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Prevalence and determinants of cognitive impairment in the euthymic phase of bipolar disorders: results from the FACE-BD cohort

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Abstract

Background. Cognitive deficits are a well-established feature of bipolar disorders (BD), even during periods of euthymia, but risk factors associated with cognitive deficits in euthymic BD are still poorly understood. We aimed to validate classification criteria for the identification of clinically significant cognitive impairment, based on psychometric properties, to estimate the prevalence of neuropsychological deficits in euthymic BD, and identify risk factors for cognitive deficits using a multivariate approach.

Methods. We investigated neuropsychological performance in 476 euthymic patients with BD recruited via the French network of BD expert centres. We used a battery of tests, assessing five domains of cognition. Five criteria for the identification of neuropsychological impairment were tested based on their convergent and concurrent validity. Uni- and multivariate logistic regressions between cognitive impairment and several clinical and demographic variables were performed to identify risk factors for neuropsychological impairment in BD.

Results. One cut-off had satisfactory psychometric properties and yielded a prevalence of 12.4% for cognitive deficits in euthymic BD. Antipsychotics use were associated with the presence of a cognitive deficit.

Conclusions. This is the first study to validate a criterion for clinically significant cognitive impairment in BD. We report a lower prevalence of cognitive impairment than previous studies, which may have overestimated its prevalence. Patients with euthymic BD and cognitive impairment may benefit from cognitive remediation.

Introduction

Bipolar disorder (BD) is a complex and chronic illness characterised by lasting cognitive dysfunction during all phases, including remission. Indeed, memory, attention, and executive functions of euthymic BD patients are impaired (Cipriani *et al.*, 2017). Cognitive impairment is a significant contributor to the overall burden of disability induced by BD, with a significant impact on functioning (O'Donnell *et al.*, 2017). It is thus crucial to establish the prevalence of

cognitive impairment in BD, as it may help planning rehabilitative care to alleviate the disabling consequences of cognitive impairment for all patients who could benefit. There have only been a few attempts to estimate the prevalence of clinically relevant levels of cognitive impairment in BD with inconsistent results. Studies that did not exclude patients who were in a current mood episode reported a prevalence of cognitive deficit between 30% and 60% (Gualtieri and Morgan, 2008; Reichenberg *et al.*, 2009). Studies which used a data-driven approach with cluster analysis also reported prevalence between 40% and 50% for global cognitive impairment (Burdick *et al.*, 2014; Van Rheenen *et al.*, 2017). A recent review, which excluded non-euthymic participants with BD, reported an average prevalence of less than 30%, but the range was very high: 5.3–57.7% for executive function; 9.6–51.9% for attention/working memory; 23.3–44.2% for speed/reaction time; 8.2–42.1% for verbal memory; and 11.5–32.9% for visual memory (Cullen *et al.*, 2016). These wide variations in the reported rates of neuropsychological impairment in BD are also due, in part, to the different criteria used to classify impairment. Indeed, researchers have been encouraged to report the prevalence of impairment at several thresholds to facilitate comparison across studies (Cullen *et al.*, 2016). Moreover, the International Society for Bipolar Disorders Targeting Cognition Task Force identified validation of a consensus concerning the definition of clinically significant cognitive impairment as a key methodological challenge for cognition trials in BD (Miskowiak *et al.*, 2017). It is thus crucial to determine which criteria for the detection of cognitive impairment should be applied to both everyday clinical evaluation and the experimental design of studies targeting cognition.

This study had two principal objectives. First, it aimed to evaluate the prevalence of cognitive deficits in a large sample of strictly euthymic participants with BD with a comprehensive cognitive test battery to assess several cognitive dimensions, using different classifications to define impairment. The criteria used in this study were not only those generally reported in the literature on BD, but also those generally used for another severe and persistent mental disorder, schizophrenia. The classifications developed to assess cognitive impairment in schizophrenia have not yet been used to estimate the prevalence of cognitive deficits in BD. The second primary objective of this study was to validate the various cut-off that detected significant neuropsychological impairment based on their psychometric properties, particularly their convergent and concurrent validity. This is the first study to perform scientific validation of the criteria generally used to assess cognitive deficit in severe and persistent mental disorders.

The secondary objective of this study was to identify specific risk factors (sociodemographic and clinical) associated with cognitive impairment in BD. Several factors may influence cognitive performance in BD: the number of mood episodes (Bourne *et al.*, 2013), residual and subthreshold depressive symptoms (Volkert *et al.*, 2015), as well as comorbid anxiety (Levy, 2013). Finally, psychotropic medication may substantially affect cognition in BD (Cullen *et al.*, 2015), with antipsychotics having a negative impact (Landau *et al.*, 2003). However, the interpretation of an association between drug exposure and cognition must consider the potential confounding factors that guide treatment decisions. For example, a history of psychosis is associated, not only with a higher likelihood of receiving antipsychotics, but also with impaired cognition (Glahn *et al.*, 2007). Careful adjustment for all potential confounders is therefore crucial when evaluating the impact of a variable, particularly medication, on cognition in BD.

Methods

Study design and characteristics of the recruiting network

This multicentre, cross-sectional study included patients recruited into the FACE-BD (FondaMental Advanced Centers of Expertise for Bipolar Disorders) cohort by a French national network of nine BD Expert Centers (Bordeaux, Créteil, Grenoble, Marseille, Monaco, Montpellier, Nancy, Paris and Versailles). This network was set up by the *Fondation FondaMental* (www.fondation-fondamental.org) which created an infrastructure and provided resources to follow clinical cohorts and comparative-effectiveness research in patients with BD. The sample was not selected based on the suspected presence or absence of cognitive impairment.

Participants

BD was diagnosed based on the structured clinical interview that assesses DSM-IV-TR criteria (First *et al.*, 1997). Outpatients with type I, II or not-otherwise-specified (NOS, including cyclothymia) BD, who were 18–65 years of age, were eligible. All patients were euthymic at the time of testing according to the DSM-IV-R criteria, with scores on the Montgomery Åsberg Depression Rating Scale (MADRS) $\leqslant$10 and the Young Mania Rating Scale (YMRS) $\leqslant$12 (Jamrozinski *et al.*, 2009). Exclusion criteria were a history of neurological or sensory disorders, dyslexia, dysorthographia, dyscalculia, dysphasia, dyspraxia, language delay, substance-related disorders in the previous month and electroconvulsive therapy in the past year to avoid cognitive deficits unrelated to BD. The assessment protocol was approved by the relevant ethics review board (*CPP-Ile de France IX*, 18 January 2010) in accordance with French laws for non-interventional studies (observational studies without any risk, constraint, supplementary or unusual procedure regarding diagnosis, treatment or monitoring). The board required that all patients be given an informational letter, but waived the requirement for written informed consent. However, we sought verbal agreement of every patient before inclusion in the study.

Assessment tools

Clinical assessments

The age at onset; number of previous mixed, hypomanic, manic and major depressive episodes; subtype of BD; and history of psychotic symptoms were recorded using the SCID. The Clinical Global Impression-Severity (CGI-S) scale assessed the severity of the BD (Guy, 1976). We used a yes/no format for recording whether the patient was taking lithium carbonate, anticonvulsants, antipsychotics, antidepressants or anxiolytics at the time of the evaluation. The state of anxiety was measured using the state subscale of the State-Trait Anxiety Inventory, form Y-A (SAI-Y-A) (Spielberger and Sydeman, 1994). Three sociodemographic characteristics were collected: sex, age and educational level.

Global functioning was measured using the Global Assessment of Functioning (GAF) (Jones *et al.*, 1995). The cognitive area of psychosocial functioning in everyday life was assessed with the cognitive subdomain of the Functioning Assessment Short Test (FAST) (Rosa *et al.*, 2007). For the GAF, higher scores are associated with higher functioning, whereas the inverse is true for the FAST cognitive functioning subdomain.

Battery of cognitive tests

Experienced neuropsychologists administered the tests in a fixed order that was the same for every centre. Testing lasted a total

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of 120 min, including 5–10-min breaks. The standardised test battery complied with the recommendations issued by the International Society for Bipolar Disorders (Yatham *et al.*, 2010). It included 11 tests and evaluated the following five cognitive domains:

- Processing speed, using the digit symbol coding and symbol search subtests from the Wechsler Adult Intelligence Scale (WAIS) version III (Wechsler, 1997), the Trail Making Test (TMT) part A (Reitan, 1958), and the word and the colour conditions of the Stroop test (Lezak, 2004)
- Attention, using the Conners' Continuous Performance Test II (omissions and commissions) (Conners and Staff, 2000)
- Executive functions, using the colour/word condition of the Stroop test, the TMT part B and verbal fluency (semantic and phonemic conditions) (Lezak, 2004)
- Verbal memory, using the California Verbal Learning Test (CVLT) immediate recall, short and long delay free recall and total recognition (Delis, 2000)
- Working memory, using the WAIS-III digit span (sum of forward and backward conditions) and the spatial span (forward and backward conditions) subtest from the Wechsler Memory Scale version III

Raw scores were transformed to demographically corrected standardised (z) scores and T scores based on normative data for each test (Golden, 1978; Wechsler, 1997, 2001; Conners and Staff, 2000; Poitrenaud *et al.*, 2007; Godefroy, 2012). Higher scores always reflected better performance. Subjects with missing data for $\geqslant$3 cognitive domains were excluded from the analysis, according to previous recommendations (Reichenberg *et al.*, 2009). Some of the cognitive data obtained using this battery have been published previously (Roux *et al.*, 2017*a*, 2017*b*).

Classification criteria for the definition of neuropsychological impairment

Five previously published classification methods were used for the identification of neuropsychological impairment, as described below (see Table 1 for a summary of the criteria for the different classifications).

The first three criteria were mainly used in schizophrenia. One was the Individual Profile Rating (IPR) procedure (Kremen *et al.*, 2000; Reichenberg *et al.*, 2009). We computed an average score for each of the five neuropsychological domain, as the mean of the z scores for every measure comprising that domain. A domain was considered to be impaired if the score was >2 S.D. below the normative mean or >2 S.D. below that of any other cognitive domain. In the latter case, the between-domain discrepancy was considered to be suggestive of a compromised neuropsychological domain due to high within-subject variability between this domain and the other domains. A participant was considered to be cognitively impaired when at least two domains were impaired. However, a participant with a score for only one domain >3 S.D. below the normative mean was also classified with cognitive impairment.

The second criterion defined a clinically significant cognitive impairment (CSCI) when at least two cognitive domains had an average z-score $\geqslant$1 S.D. below the normative mean (Palmer *et al.*, 1997; Miskowiak *et al.*, 2017).

The third criterion, the Global Deficit Score (GDS), first requires that T scores for all cognitive variables be converted to deficit scores, providing a measure of the severity of impairment (Heaton *et al.*, 2004; Lezak, 2004; Reichenberg *et al.*, 2009). T scores were coded as follows: 0 (T score $\geqslant$40; no impairment), 1 (T score of 35–39; mild impairment), 2 (T score of 30–34; mild-to-moderate impairment), 3 (T score of 25–29; moderate impairment), 4 (T score of 20–24; moderate-to-severe impairment) or 5 (T score <20; severe impairment). The deficit scores for all variables were then averaged: a participant was considered to be cognitively impaired if the mean score was $\geqslant$0.5, i.e. when, on average, half of the neuropsychological variables were mildly impaired.

Finally, Martino *et al.*, used two cut-offs for the detection of cognitive impairment in BD (Martino *et al.*, 2014). They defined a soft criterion (MSC) for a cognitive deficit, when at least one cognitive domain had at least one measure <1.5 S.D. below the normative mean, and a hard criterion (MHC), when at least two different cognitive domains had at least one measure each <2 S.D. below the normative mean.

Statistical analyses

Classifications validation

We investigated the psychometrical properties of the different criteria, particularly their convergent validity (i.e. the ability to detect cognitive deficit in the same participants across the different classifications) and their concurrent validity (i.e. the ability to predict other outcomes that have previously been shown to be linked with cognitive impairment).

We computed convergence in the classification of patients as cognitively impaired or preserved between each pair of criteria. The agreement between different classifications was evaluated using Cohen's κ for categorical data: a value <0.40 indicates

Table 1. Summary of the criteria for the classifications

Classification name	Criteria
IPR	At least two domains impaired (domain impairment definition: mean domain score <2 S.D. below the normative mean or <2 S.D. below any other cognitive domain) or one domain <3 S.D. below the normative mean
CSCI	At least two domains $\leqslant$1 S.D. below the normative mean
GDS	A mean deficit score $\geqslant$0.5 (the deficit score was computed from the mean of the T scores of all variables)
MSC	At least one measure of any cognitive domain <1.5 S.D. below the normative mean
MHC	At least two measures of two different cognitive domains <2 S.D. below the normative mean

IPR, Individual Profile Rating; CSCI, Clinically Significant Cognitive Impairment; GDS, Global Deficit Score; MSC: Martino *et al.*, Soft Criteria; MHC, Martino *et al.*, Hard Criteria.

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poor; 0.40–0.75, fair to good; and >0.75, excellent convergent validity (Fleiss, 1981). We also reported the $\alpha/2$ confidence intervals of the Cohen's κ values. The criteria were classified as reliable if the Cohen's κ between each pair of reliable criteria was $\geqslant 0.4$ and unreliable if the Cohen's κ between a criterion and any other reliable criterion was <0.4.

We tested the concurrent validity of the five criteria to detect cognitive impairment against global functioning (GAF) and the cognitive area of psychosocial functioning in everyday life (FAST cognitive functioning subdomain). We then ran successive ANOVA (type III) on the two concurrent variables, with the presence of a cognitive deficit assessed with the neuropsychological test battery according to the five criteria as the independent factor. The criterion was considered to have good concurrent validity if global functioning and cognitive area of psychosocial functioning in everyday life were significantly lower for the impaired group.

Clinical determinants of cognitive impairment

Only validated classifications were included in the analyses of the clinical determinants of cognitive impairment as determined by the neuropsychological tests battery. There were two steps in the statistical analysis strategy to identify the clinical determinants of cognitive impairment. We first ran consecutive bivariate logistic regressions with cognitive impairment as the dependent variable and several successive variables as the independent variables: age; sex; education level; type of BD (BD2 and NOS were combined into the same category); history of psychosis; number of mixed, hypomanic, manic and major depressive episodes; depression symptoms with MADRS, mania symptoms with YMRS, state of anxiety with STAI-Y-A and severity of the BD with CGI-S; and current prescriptions of lithium carbonate, anticonvulsants, antipsychotics, antidepressants or anxiolytics. These bivariate logistic regressions were run to select the independent variables that should be included in the multivariate logistic regression. We selected the variables that were associated with a p value $\leqslant 0.1$ with cognitive impairment as determined by the neuropsychological tests battery. We then ran multivariate logistic regression with cognitive impairment as the dependent variable and the independent variables that were selected by the bivariate analyses. For the multivariate logistic regression, missing data were estimated using multivariate imputations by chained equations (50 imputations, *mice* package of R).

Results

Participants

We included 476 patients (the selection procedure is presented in online Supplementary Fig. S1). Their sociodemographic, clinical and cognitive characteristics are reported in Table 2.

Prevalence rates of neuropsychological impairment

The prevalence of cognitive impairment was 4% with IPR, 17.4% with CSCI, 12.4% with GDS, 66.8% with MSC and 16.4% with MHC. The percentages of cognitive impairment separately by diagnosis and history of psychosis are reported in online Supplementary Table S1. The results of the battery of cognitive tests for participants with and without cognitive deficit according to the five classification criteria are reported in online Supplementary Information 1.

Convergence of classifications for the identification of neuropsychological impairment

The results are reported in Table 3. The convergence in classification between CSCI and GDS, CSCI and MHC, and GDS and MHC was fair (between 0.5 and 0.6), thus showing that the criteria for impairment were reliable for CSCI, GDS and MHC. The convergence in classification between IPR and all other criteria, and between MSC and all other criteria were poor (between 0.03 and 0.26), thus indicating that the criteria for impairment were unreliable for these two classifications. CSCI, GDS and MHC identified roughly the same participants with a cognitive deficit, whereas the patients with a cognitive deficit identified by IPR and MSC were different from those identified by the other classifications.

Concurrent validity of criteria for cognitive impairment with FAST cognitive functioning subdomain and GAF

The results are reported in Table 4. Cognitive area of psychosocial functioning in everyday life measured using the FAST cognitive functioning subdomain was significantly lower for cognitively impaired participants identified with the neuropsychological tests battery by CSCI [$F_{(1,451)} = 8.4$; $p = 0.004$], GDS [$F_{(1,451)} = 6.1$, $p = 0.014$], MSC [$F_{(1,451)} = 4.2$, $p = 0.041$] and MHC [$F_{(1,451)} = 5.7$, $p = 0.017$]. Global functioning measured using the GAF was significantly lower for cognitively impaired participants identified by GDS [$F_{(1,430)} = 4.2$; $p = 0.042$]. There was no other significant difference between impaired and unimpaired patients as determined with the neuropsychological tests battery. The concurrent validity was thus satisfactory for GDS but unsatisfactory for IPR, CSCI, MSC and MHC.

Determinants of cognitive impairment

IPR and MSC were discarded from the following analyses due to poor convergent and concurrent validity. MHC and CSCI were discarded because of poor concurrent validity. Only GDS was thus selected for the following analyses because of its satisfactory convergent and concurrent validity.

The results of the bivariate logistic regressions between cognitive impairment and the clinical and demographic variables are reported in online Supplementary Table S2. The variables significantly associated with cognitive impairment identified by GDS were having type 1 BD (OR 2.14, $p = 0.011$), a history of psychosis (OR 2.46, $p = 0.004$), and being on antipsychotic (OR 2.93, $p = 0.001$). No other association was significant.

We then ran multivariate logistic regressions with cognitive impairment as determined by the neuropsychological tests battery by GDS as the dependent variable. The independent variables were those that were associated with a p value $\leqslant 0.1$ with cognitive impairment as determined with the neuropsychological tests battery by GDS in the bivariate analyses: type of BD, history of psychosis, state of anxiety and antipsychotic medication. A power analysis revealed that enough participants were recruited to run this analysis (see online Supplementary Information 2). The results are reported in Table 5. The relationship between antipsychotic and cognitive impairment remained significant (OR 2.47, $p = 0.005$). No other association was significant.

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Table 2. Participant sociodemographic, clinical and cognitive characteristics

Clinical or sociodemographic variable	Mean	S.D.	Range
Age (years)	41.7	11.7	18/65
Educational level (years)	14.3	2.8	5/22
Age at onset (years)	25.2	10	7/60
Number of mixed episodes	0.3	1.5	0/23
Number of hypomanic episodes	3.3	5.9	0/35
Number of manic episodes	1.3	2	0/10
Number of major depressive episodes	5.6	6	0/35
MADRS (0–60)	4	3.3	0/10
YMRS (0–60)	1.5	2.4	0/12
SAI-Y-A (20–80)	36.1	13.2	20/75
CGI Severity (0–6)	2.4	1.3	0/6
FAST cognitive subdomain (0–15)	2.9	3.4	0/15
GAF (1–100)	72.2	12.4	31/100
		Percentage	
Sex (percentage of males)	41.6		
Bipolar disorder	53.8 (type 1)	33.8 (type 2)	12.4 (NOS)
History of psychosis	46.9		
Antidepressant	25.1		
Lithium carbonate	25.1		
Anticonvulsant	35.1		
Antipsychotic	23.1		
Anxiolytic	18.4		

Cognitive domain or test	Cognitive variable	Mean (*z* score)	S.D. (*z* score)	Range (*z* score)
Processing speed		−0.2	0.7	−2.45/1.69
Digit/symbol coding		−0.3	0.9	−3/2.67
Symbol search		0.1	1.1	−3/3
TMT	Part A	−0.1	1	−4.5/1.71
Stroop test	Word	−0.2	0.8	−2.95/3
	Colour	−0.5	0.9	−3/2
Attention		−0.2	0.8	−2.33/1.28
CPT	Omissions	−0.4	1.1	−2.33/0.91
	Commissions	−0.1	1	−2.33/1.74
Executive functions		−0.2	0.8	−3.02/2
Stroop test	Colour/word	−0.1	0.8	−2.95/3
TMT	Part B	−0.3	1.4	−8.82/1.79
Verbal fluency	Semantic	−0.3	1	−2.99/2.78
	Phonemic	0	1.1	−2.65/3.33
Verbal memory		−0.3	1	−2.76/1.59
CVLT	Immediate recall	−0.5	1.3	−3.83/2.41
	Short delay free recall	−0.3	1.1	−3.75/2.16
	Long delay free recall	−0.3	1.2	−4.47/2.31
	Total recognition	0	0.8	−2.58/0.67

(*Continued*)

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Table 2. (*Continued.*)

Cognitive domain or test	Cognitive variable	Mean (*z* score)	S.D. (*z* score)	Range (*z* score)
Working memory		−0.2	0.7	−2.33/2.33
Digit span	Forward & backward	−0.2	0.9	−3/2.67
Spatial span	Forward	−0.2	0.8	−2.33/2.33
	Backward	−0.2	0.8	−3/2

MADRS, Montgomery Åsberg Depression Rating Scale, higher scores indicate more severe depressive symptoms; YMRS, Young Mania Rating Scale, higher scores indicate more severe manic symptoms; SAI-Y-A, state subscale of the State-Trait Anxiety Inventory, form Y-A, higher scores indicate more severe anxiety symptoms; CGI, Clinical Global Impression scale, higher scores indicate more severe illness; FAST, Functioning Assessment Short Test, higher scores indicate poor functioning; GAF, Global Assessment of Functioning scale, higher scores indicate good functioning; NOS, not-otherwise-specified; TMT, Trail Making Test; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test.

Table 3. Cohen's κ for each pair of classification criteria for the definition of neuropsychological impairment, with their confidence intervals

	IPR	CSCI	GDS	MSC
CSCI	0.22 (0.12–0.33)	–	–	–
GDS	0.26 (0.13–0.4)	0.56 (0.45–0.66)	–	–
MSC	0.03 (0.01–0.05)	0.19 (0.15–0.23)	0.13 (0.1–0.17)	–
MHC	0.22 (0.11–0.33)	0.6 (0.51–0.7)	0.5 (0.39–0.61)	0.18 (0.14–0.22)

IPR, Individual Profile Rating; CSCI, Clinically Significant Cognitive Impairment; GDS, Global Deficit Score; MSC, Martino *et al.*, Soft Criteria; MHC, Martino *et al.*, Hard Criteria.

Table 4. Concurrent validity of the classification criteria for the definition of neuropsychological impairment against FAST cognitive functioning subdomain and GAF

Classification	Mean (S.D.) with deficit	Mean (S.D.) without deficit	Statistics	*p*
	FAST cognitive functioning subdomain			
IPR	3.4 (4)	2.9 (3.4)	$F(1,451) = 0.4$	0.509
CSCI	3.9 (4.2)	2.7 (3.2)	$F(1,451) = 8.4$	0.004
GDS	3.9 (4.3)	2.8 (3.2)	$F(1,451) = 6.1$	0.014
MSC	3.1 (3.6)	2.5 (2.9)	$F(1,451) = 4.2$	0.041
MHC	3.8 (4.1)	2.7 (3.2)	$F(1,451) = 5.7$	0.017
	GAF			
IPR	69.8 (15.4)	72.3 (12.3)	$F(1,430) = 0.7$	0.402
CSCI	69.7 (14.1)	72.7 (12)	$F(1,430) = 3.6$	0.059
GDS	68.9 (14.1)	72.6 (12.1)	$F(1,430) = 4.2$	0.042
MSC	71.4 (12.4)	73.8 (12.4)	$F(1,430) = 3.5$	0.061
MHC	70.1 (13.4)	72.6 (12.2)	$F(1,430) = 2.5$	0.114

FAST, Functioning Assessment Short Test; higher scores indicate poor functioning; IPR, Individual Profile Rating; CSCI, Clinically Significant Cognitive Impairment; GDS, Global Deficit Score; MSC, Martino *et al.*, Soft Criteria; MHC, Martino *et al.*, Hard Criteria; GAF, Global Assessment of Functioning scale, higher scores indicate good functioning; NOS: not-otherwise-specified.

Discussion

Here, we used five different classification criteria to evaluate the prevalence of clinically significant cognitive impairment in a large sample of euthymic patients with BD, using a comprehensive neuropsychological battery, including multiple measures across five domains. We also investigated the psychometric properties of the classifications for determining individual impairment status and the clinical characteristics of BD that were associated with the presence of a cognitive deficit.

The different classifications produced different prevalence with a very large range (4.1–67%). Three criteria, CSCI, GDS and MHC, reported proportions of cognitive impairment in the same intermediate range (15%), whereas IPR gave a much lower prevalence and MSC a much higher one. This extensive range may have implications for interpreting the psychometric properties of the classifications criteria. One explanation for the reduced convergent validity for the MSC was the low threshold for cognitive impairment used by this classification, leading to the identification of many more patients with a cognitive deficit than other classifications, and thus to a week convergence with them. For the same reason, the convergent validity was low between IPR and all other criteria, as far fewer participants with cognitive deficit were

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Table 5. Multiple logistic regressions between cognitive impairment as determined with the neuropsychological tests battery by the Global Deficit Score and clinical characteristics

	OR	(95% CI)	Stat.	*p* val.	fmi	lambda
Type 1 bipolar disorder	1.23	(0.57 to 2.64)	$t(441) = 0.5$	0.596	0.05	0.04
History of psychosis	1.81	(0.85 to 3.84)	$t(388) = 1.5$	0.124	0.11	0.1
STAI-Y-A	0.98	(0.96 to 1.01)	$t(466) = -1.5$	0.139	0.01	0.01
Antipsychotic	2.47	(1.32 to 4.64)	$t(356) = 2.8$	0.005	0.14	0.13

Coeff, log odds; the presence of cognitive impairment is coded 1 and the absence of cognitive impairment is coded 0; SAI-Y-A, state subscale of the State-Trait Anxiety Inventory; form Y-A, higher scores indicate more severe anxiety symptoms.

identified with IPR than other criteria. Another reason for this may be that IPR was the only classification that took into account for differences between the different cognitive domains.

One of the five methods, GDS, had satisfactory psychometric properties, with good convergent and concurrent validity. GDS was the only criterion that was not influenced by the classification of tests into domains according to an *a priori* definition, as it averaged all cognitive variables. We conclude that the classification of cognitive tests to specific domains did not have an impact on the selection of GDS as a valid criterion. GDS gave a prevalence of 12.4% for cognitive impairment in BD, and the prevalence obtained with the different criteria in this study was lower than that usually reported with the same classifications (Reichenberg *et al.*, 2009; Martino *et al.*, 2014). This discrepancy cannot be solely explained by a higher rate of BD1 and history of psychosis than in our study, as the prevalence for cognitive impairment we obtained for BD1 or history of psychosis was still lower than those reported in previous studies (see online Supplementary Table S1). The selection criteria may better explain variation in these prevalence estimates, particularly the exclusion of comorbidity (substance misuse, neurodevelopmental disorders, etc.) and the definition of euthymia. Our study confirmed a recent review suggesting that previous studies may have upwardly biased the estimates of the prevalence of cognitive impairment in BD due to a sampling bias favouring the recruitment of patients with cognitive deficits, as the representativeness was questionable in many of these studies (Cullen *et al.*, 2016). Our study used a clinical sample; it is therefore not possible to ensure that our sample was representative of the general population of BD, although the sample size was larger than in previous studies. More efforts should be made to recruit epidemiological samples to ensure that all individuals with BD have an equal chance of being tested with a cognitive battery. Only representative samples can provide a correct picture of the disability induced by cognitive impairment in BD.

The results have several implications for clinical and research perspectives. Further studies should identify cognitive impairment with several classifications, and particularly the GDS criteria. A careful choice of criteria for neuropsychological impairment is recommended in clinical settings and the design of interventional studies targeting cognition, because of the moderate convergence across criteria. Criteria with liberal thresholds may be recommended for interventions consuming little resources, like for example ruling out potentially treatable causes of cognitive impairments. These causes can be biological, with hypothyroidism and diabetes, psychiatric with attention-deficit hyperactivity disorder and alcohol use disorder, and iatrogenic with elevated serum levels of mood stabiliser and benzodiazepines (Miskowiak *et al.*, 2018). In contrast, criteria with stringent thresholds may be used to select patients for intensive interventions involving many resources, like cognitive remediation. However, the decision to propose cognitive remediation should not only rely on the presence of a cognitive impairment defined with a binary classification. This decision should instead consider the profile of performance across the several cognitive domains investigated by the neuropsychological tests battery to adapt the intervention to the specific need of the patient. The relatively low prevalence of cognitive impairment reported in this study suggests implementing brief and easy-to-administer cognitive screening tools in the clinical management of bipolar disorder before a complete neuropsychological evaluation.

Cognitive impairment was associated with the presence of BD1, a history of psychosis, and antipsychotic use by univariate analyses. Only antipsychotic use was associated with cognitive impairment by multivariate analysis. Our results suggest a possible link between antipsychotic medication and cognitive impairment, in accordance with prior studies (Bourne *et al.*, 2013). However, it is not possible to conclude to a causal link of antipsychotics on cognitive impairment, as the dose effect of antipsychotics on cognition was not investigated in this study. Longitudinal studies are needed to clarify the effect of antipsychotics on cognition in BD and should take into account the specific psychopharmacological properties of each molecule, along with the daily dosage and serum level, duration of exposure and therapeutic response. Any decision to discontinue antipsychotics due to cognitive side effects should be prudent, after a careful clinical medication review, and evaluation of benefit-to-risk ratio in collaboration with patients. If switching antipsychotic to another class of mood stabiliser is not possible, then cognitive remediation could be a useful complementary therapeutic strategy. We found no negative associations between cognition and the number of mood episodes or younger age at onset. However, a longitudinal study is needed to investigate more efficiently the staging model of progressive cognitive impairment throughout BD. Subthreshold mood and anxiety symptoms were also not associated with cognition. Similarly, cognition in euthymic BD was largely independent of residual mood symptoms in a previous study (Bonnin *et al.*, 2010). However, this relationship may appear for higher levels of depressive symptoms, as depression was shallow in this sample of euthymic participants.

Limitations of our study include the cross-sectional design, which precludes an assessment of potential causal relationships between medications, clinical history and cognitive deficit. A longitudinal study to assess the stability of the cognitive deficit over time according to the selected criterion may also be informative. If the deficit was shown to be stable over several years, it would validate the classification from which it was identified and the cognitive deficit would thus be a good candidate for studies on the pathophysiology of BD. The present study had no control group of healthy individuals, and the cognitive data were adjusted for

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different variables (age, sex and education, according to the published reference values for the cognitive tests). Another limitation was related to the fact that participants included in this study were not screened for attention-deficit hyperactivity disorder (ADHD) and were thus not excluded, although a recent study reported that individuals with BD and ADHD showed the same cognitive performance as individuals with BD alone (Torres *et al.*, 2017). The idea that there is a single consensus threshold to define impairment in clinical practice is questionable: a clinically significant cognitive deficit may rely on contextual factors such as premorbid ability. A cognitive deficit might thus be defined as a failure to reach the expected level of cognitive performance predicted by premorbid estimates (Keefe *et al.*, 2005), and our study lacks a measure of premorbid intellectual functioning. The rationale that only patients with a cognitive deficit would benefit from cognitive enhancement has been challenged by studies reporting that individuals with the least severe cognitive deficits demonstrated the greatest benefit from treatment (Friedman *et al.*, 2002). Finally, in our assessment of associations between medications and cognition, we did not consider drug–drug interactions, and neither did we seek to differentiate cognitive performance between first- and second-generation antipsychotics.

In conclusion, we found that 12.4% of participants with euthymic BD had a clinically relevant cognitive impairment. The main risk factor for cognitive impairment was the prescription of an antipsychotic. Our study suggests orienting clinical resources towards neuropsychological rehabilitation for individuals identified as being neuropsychologically impaired according to the GDS classification criterion.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718001186

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with Helsinki Declaration of 1975, as revised in 2008.

References

Bonnin CM *et al.* (2010) Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. *Journal of Affective Disorders* **121**, 156–160.

Bourne C *et al.* (2013) Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatrica Scandinavica* **128**, 149–162.

Burdick KE *et al.* (2014) Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. *Psychological Medicine* **44**, 3083–3096.

Cipriani G *et al.* (2017) Bipolar disorder and cognitive dysfunction: a complex link. *The Journal of Nervous and Mental Disease* **205**, 743–756.

Conners CK and Staff M (2000) *Conners' Continuous Performance Test II*. North Tonawanda, NY: Multi-Health Systems Inc.

Cullen B *et al.* (2015) Cognitive function and lifetime features of depression and bipolar disorder in a large population sample: cross-sectional study of 143,828 UK Biobank participants. *European Psychiatry : the Journal of the Association of European Psychiatrists* **30**, 950–958.

Cullen B *et al.* (2016) Prevalence and correlates of cognitive impairment in euthymic adults with bipolar disorder: a systematic review. *Journal of Affective Disorders* **205**, 165–181.

Delis DC (2000) *CVLT-II: California Verbal Learning Test: Adult Version*. San Antonio, TX: The Psychological Corporation.

First MB *et al.* (1997). *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version*. Washington, DC: American Psychiatric Pub.

Fleiss JL (1981) *Statistical Methods for Rates and Proportions*, 2nd Edn. New York: John Wiley & Sons.

Friedman JI *et al.* (2002) A double blind placebo controlled trial of donepezil adjunctive treatment to risperidone for the cognitive impairment of schizophrenia. *Biological Psychiatry* **51**, 349–357.

Glahn DC *et al.* (2007) The neurocognitive signature of psychotic bipolar disorder. *Biological Psychiatry* **62**, 910–916.

Godefroy O (2012) La batterie GREFEX: données normatives. In *Fonctions exécutives et pathologies neurologiques et psychiatriques: Évaluation en pratique clinique*. Paris: De Boeck Supérieur - Solal, pp. 231–252.

Golden CJ (1978) *A Manual for the Clinical and Experimental Use of the Stroop Color and Word Test*. Chicago, IL: Stoelting.

Gualtieri CT and Morgan DW (2008) The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. *The Journal of Clinical Psychiatry* **69**, 1122–1130.

Guy W (1976) Clinical global impression scale. In Guy W (ed.), *The ECDEU Assessment Manual for Psychopharmacology*, vol. **76**. Rockville, MD: U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs, pp. 218–222

Heaton R *et al.* (2004) *Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults*. Lutz, FL: Psychological Assessment Resources.

Jamrozinski K *et al.* (2009) Neurocognitive functions in euthymic bipolar patients. *Acta Psychiatrica Scandinavica* **119**, 365–374.

Jones SH *et al.* (1995) A brief mental health outcome scale-reliability and validity of the Global Assessment of Functioning (GAF). *The British Journal of Psychiatry* **166**, 654–659.

Keefe RS, Eesley CE and Poe MP (2005) Defining a cognitive function decrement in schizophrenia. *Biological Psychiatry* **57**, 688–691.

Kremen WS *et al.* (2000) The paradox of normal neuropsychological function in schizophrenia. *Journal of Abnormal Psychology* **109**, 743.

Landau S, Raymont V and Frangou S (2003) The maudsley bipolar disorder project: the effect of medication, family history, and duration of illness on IQ and memory in bipolar I disorder. *Journal of Clinical Psychiatry* **64**, 86–93.

Levy B (2013) Autonomic nervous system arousal and cognitive functioning in bipolar disorder. *Bipolar Disorders* **15**, 70–79.

Lezak MD (2004) *Neuropsychological Assessment*. New York: Oxford University Press.

Martino DJ *et al.* (2014) Toward the identification of neurocognitive subtypes in euthymic patients with bipolar disorder. *Journal of Affective Disorders* **167**, 118–124.

Miskowiak K *et al.* (2017) Methodological recommendations for cognition trials in bipolar disorder by the international society for bipolar disorders targeting cognition task force. *Bipolar Disorders* **19**, 614–626.

Miskowiak K *et al.* (2018) Assessing and addressing cognitive impairment in bipolar disorder: the international society for bipolar disorders targeting cognition task force recommendations for clinicians. *Bipolar Disorders*. Jan 18. doi: 10.1111/bdi.12595. [Epub ahead of print].

O'Donnell LA *et al.* (2017) Depression and executive functioning deficits predict poor occupational functioning in a large longitudinal sample with bipolar disorder. *Journal of Affective Disorders* **215**, 135–142.

Palmer BW *et al.* (1997) Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology* **11**, 437.

Poitrenaud J *et al.* (2007) *Adaptation en langue française du California Verbal Learning Test*. Paris: Les Editions du Centre de Psychologie Appliquée.

Reichenberg A *et al.* (2009) Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophrenia Bulletin* **35**, 1022–1029.

Reitan RM (1958) Validity of the trail making test as an indicator of organic brain damage. *Perceptual and Motor Skills* **8**, 271–276.

Rosa AR *et al.* (2007) Validity and reliability of the functioning assessment short test (FAST) in bipolar disorder. *Clinical Practice and Epidemiology in Mental Health* **3**, 5.

Roux P *et al.* (2017*a*) Associations between residual depressive symptoms, cognition, and functioning in patients with euthymic bipolar disorder: results from the FACE-BD cohort. *The British Journal of Psychiatry* **211**, 381–387.

Roux P *et al.* (2017*b*) Cognitive profiles in euthymic patients with bipolar disorders: results from the. *Bipolar Disorders* **19**, 146–153.

Spielberger CD and Sydeman SJ (1994) State-trait anxiety inventory and state-trait anger expression inventory. In Maruish ME (ed.), *The Use of Psychological Testing for Treatment Planning and Outcome Assessment*. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc., pp. 292–321.

Torres I *et al.* (2017) Are patients with bipolar disorder and comorbid attention-deficit hyperactivity disorder more neurocognitively impaired? *Bipolar Disorders* **19**, 637–650.

Van Rheenen TE *et al.* (2017) Characterizing cognitive heterogeneity on the schizophrenia–bipolar disorder spectrum. *Psychological Medicine* **47**, 1848–1864.

Volkert J *et al.* (2015) Evidence for cognitive subgroups in bipolar disorder and the influence of subclinical depression and sleep disturbances. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* **25**, 192–202.

Wechsler D (1997) *WAIS III: Echelle d'intelligence pour adultes*. Paris, France: Les éditions du Centre de Psychologie appliquée (ECPA).

Wechsler D (2001) *Echelle de mémoire de Wechsler MEM III*. Paris: Les éditions du Centre de Psychologie appliquée.

Yatham LN *et al.* (2010) The International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (ISBD-BANC). *Bipolar Disorders* **12**, 351–363.

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