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Title:

Cognitive impairment in euthymic patients with bipolar disorder: prevalence estimation and model selection for predictors of cognitive performance

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Abstract:

Objectives. Although cognitive dysfunction is a prominent feature of bipolar disorder (BD), previous research presents limitations in estimating the proportion of euthymic patients experiencing clinically relevant deficits and identifying predictors of cognitive difficulties. We explored the relevance of recommended definitions of clinically significant cognitive impairment for functional outcomes, estimated its prevalence, and identified patient characteristics associated with cognition.

Methods. We assessed cognitive performance across four domains in 80 euthymic participants with BD. Participants were categorized based on two criteria for clinically significant cognitive impairment and we assessed the ability of these criteria to differentiate participant performance on established functional outcomes. Variable selection with elastic net regression was used to identify sociodemographic and clinical factors associated with cognitive performance. Selected variables were examined as predictors of clinically significant cognitive impairment with logistic regression.

Results. According to the selected criterion, 34% presented with clinically significant cognitive impairment. Poorer current cognitive performance was associated with older age, lower estimated premorbid IQ, more currently prescribed psychotropic medications, fewer previous psychological therapies, and current use of antipsychotics. A model with premorbid IQ, psychotropic medications and previous psychological therapies as predictors of cognitive impairment correctly classified 75% of the participants.

Conclusions. This is one of the first studies to use a model selection approach to identify factors associated with cognitive difficulties in BD. Our findings offer the initial steps towards a predictive model for cognitive impairment. This could improve treatment decisions and prioritization for euthymic patients with BD, particularly the implementation of cognitive interventions.

Keywords: bipolar disorder; cognitive impairment; euthymia; prevalence; model selection; elastic net.

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Introduction

Bipolar disorder (BD) is a chronic affective disorder influencing cognitive functioning, where neuropsychological deficits often persist across illness phases including periods of remission. Deficits span multiple cognitive domains including attention and processing speed, memory and executive functioning (Bourne et al., 2013; Li et al., 2020). Importantly, cognitive dysfunction is a contributor to daily-life functioning difficulties and poor quality of life in people with BD (O'Donnell et al., 2017; Sanchez-Moreno et al., 2018). It is thus pivotal to estimate the prevalence of clinically significant cognitive impairment. Besides, identifying patient characteristics associated with cognitive impairment may help clinical services orient cognitive testing resources towards patients who are more likely to experience significant cognitive difficulties. This could facilitate the implementation of treatment strategies targeting cognitive impairment.

Studies attempting to estimate the prevalence of cognitive impairment in BD report inconsistent findings. Reviews suggest high impairment rates, ranging between 30% and 57% (Szmulewicz, Samamé, Martino, & Strejilevich, 2015), but vary depending on the adopted inclusion criteria for euthymia, with a recent one finding lower estimates (less than 30% for global cognitive impairment; (Cullen et al., 2016). Impairment rates ranged widely across included studies for individual domains, with margins as large as 5.3–57.7% for executive functioning and 8.2–42.1% for verbal memory (Cullen et al., 2016). The use of variable thresholds to define cognitive impairment adopted by individual studies is a key reason for the heterogeneity in prevalence, even when estimated for euthymic patients only. In addition, the absence of a consensus definition of clinically significant impairment presents challenges for evaluating cognition in clinical practice and assessing the outcomes for cognitive interventions (Miskowiak et al., 2017).

Studies examining correlates of cognition also report inconsistent results. Variables associated with lower cognitive performance include poorer cognitive reserve (Forcada et al., 2015), a positive history of psychotic symptoms (Bowie et al., 2018), use of antipsychotic medication (Roux et al., 2018), a longer illness duration and more manic episodes (Cullen et al., 2016), but negative findings for each of these variables have also been reported. One reason is that previous studies relating these factors to cognitive outcomes have been limited by statistical issues including *a priori* selection of certain candidate factors, median-split comparisons, or multivariable linear models without sufficient power. This results into multiple comparison issues and produces models explaining high proportion of the variance in the examined sample (inflated R^2 values) but with limited predictive value for new data or ability to generalize findings to the relevant population. Adopting more advanced, data-driven approaches that allow including multiple predictors and minimise the risk of overfitting may offer a solution to these challenges (James, Witten, Hastie, & Tibshirani, 2013).

This study had three objectives:

1) To investigate the prevalence of cognitive impairment in a cohort of euthymic patients with BD and examine whether the two recommended definitions of clinically significant impairment differentiate participants in established functional outcomes (Miskowiak et al., 2017).

2) To identify sociodemographic and clinical characteristics associated with cognitive performance. We used a regularized regression approach with elastic net which allows considering a large number of potential predictors and overcomes limitations related to overfitting (Zou & Hastie, 2005).

3) To examine the identified factors (objective 2) as predictors of clinically significant cognitive impairment (objective 1).

Methods

Study design

This is a cross-sectional secondary analysis of baseline data from the Cognitive Remediation in Bipolar (CRiB) study (Strawbridge et al., 2016; Strawbridge et al., 2020). Written informed consent was obtained from all participants prior to inclusion. The trial was reviewed and approved by the City Road & Hampstead NHS Research Ethics Committee (reference 15/LO/1557).

Participants

80 outpatients with a DSM-5 diagnosis of BD were included, recruited from the community (via online advertisement and through mental health organisations) and primary/secondary care services. All participants were fluent in English and aged between 18 and 65 years. We used the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) to confirm BD subtype. Participants had been free of acute mood symptoms for ≥1 month prior to inclusion, with euthymia defined as scoring ≤7 on the *Hamilton Depression Rating Scale 17-item* (HAMD) (Hamilton, 1960) and *Young Mania Rating Scale* (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) screened over the 1-month period. Participants with a neurological disorder, personality disorder diagnosis, abuse or dependence on alcohol or illicit substances over the past six months were excluded.

Measures

Clinical assessment

Sociodemographic (e.g., age, gender, education), clinical (e.g., age of onset, BD subtype, illness duration) and current medication (e.g., number of psychotropic medications, medication classes) information was collected with a structured interview. Depressive symptoms were assessed using the HAMD and hypomanic/manic symptoms with the YMRS. Psychosocial functioning was assessed using the *Functional Assessment Short Test* (FAST) (Rosa et al., 2007), while functional capacity was evaluated with the *UCSD Performance-based Skills Assessment* brief version (UPSA-B) (Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001).

Cognitive assessment

Participants were administered a cognitive battery in a standardised order by a trained psychologist. The battery included tests assessing four cognitive domains:

- ***Processing speed***, using the *Digit-symbol coding* and *Symbol search* from the Wechsler Adult Intelligence Scale 4th edition (Wechsler, 2014)
- ***Attention and working memory***, using the *Digit span* (sum of forward, backward and sequencing conditions) from the Wechsler Adult Intelligence Scale 4th edition (Wechsler, 2014)
- ***Verbal learning and memory***, using the *Verbal paired associates I* (VPA1) and *II* (VPA2) from the Wechsler Memory Scale 4th edition (Wechsler, 2009)
- ***Executive functioning***, using the *Hotel test* (Manly, Hawkins, Evans, Woldt, & Robertson, 2002), the *Matrix reasoning* subtest from the Wechsler Abbreviated Scale of Intelligence 2nd Edition (Dumont, Willis, Veizel, & Zibulsky, 2014), and the *FAS letter fluency* from the Delis-Kaplan Executive Function System (Delis, 2001).

We also administered an estimate of premorbid IQ, using the *Test of Premorbid Function* (TOPF) (Wechsler, 2011).

Statistical analysis

All analyses were conducted using SPSS (version 25; IBM, New York) and R software (version 3.6, www.r-project.org). All continuous variables were checked for normality of distributions using the Shapiro-Wilk test and log transformation was applied to conform non-normally distributed variables.

Computing cognitive variables

For each cognitive test, raw scores were transformed to age- and education-corrected standardised scores (*z* scores; *Mean* = 0, *SD* = 1) from test manuals. Higher scores reflected better performance for all tests. A global cognition composite score was computed as the pooled set of *z* scores from all individual tests.

Defining and estimating cognitive impairment

We used multiple criteria to define and estimate the prevalence of cognitive impairment, as in the previous studies (Douglas et al., 2018; Iverson, Brooks, Langenecker, & Young, 2011):

- Number of cognitive domains showing impairment
- Percentage of participants showing impairment in each cognitive domain
- Percentage of impaired participants on at least two individual cognitive tests
- Percentage of impaired participants based on the global cognition composite score.

In the absence of a consensus cut-off for severity, we examined four different cut-offs for all criteria: 0.5, 1, 1.5 and 2 SDs below the normative mean.

In addition, we adjusted global cognitive performance for premorbid IQ in order to estimate the percentage of globally impaired participants accounting for their cognitive reserve (Douglas et al., 2018). The global cognition score corrected for premorbid IQ was calculated by subtracting each participant's premorbid IQ (TOPF) *z* score from their global composite *z* score. Considering cognitive reserve is relevant since cognitive scores based on normative data may underestimate cognitive decline for participants with above-normal premorbid cognitive functioning (Miskowiak et al., 2017).

Validating clinically significant cognitive impairment

We examined two definitions recommended by the International Society for Bipolar Disorders (ISBD; Miskowiak et al., 2017): a) impairment of ≥1SD below the normative mean in ≥2 individual cognitive tests from different domains (Definition 1), and b) impairment of ≥0.5SD below the normative mean on the global cognition composite score (Definition 2).

First, we evaluated the convergence in identifying the same participants as cognitively impaired between the two definitions, using Cohen's *kappa* for agreement in categorical data. To ensure the definitions were clinically significant, we examined whether participant classification according to these definitions was meaningful at a functional level. We used one-way ANOVA to examine whether there was a significant difference between participants classified as impaired versus preserved in psychosocial functioning (FAST) and functional capacity (UPSA-B).

Identifying predictors of cognitive performance

We ran an elastic net regression using the GLMNET package in R (Friedman, Hastie, & Tibshirani, 2010), with sociodemographic and clinical characteristics as potential predictors of the global cognitive composite. Elastic net is a combination method of the LASSO and the Ridge regression, thus allowing variable selection and coefficient shrinking (Zou & Hastie, 2005). Elastic net was applied with repeated 10-fold cross-validation to identify the optimal tuning parameters (*alpha* and *lambda*) within one

standard error from the minimum cross-validated prediction error (1SE *MSE*) in order to select the most parsimonious model (Friedman et al., 2010; Krstajic, Buturovic, Leahy, & Thomas, 2014). The final model retained only the penalized predictors with non-zero coefficients. Elastic net regression allowed considering at the same time multiple potential predictors of cognitive performance which have been selectively examined in previous studies (full list in Supplementary Table 1). A post-hoc multiple linear regression including only the retained predictors was conducted to estimate interpretable standardised coefficients for these predictors and evaluate model fit.

Modelling cognitive impairment

Logistic regression was used as a binary classifier to ascertain whether the factors significantly associated with *cognitive performance* in the post-hoc linear regression (independent variables) predict the presence of clinically significant *cognitive impairment* (dependent variable). Classification accuracy (percentage of correct predictions), sensitivity (true positive rate) and specificity (true positive rate) were used to evaluate the model's ability to discriminate between impaired and non-impaired participants and area under the receiver-operating-characteristic (ROC) curve (AUC) as an aggregate measure of the model's performance.

Results

Table 1 reports the sample's sociodemographic and clinical characteristics and normative cognitive performance. There were no missing data in any of the variables considered.

-- Table 1 around here –

Prevalence rates of cognitive impairment

Few participants (≤10%) were impaired across criteria when applying the most conservative threshold of 2 SD, therefore we focused on the other three cut-offs (Table 2). Cut-offs of 0.5 and 1 SD indicated an impairment rate between 13 and 48% in multiple domains. There was variability between domains, with verbal learning and memory significantly impaired at every cut-off (16-45%) and the highest impairment rate among domains, followed by executive functioning. Considering impairment in two or more individual tests, half of the participants (50%) were impaired using the 1 SD cut-off, while the composite score criterion showed intermediate impairment up to the 1 SD threshold (13-34%).

Extending the global cognitive score approach to account for estimated premorbid IQ led to an increase in cognitive impairment rates across cut-offs (Figure 1). This increase was statistically significant for the 0.5 SD cut-off (34% vs 73%; $\chi^2 = 15.46$, $p < 0.001$) and the 1 SD cut-off (13% vs 34%; $\chi^2 = 6.72$, $p = 0.01$), but not significant for the 1.5 and 2 SD cut-offs.

-- Table 2 around here --

-- Figure 1 around here –

Definitions of clinically significant impairment

Supplementary Figure 1 compares the cognitive profile of impaired and preserved participants under the examined definitions. The convergence between the two definitions was good (Cohen's *kappa* = 0.68, $p < 0.001$), indicating that both approaches classified a significant proportion of the same participants as impaired. Psychosocial functioning (FAST) was greater for cognitively impaired participants (Definition 1 $F(1,79) = 9.22$, $p < 0.01$; Definition 2 $F(1,79) = 7.55$, $p < 0.01$). For both definitions, the mean FAST score for cognitively impaired participants corresponded to moderate

functional difficulties (FAST ≥ 21) and the mean score for cognitively preserved participants fell within the category of mild difficulties (FAST ≤ 20). However, the association between cognitive impairment level and functional recovery (FAST ≤ 11) was only significant for Definition 2 ($\chi^2(1,79) = 4.08$, $p = 0.04$), with only one participant classified as impaired according to this definition reporting a FAST score corresponding to recovery. Functional capacity (UPSA-B score) was significantly different between cognitive impairment groups only for Definition 2 ($F(1,79) = 7.32$, $p < 0.01$). Definition 2 was therefore considered more appropriate to determine clinically significant cognitive impairment, for which 33.8% of the sample was classified as cognitively impaired.

Predictors of cognitive performance

A repeated 10-fold cross-validation of elastic net regression selected five variables associated with poorer global cognitive performance: older age, lower premorbid IQ, higher number of currently prescribed psychotropic medications, fewer completed psychological therapies and taking antipsychotic medication (*alpha* = 0.68, *lambda* = 0.16, minimum 1SE *MSE* = 0.30). A post-hoc linear regression was conducted, containing these five variables as predictors of global cognitive composite score. Premorbid IQ, number of psychotropic medications and previous psychological therapies remained significant predictors. The full model was significant ($F = 8.72$, $p < 0.001$) and accounted for 37% of the variance on global cognition. Factor coefficients and model statistics for both regression models are reported in Table 3.

-- Table 3 around here --

A model of cognitive impairment

The three factors significantly associated with cognitive performance were included as predictors of clinically significant cognitive impairment (Definition 2) in a logistic regression model. The model showed adequate classification accuracy, correctly classifying 75% of participants, had good sensitivity (0.83), but low specificity (0.59). The AUC was 0.77 indicating a good overall performance for the model and suggesting that a pair of participants randomly selected from each group would be correctly classified in 77% of the cases (Figure 2; AUC for Definition 1 included for reference). See Supplementary Table 2 for further details.

-- Figure 2 around here --

Discussion

This study found that a recommended definition of cognitive impairment (i.e., ≥0.5 SD below the normative mean in global cognitive composite) was able to differentiate impaired from preserved participants in established functional measures. Variable selection with elastic net regression showed that lower cognitive performance was associated with demographic (older age, poorer premorbid IQ) and clinical characteristics (number of psychiatric medications, use of antipsychotics, number of psychological therapies undertaken). Using the selected definition, a model including three of these factors (premorbid IQ, medications, psychological therapies) demonstrated good ability to discriminate between participants with and without clinically significant cognitive impairment.

What is the prevalence of clinically significant cognitive impairment?

Prevalence estimations varied greatly in our sample depending on the definition used, ranging from as low as 7.5% for conservative criteria to 70% for inclusive criteria. This wide variation is consistent with previous findings from studies examining multiple definitions of cognitive impairment in

euthymic people with BD (Reichenberg et al., 2009; Roux et al., 2018), albeit lower than those reported for a similar sample employing similar definitions to estimate impairment (Douglas et al., 2018). Our sample was on average younger, with a lower proportion of patients with BD type I and these factors might explain the differences with others. Recently, it was suggested that studies often overestimate the prevalence of cognitive impairment due to recruitment methods (e.g. clinical samples) biasing in favor of participants with cognitive deficits (Cullen et al., 2016). Our cohort was primarily recruited from primary services and the community, and included only fully remitted participants, which may reflect a cohort more representative of those with euthymic BD.

A consensus definition of clinically significant cognitive impairment is crucial for research and clinical practice (e.g., for pooling data, identifying patients in need for cognitive interventions). Adopting such a definition may parse the variation of cognitive impairment estimations. Recent guidelines from the ISBD cognitive taskforce recommended two thresholds for cognitive impairment, one based on individual tests and one based on a composite score (Miskowiak et al., 2017). Our findings support the use of composite score definition for classifying clinically significant and functionally relevant cognitive impairment, in accordance with previous evidence suggesting composite scores are more sensitive compared to individual tests (Jensen et al., 2015). Based on this definition, one third (34%) of patients recruited without any cognitive screening restrictions may present with clinically significant cognitive impairment, which is in consistent with the mean prevalence reported across euthymic samples (Cullen et al., 2016). Trials choosing to enrich their sample for objective cognitive impairment may consider this finding for predefining thresholds of impairment and for recruitment planning purposes.

An extension of this definition involves correcting the global cognitive score to account for estimated premorbid IQ. This adjusts estimates of impairment according to individual premorbid level of cognitive functioning rather than population-based normative data (Miskowiak et al., 2017). In our study, this approach significantly increased the rate of participants classified as impaired which may be due to the high proportion of participants with above average premorbid IQ (*Mean* = 109). Compared to normative data, many of these participants did not show significant impairment, but they did in relation to their own level of premorbid cognitive functioning. Our results contrast with Douglas et al. (2018) who suggested no change in impairment rates when correcting for premorbid IQ. However, they used the 1.5 SD impairment cut-off, whereas we only observed significant increase of impairment rates at cut-offs below 1.5 SD. We suggest that even objectively preserved patients may have experienced a clinically relevant decline from premorbid level. Cognitive intervention trials enriching their sample may consider this alternative screening approach as a means to improve recruitment rates but still identify participants with "*room-for-improvement"* in cognitive outcomes.

Which are the characteristics associated with cognitive performance?

We used variable selection with regularized regression to identify sociodemographic and clinical characteristics associated with cognitive performance in BD. This produced a sparse model with higher predictive ability for unexamined cases than linear modelling. Some of our findings were in line with previous studies. Evidence suggests that normal ageing effects on cognition are accelerated compared to healthy controls in people with psychotic disorders (Fett et al., 2020). A recent study found that accelerated age-related and illness-related cognitive decline is moderated by cognitive reserve in patients with schizophrenia-spectrum disorders (Van Rheenen et al., 2019). In our analysis, estimated premorbid IQ was associated with reduced cognitive decline, suggesting it may ameliorate the effects of neuropathology and ageing or reflect better capacity to compensate for these effects, similar to previous evidence (Anaya et al., 2016; Grande et al., 2017). This is in line with the theoretical concept of cognitive reserve in dementia and schizophrenia research, as representative of a patient's enhanced tolerance and greater ability to employ alternative functional networks in the presence of brain

pathology (Stern, 2012; Watson & Joyce, 2015). Cognitive reserve, reflected by premorbid IQ, potentially moderates how early or to what extent age- and illness-related cognitive decline transpires and, thus, may be one of the factors explaining cognitive variability in patients with BD.

To our knowledge, number of previous psychological therapies has not been previously associated with cognition in BD. It is not clear whether the association between completing more psychological therapies and higher cognitive performance represents a protective effect of psychotherapy or simply reflects a greater ability to access psychological services and engage with therapy for patients not experiencing cognitive difficulties. The effect of medication on cognition has been the subject of much debate, but studies commonly assess medication use by class whereas we additionally examined the number of psychotropic medications taken. However, this does not imply a causal relationship as a reverse association between medication use and cognitive performance might exist, since often treatment decisions are based on illness severity, including cognitive impairment. Previous evidence has linked poorer cognition with the use of antipsychotic medication (Cullen et al., 2016), similar to that we found. As in previous studies, we used a binary variable for antipsychotic medication which does not allow an estimation of dose-effect relationships (Roux et al., 2018). The interpretation of this finding is therefore complex and needs further investigation.

None of the illness severity indices (e.g., age of onset, illness duration, number of mood episodes or hospitalisations) were associated with cognitive performance in our sample following the surfacing of stronger associations. Although these clinical characteristics have been previously shown to correlate with worse cognitive performance (Bourne et al., 2013), more recent meta-analytic findings have indicated that patients with BD may follow a cognitive trajectory largely independent of illness progression across the adult-life span (Bora & Ozerdem, 2017; Szmulewicz, Valerio, & Martino, 2020). Thus, neurodevelopmental factors may have a significant role in cognitive decline at least for a proportion of people with BD, similar to schizophrenia (Bora & Pantelis, 2015). Our findings on the role of premorbid IQ for cognitive performance are consistent with this notion.

Can we predict cognitive impairment in clinical practice?

Addressing cognition is a major challenge in the clinical management of BD, and part of this process is promptly and accurately recognizing the criteria for providing cognitive interventions (Miskowiak et al., 2018). Despite the undeniable importance of cognition, the reality of clinical practice poses serious limitations in terms of access to assessment resources (e.g. testing materials, time allocated, availability of trained personnel to administer, score and interpret cognitive measures). Given these challenges, recognizing cognitive impairment based on patient characteristics might offer an alternative approach, particularly for services without access to these resources.

We suggested a model able to classify clinically significant cognitive impairment and adequately detect cognitively impaired participants. Those with lower estimated premorbid IQ, multiple current psychotropic medications and fewer previous psychological therapies had a higher probability to be classified as cognitively impaired. The benefit of this approach is that two predictors are patient characteristics routinely collected during intake, while premorbid IQ can be easily assessed with a reading test requiring minimal time and training for administration and scoring. Although our model cannot provide a cut-off score, evaluating these factors may provide an informed estimate on whether a patient experiences cognitive difficulties that need to be further examined with a neuropsychological assessment or addressed with appropriate interventions. Predictive modelling cannot replace comprehensive assessments, but it may provide an alternative for clinical services limited by resources, time or specialized personnel.

Our model, although parsimonious, is not exhaustive in terms of included factors and requires external validation with the model's accuracy and predictive strength examined in cohorts different to the one used for selecting predictors of cognitive performance. This would provide further validation of the model's ability to detect clinically relevant cognitive impairment. However, our findings also have direct implications for clinical practice. We investigated criteria for clinically significant impairment and established one approach which can be applied in clinical settings with the capacity to conduct neuropsychological assessments to detect patients in greatest need of intensive interventions such as cognitive remediation.

Limitations

Although our sample was primarily recruited from community settings and primary services, estimations of the prevalence of cognitive impairment prevalence using patients who expressed an interest to participate in a cognitive remediation trial should be considered tentatively. Our model selection could have possibly eliminated some potential predictors of smaller strength (i.e., potential type II error), but we were mainly interested in those which were large enough to be useful in clinical or research settings. The cross-sectional design prevents any causal inferences, but most selected predictors were retrospectively measured and thus temporally preceded our measures of 'real-time' cognition. Longitudinal studies need to validate both the prevalence of cognitive impairment based on the definition we identified as most clinically relevant, and the durability of the association between patient characteristics and cognition over time.

The ability to generalize the associations detected in this study might be limited by certain characteristics of our sample, which primarily consisted of middle-aged participants with an established BD diagnosis in terms of illness duration. Thus, our findings might not be representative of younger or early-stage patients. Our variable selection process was only attempted for global cognition; although previously recommended as the clinically relevant outcome and less susceptible to multiple comparisons issues, this did mean that we did not model individual cognitive domains. Finally, there are further putative factors that might influence cognition in BD, such as sleep and circadian rhythms (Bradley, Anderson, Gallagher, & McAllister-Williams, 2019), which were not examined in this study. The same applied for medical comorbidities which might be associated with cognition through different pathophysiological mechanisms, but for which data were not available.

Conclusions

One third presented with clinically significant cognitive impairment in this cohort of euthymic participants with BD. Accounting for premorbid IQ increased this rate. We investigated multiple factors potentially associated with cognition. Age, current number of medications and use of antipsychotics were negative factors, while premorbid IQ and previous psychological therapies were positive factors. Modelling cognitive impairment as a function of three factors (premorbid IQ, number of medications, previous psychological therapies) correctly classified 75% of participants. Pending further validation in larger longitudinal studies, we suggest that the criterion for clinically significant cognitive impairment validated in this study (i.e., ≥0.5SD below the normative mean on a global cognition composite score) could have translational impact in identifying those with a greater need for cognitive interventions.

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Tables

Table 1. Sample characteristics and cognitive performance (N = 80).

Sociodemographic / clinical characteristics		**Mean**	**SD**	**Range**
Age		42.2	12.8	19 – 65
Education (years)		15.9	2.1	11 – 21
Premorbid IQ (TOPF)		109.2	6.9	93 – 121
Age BD diagnosed		30.9	11.7	16 – 61
Diagnosis duration (years)		10.8	8.9	0 – 34
Duration of untreated illness (years)		10.7	9.6	0 – 44
Number of depressive episodes		11.8	11.9	1 – 48
Number of (hypo)manic episodes		8.5	7.2	1 – 32
Number of hospitalizations		2.4	22.9	0 – 14
Current euthymia (months)		13.8	24.6	1 – 168
Number of current medications		2.4	1.5	0 – 7
Psychological therapies undertaken		1.9	1.5	0 – 8
HAMD		3.8	2.6	0 – 7
YMRS		2.3	2.4	0 – 7
FAST		21.8	9.8	3 – 43
UPSA		75.4	11.7	44 – 100
		n	**%**	
Gender (F/M)		57/23	71 / 29	
BD type (I/II)		53/27	66 / 34	
Family history of affective disorders		43	54	
History of psychosis		52	65	
Current medications				
Mood stabilizers		60	75	
Antipsychotics		59	74	
Antidepressants		39	49	
Anxiolytics		13	16	
Cognitive domains / tests	**Raw mean (SD)**	**Mean (*z* scores)**	**SD (*z* scores)**	**Range (*z* scores)**
Processing speed	-	-0.14	0.7	-1.67/1.50
Digit/Symbol coding	63.3 (12.9)	-0.25	0.7	-1.67/1.33
Symbol search	31.4 (6.9)	-0.03	0.8	-1.67/1.67
Working memory	-	-0.09	0.7	-1.33/1.67
Digit span total (for/back/seq)	28.3 (4.3)	-0.09	0.7	-1.33/1.67
Verbal learning and memory	-	-0.26	1.1	-2.50/1.67
VPA immediate recall	30.3 (12.7)	-0.22	1.1	-2.00/2.00
VPA delayed recall	9.1 (3.7)	-0.31	1.1	-3.00/1.67
Executive functioning	-	-0.22	0.7	-1.78/1.22
Hotel test - deviation time	377.6 (213.7)	-0.45	1.1	-2.33/1.67
Matrix reasoning	19.2 (3.7)	-0.03	0.9	-1.67/2.33
Phonemic fluency *FAS*	42.3 (12.1)	-0.22	1.0	-2.67/2.33
Global cognitive composite	-	-0.17	0.6	-1.56/1.17

Notes: BD: Bipolar Disorder; CTQ: Childhood Trauma Questionnaire; FAST: Functional Assessment Short Test; HAMD: Hamilton Depression Rating Scale 17 items; TOPF: Test of premorbid functioning; UPSA: UCSD Performance-based Skills Assessment; VPA: Verbal paired associates; YMRS: Young Mania Rating Scale.

Table 2. Prevalence rates of cognitive impairment using different classification approaches.

Number of impaired domains	***n***	**%**	**Impairment on each domain**	***n***	**%**
0.5 SD			*Processing speed*		
No domains	24	30.0	≥ 0.5 SD	32	40.0
≥ 1 domain	56	70.0	≥ 1 SD	15	18.8
≥ 2 domains	38	47.5	≥ 1.5 SD	5	6.3
≥ 3 domains	20	25.0	≥ 2 SD	0	0.0
1 SD			*Working memory*		
No domains	52	65.0	≥ 0.5 SD	22	27.5
≥ 1 domain	28	35.0	≥ 1 SD	11	13.8
≥ 2 domains	17	21.3	≥ 1.5 SD	0	0.0
≥ 3 domains	10	12.5	≥ 2 SD	0	0.0
1.5 SD			*Verbal learning & memory*		
No domains	64	80.0	≥ 0.5 SD	36	45.0
≥ 1 domain	16	20.0	≥ 1 SD	30	37.5
≥ 2 domains	7	8.8	≥ 1.5 SD	13	16.3
≥ 3 domains	3	3.8	≥ 2 SD	7	8.8
2 SD			*Executive functioning*		
No domains	72	90.0	≥ 0.5 SD	34	42.5
≥ 1 domain	8	10.0	≥ 1 SD	20	25.0
≥ 2 domains	2	2.5	≥ 1.5 SD	3	3.8
≥ 3 domains	0	0.0	≥ 2 SD	0	0.0
Two individual cognitive tests	***n***	**%**	**Global cognition composite score**	***n***	**%**
≥ 0.5 SD on ≥ 2 tests	54	67.5	**≥ 0.5 SD**	**27**	**33.8**
≥ 1 SD on ≥ 2 tests	**40**	**50.0**	≥ 1 SD	10	12.5
≥ 1.5 SD on ≥ 2tests	19	23.8	≥ 1.5 SD	4	5
≥ 2 SD on ≥ 2 tests	6	7.5	≥ 2 SD	0	0.0

Notes: SD: Standard deviation; Definitions of *clinically significant* cognitive impairment **in bold**.

Table 3. Elastic net and linear regression models for the global cognition composite score.

	Elastic net regression	**Linear regression**				
Predictors	**Coefficient**	**Estimate (B)**	**SE (B)**	***beta***	***t***	***P***
(Intercept)	-1.57	-2.97	0.89	-	-3.32	0.001
Age	-4.43	-0.07	0.05	**-0.15**	-1.55	0.13
Premorbid IQ	1.41	0.03	0.01	**0.35**	3.68	<0.001
Number of medications	-4.66	-0.10	0.04	**-0.26**	-2.47	0.02
Previous psychotherapies	3.31	0.11	0.04	**0.27**	2.86	0.01
Antipsychotic medication	-1.08	-0.22	0.14	**-0.16**	-1.51	0.14

Notes: B: Unstandardized coefficient; Beta: Standardized coefficient; SE: Standard error.
Elastic net model includes retained predictors after 10-fold cross validation to identify optimal tuning parameters *alpha* and *lambda*. Post-hoc linear regression model included all retained predictors and was significant, $F = 8.72$ *(df 5, 74),* $\boldsymbol{R^2 = 0.37}$*,* $p < 0.001$.

Figure legend

Figure 1. Percentage of cognitively impaired participants at different cut-offs on the global cognitive composite and on the same score after correction for premorbid IQ.
** Chi-square test significant at $p < 0.001$
* Chi-square test significant at $p < 0.05$

Figure 2. Receiver operating characteristics (ROC) and area under the curve (AUC) diagram for a model including premorbid IQ, number of medications, and previous psychological therapies using two thresholds for cognitive impairment.

Figure 1

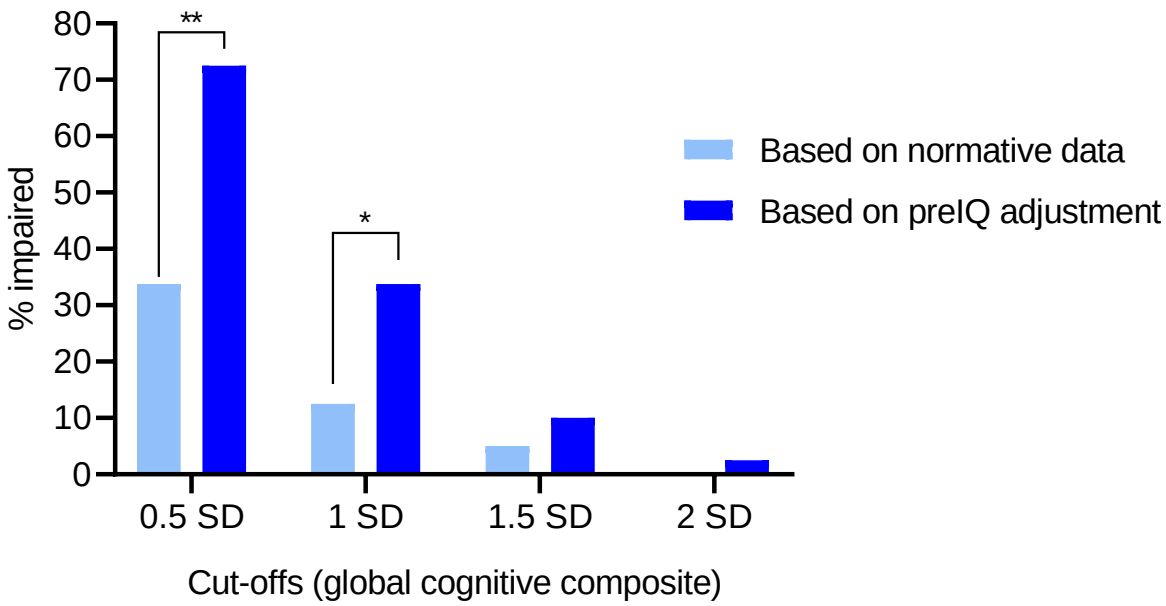
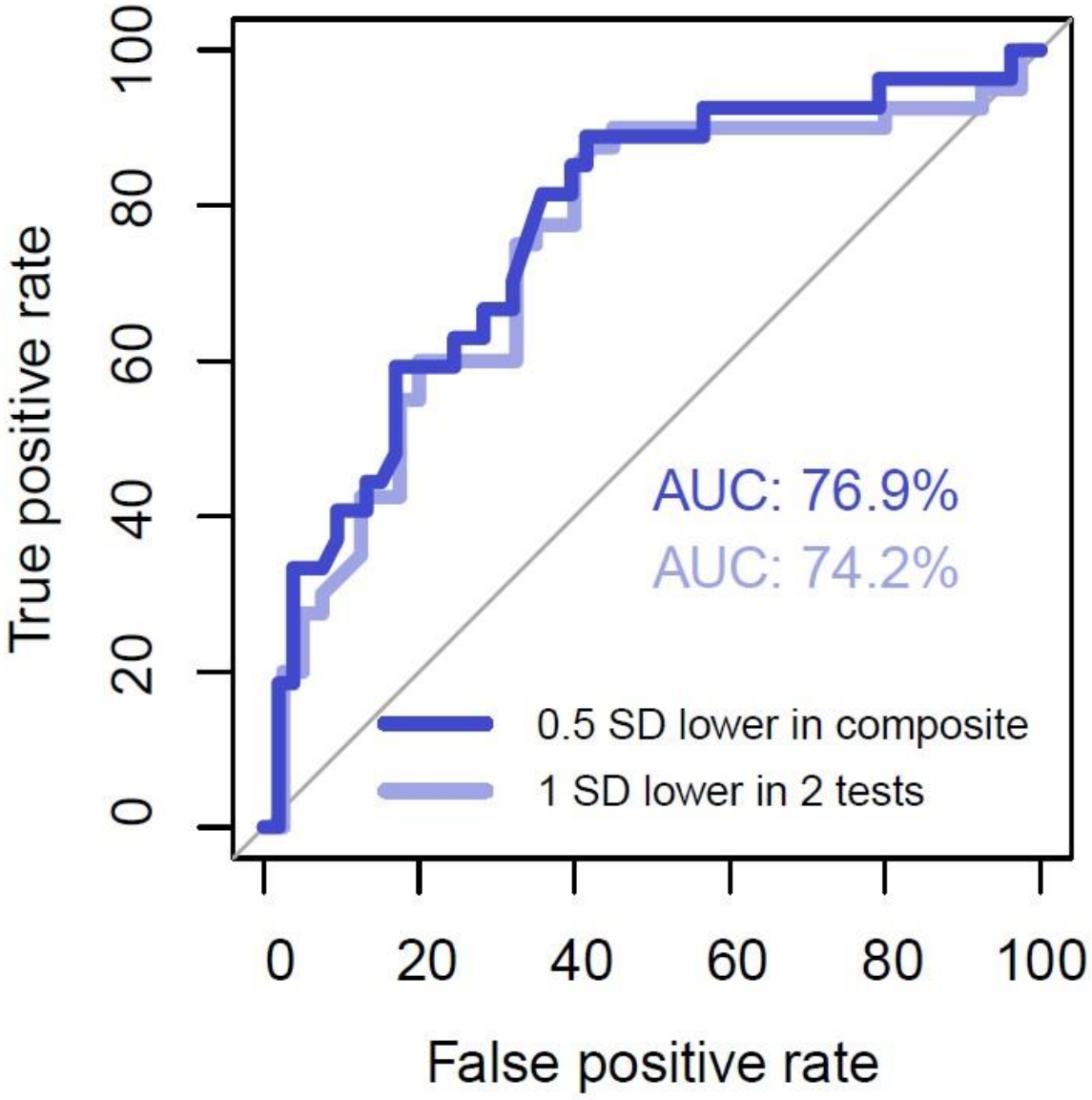

80
70
60
50
40
30
20
10
0
% impaired
**
*
0.5 SD
1 SD
1.5 SD
2 SD
Cut-offs (global cognitive composite)
Based on normative data
Based on preIQ adjustment

Figure 2


True positive rate
0
20
40
60
80
100
False positive rate
0
20
40
60
80
100
AUC: 76.9%
AUC: 74.2%
0.5 SD lower in composite
1 SD lower in 2 tests