convenience. Only large, representative samples can provide an accurate picture of the burden of cognitive dysfunction in adults living with BD, through which we can understand the factors that influence risk and resilience.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2016.06.063.

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