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Predictors of the discrepancy between objective and subjective cognition in bipolar disorder: a novel methodology.

***Acta Psychiatrica Scandinavica* 2016, 134(6), 511-521**

Title: Predictors of the discrepancy between objective and subjective cognition in bipolar disorder: a novel methodology

Running title: Subjective versus objective cognition discrepancy

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Word count: Abstract: **199/** Article body (excl. abstract, acknowledgments and references): **4.166**

Figures/tables: 2/3

Supplementary information: 0

Abstract

Objective: The poor relationship between *subjective* and *objective* cognitive impairment in bipolar disorder (BD) is well-established. However, beyond simple correlation, this has not been explored further using a methodology that quantifies the *degree* and *direction* of the discrepancy. This study aimed to develop such a methodology to explore clinical characteristics predictive of subjective-objective discrepancy in a large BD patient cohort.

Methods: Data from 109 remitted BD patients and 110 healthy controls were pooled from previous studies, including neuropsychological test scores, self-reported cognitive difficulties and ratings of mood, stress, socio-occupational capacity and quality of life. Cognitive symptom 'sensitivity' scores were calculated using a novel methodology, with positive scores reflecting disproportionately more subjective complaints than objective impairment and negative values reflecting disproportionately more objective than subjective impairment ('stoicism').

Results: More sub-syndromal depressive and manic symptoms, hospitalisations, BD type II and being male positively predicted 'sensitivity', while higher verbal IQ predicted more 'stoicism'. 'Sensitive' patients were characterized by greater socio-occupational difficulties, more perceived stress and lower quality of life.

Conclusion: Objective neuropsychological assessment seems especially warranted in patients with (residual) mood symptoms, BD type II, chronic illness and/or high IQ for correct identification of cognitive deficits before commencement of treatments targeting cognition.

Keywords: bipolar disorder, cognition, stress, quality of life, methodology

Significant outcomes

- Patients with more mood symptoms, greater illness chronicity, bipolar disorder type II and male gender showed greater subjective than objective cognitive impairment.
- Patients with high premorbid IQ tended to *under-report* objective cognitive impairment.
- Self-reports of cognitive difficulties cannot replace objective neuropsychological testing.

Limitations

- The study involves secondary analysis of data from previously published/ongoing studies and the findings should therefore be regarded as preliminary.
- The study is cross-sectional, which limits causal inferences regarding the relationship between clinical characteristics and the discrepancy between subjective and objective cognition.

Introduction

Cognitive dysfunction in bipolar disorder (BD) occurs across several domains including attention, verbal memory and executive function (Bora *et al.*, 2016; Bourne *et al.*, 2013; Martinez-Aran *et al.*, 2000; Robinson *et al.*, 2006), and is evident both during acute mood episodes and in remission (Bora, Yucel, & Pantelis, 2009; Gallagher *et al.*, 2014; Harvey *et al.*, 2010; Jensen *et al*., 2016 in review). The cognitive deficits contribute directly to impaired socio-occupational capacity (Baune & Malhi, 2015; Depp *et al.*, 2012; Tse *et al.*, 2014), which constitutes the greatest socio-economic burden of BD (Olesen *et al.*, 2012; Wyatt & Henter, 1995). However, there is no reliably efficacious treatment with enduring pro-cognitive effects in BD, possibly due to several methodological challenges in cognition trials (Miskowiak *et al*., 2016 in review). A major difficulty is the limited understanding of the nature and pattern of cognitive impairment in BD. In particular, there is compiling evidence for a discrepancy between patients' *subjectively* experienced and *objectively* measured cognitive impairment, indicating that it may not be the patients with the greatest complaints who display most objective deficits and vice versa (Burdick, Endick, & Goldberg, 2005; Demant *et al.*, 2015; Jensen *et al.*, 2015). This may be a general phenomenon, since this discrepancy has also been observed in other patient groups, including unipolar disorder (UD) (Ott *et al.*, 2016; Svendsen *et al.*, 2012) and in healthy controls (HC) (Stenfors *et al.*, 2014; Van der Elst *et al.*, 2008). Indeed, several studies by our and other groups indicate that subjective cognitive impairment in BD and UD may not reflect objective cognition per se, as it is largely influenced by depression severity, comorbidity, and/or adverse effects of medications (Burdick, Endick, & Goldberg, 2005; Dias *et al.*, 2012; Martínez-Arán *et al.*, 2005; Ott *et al.*, 2016; Svendsen *et al.*, 2012; van der Werf-Eldering *et al.*, 2011; Vieta, 2009). A potential explanation for the subjective-objective discrepancy is that subjective measures may better capture patients' *decline* in cognitive capacity from supra-normal premorbid levels than objective tests, which simply rely on

the comparison with a normative group (Forcada *et al.*, 2015). Further, objective tests are also limited by insufficient ecological validity and may not fully capture patients' cognitive difficulties in their daily lives (Mohn & Rund, 2016; Van der Elst *et al.*, 2008).

Whilst there are reasons to believe that subjective and objective measures capture somewhat different processes, the methodology of simply correlating them with one another sets limits on how any discrepancy can be further-understood. Some patients will have a relatively *accurate* sense of their cognitive abilities, whereas others may be *sensitive* to cognitive problems and over-report them or be *stoical* and under-report difficulties. Indeed, insight into one's own cognitive abilities is likely to depend on meta-cognitive capacity (Torres *et al.*, 2016), which is often affected by psychiatric illness and subjective distress (Ladegaard *et al.*, 2015; Lysaker *et al.*, 2015a; Lysaker *et al.*, 2015b). Simple correlational analysis cannot identify differences between patients in the *direction* of the discrepancy between objective and subjective cognition and therefore does not enable further exploration of predictive factors. The issue of subjective-objective discrepancies is pertinent to BD since patients present frequent cognitive complaints (Miskowiak *et al.*, 2012) but are objectively cognitively intact in approximately 30-50% cases (Bora *et al.*, 2016; Burdick *et al.*, 2014; Jensen *et al*., 2016 in review; Sole *et al.*, 2016). This introduces a risk of including patients with no or only subtle objective cognitive deficits in treatment trials targeting cognition, which increases the risk of type II error and thus the rates of negative findings (Miskowiak *et al*., 2016 in review). This highlights a need for better understanding of what contributes to the discrepancy between subjective and objective measures of cognition.

In a different field of inquiry, Delbaere *et al.* (2010) separated a cohort of elderly patients according to the relationship between their *perceived* and *objective* physiological risk of falling. They identified 'accurate' patients, whose perceived risk matched their objective risk, as well as 'sensitive' patients, whose perceived risk was higher than their objective risk, and 'stoical' patients,

whose perceived risk was lower than their objective risk. Sensitive patients had higher levels of depressive symptoms and neuroticism, whereas stoical patients had a more positive outlook on life. We have previously adapted this methodology to explore symptom-sensitivity in other conditions (Bezzina *et al*., 2016 in review; Robinson *et al*., 2014). However, it could be further-adapted to explore discrepancies in subjective and objective cognitive function in BD.

1.1 Aims of the study

The study aims to apply a new methodology to explore clinical factors predictive of the discrepancy between subjective and objective cognitive impairment in remitted BD patients. The insights may improve targeting of resources for objective neuropsychological assessments in clinical settings and in cognition trials. We hypothesized that more subsyndromal mood symptoms would be associated with more subjective than objective cognitive impairment (i.e., greater sensitivity).

Materials and methods

Pooling of data

We pooled available baseline data from a previously published study (Jensen *et al.*, 2015; Ott *et al.*, 2016) (BD: N=84, HCs: N=103) and an ongoing study (BD: N=25, HCs: N=7). The sample included a total of 219 participants (BD: N=109, HCs: N=110).

Participants

Patients were recruited from the outpatient clinic Copenhagen Clinic for Affective Disorders, Psychiatric Centre Copenhagen, and age- and gender matched HCs were recruited consecutively from the blood bank at Copenhagen University Hospital, Rigshospitalet.

Patients in the original studies were eligible if they met the following inclusion criteria 18-65 years of age, an ICD-10 diagnosis of BD and being in full or partial remission (scores <14 on the Hamilton Depression Rating Scale-17 (HDRS-17; Hamilton, 1960) and the Young Mania Rating Scale (YMRS; Young *et al.*, 1978) and being fluent in Danish. Exclusion criteria were current substance abuse, substantial somatic disease, prior history of schizophrenia or a daily use of benzodiazepines >22.5 mg oxazepam. Healthy controls were excluded if they were dyslexic or had a personal or first-degree family history of mental illness. All participants provided written informed consent prior to participation. The local ethics committee stated that there was no need for approval of the completed study from which part of the data was pooled (Jensen *et al.*, 2015; Ott *et al.*, 2016), as it did not entail invasive or biomedical procedures. The other ongoing study from which data was pooled has been approved by the local ethics committee (ref.no. H-6-2014-006).

2.3 Procedure

Participants attended the Psychiatric Centre Copenhagen, Rigshospitalet, for one assessment of 1.5-2 hours. They were given a neuropsychological test battery to assess objective cognitive functioning and completed a set of questionnaires and a clinical interview, measuring subjective cognitive complaints, quality of life, socio-occupational capacity, perceived stress, and mood symptoms. Verbal intelligence was established using the Danish Adult Reading Test (DART; Crawford *et al.*, 1987).

Measures

<u>Measures of objective and subjective cognition</u>

Objective cognition was assessed with neuropsychological tests, which covered the domains of verbal learning and memory, working memory and executive functions, and attention and

processing speed. Specifically, data included performance scores on the following tests: the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 2004), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Digit Span (Forward) (Randolph *et al.*, 1998), the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III) Letter-Number Sequencing (Wechsler, 1997), Verbal Fluency with the letters S and D (Borkowski, Benton, & Spreen, 1967), Trail Making Test Part A (TMT-A; Army Individual Test Battery, 1944) and the five tests comprising the Screen for Cognitive Impairment in Psychiatry (SCIP; Purdon, 2005): verbal learning (VLT-I) and delayed memory (VLT-D), working memory (WMT), verbal fluency (VLF), and processing speed test (PST). Self-rated cognitive difficulties were assessed with the 16-item questionnaire, Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA; Rosa *et al.*, 2013).

Measures of mood, socio-occupational function and quality of life

Symptoms of depression and mania were rated with the HDRS-17 and the YMRS, respectively. Socio-occupational capacity was assessed with the Work and Social Adjustment Scale (WSAS; Mundt *et al.*, 2002) and the interviewer-administered instrument, the Functional Assessment Short Test (FAST; Rosa *et al.*, 2007). Quality of life was assessed with the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF; WHOQOL Group, 1994), and perceived stress was assessed with the Global Measure of Perceived Stress (Cohen, Kamarck, & Mermelstein, 1983).

Statistical procedures

Computation of sensitivity index scores

We adapted our previous methodology (Bezzina *et al*., 2016 in review; Robinson *et al*., 2014) to derive a 'sensitivity' score, which reflected the discrepancy between patients' *subjective* cognitive difficulties and *objective* deficits on neuropsychological tests. The index was based on the premise that absolute accuracy of symptom-perception would result in the same rank-ordering of patients on the basis of their objective performance as it would for their subjective performance (assuming both sets of measures are valid measures of the same fundamental construct). Those whose rank-ordering for their objective performance was lower (worse) than their subjective rating scored negatively (i.e., 'stoical') whereas those whose rank-ordering for their objective performance was higher (better) than their subjective rating scored positively (i.e., 'sensitive'). Raw scores on the objective and subjective measures were standardized against the control group to adjust for the degree of discrepancy between objective and subjective measures seen in the control group.

The index was computed for the BD group as a continuous variable with a range from -10 to +10 (see details later). A score of -10 represents maximum 'stoicism', with patients reporting the least subjective difficulties despite performing the worst on neuropsychological tests. A score of +10 thus represents maximum 'sensitivity', with patients reporting the most severe subjective cognitive complaints despite showing the least objective cognitive impairment. Scores towards zero indicate greater concordance between subjective ratings and objective performance (i.e., high cognitive complaints in those with pronounced objective deficits and no complaints in those who are cognitively intact).

Specifically, sensitivity scores were computed by first z-transforming raw scores on each neuropsychological test, the total score and individual sub-scores on the COBRA (self-rated cognitive difficulties) using data from both the BD and HC groups. Because lower scores on the TMT-A reflect better performance, we inversed the z-scores for the TMT-A measure to ensure uni-directionality of all scores before creating composite scores.

Three ‘domain composite scores’ were computed for (i) ‘attention and processing speed’, (ii) ‘verbal learning and memory’, and (iii) ‘working memory and executive functions’ in the BD group. In addition, a ‘global sensitivity composite’ score, comprising the overall performance scores across the domains, was computed by averaging patients’ scores on the three objective domains. Table 1 displays the grouping of objective neuropsychological tests and subjective COBRA-items within each cognitive domain.

<Please insert Table 1 around here>

Patients’ domain scores were re-scaled using the formula below. Old_{max} and old_{min} denote the highest and lowest values of the patient scores within each domain, on the global objective cognitive composite score and for subjective COBRA total score, respectively. The new/converted minimum and maximum values, new_{min} and new_{max} were chosen to be 0 and 10, respectively. The ‘x’ represents each individual patient z-score. All the scores were re-scaled into a value of 0 to 10.

$$Re\text{-}scale\ formula = \left(\frac{(new_{max} - new_{min})}{(old_{max} - old_{min})} \cdot (x - old_{max})\right) + new_{max}$$

Sensitivity scores were then computed by subtracting the re-scaled subjective scores (based on the COBRA) from the corresponding re-scaled objective scores (based on the neuropsychological tests). The main sensitivity score was derived from the rescaled global objective composite score and the re-scaled global subjective scores. In addition, we calculated three domain-specific ‘sensitivity’ scores (for ‘attention and processing speed’, ‘verbal learning and memory’, and ‘working memory and executive functions’, respectively) to examine whether any particular

cognitive domains were characterized by larger discrepancy between subjective and objective measures than others (for details see Table 1).

Data analysis

Data were checked for normality using the Shapiro-Wilk test. Independent samples or paired samples *t*-tests were used to compare continuous variables, while Pearson's χ^2-tests were conducted in order to compare categorical variables. Multiple linear regression analyses were conducted to identify possible predictors of the sensitivity scores (i.e., global as well as domain-specific sensitivity scores) using the following clinical and demographic variables as predictor variables: age, gender, years of education, depressive symptoms (HDRS-17), manic symptoms (YMRS), BD type (BD-I vs. BD-II), number of hospitalisations, number of medications (sum of the following drug classes: anticonvulsants, antidepressants, lithium, antipsychotics, benzodiazepines, and melatonin), years of illness, and verbal IQ. For exploratory purposes, we conducted Pearson's correlations between the global composite sensitivity score and the variables measuring socio-occupational capacity, quality of life, and stress due to high collinearity with mood symptoms. These variables were not included in the above multiple regression analyses. Repeated measures analysis of variance (ANOVA) was performed to investigate potential differences between the domains in the degree of discrepancy between subjective and objective measures.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM Corporation, Armonk, New York). Statistical significance for all analyses was set at an alpha level of $p<0.05$ (two-tailed).

Results

Missing data and group characteristics

Data was z-transformed for a total of 109 BD patients and 110 HCs. Information was missing for eight patients regarding manic symptoms, BD type, illness duration and/or number of hospitalisations. Consequently, the multiple regression analyses in the BD group included data from 101 patients. The global sensitivity score and all domain specific sensitivity scores except for the 'attention and processing speed' domain were normally distributed (Shapiro-Wilk test: *p*-levels >0.70). After Winsorizing a single outlier with a value of +6.7 to +3.0, the 'attention and processing speed' domain variable also became normally distributed (p=0.18).

The BD and HC groups were comparable for gender composition and age. While BD patients had marginally shorter education than HCs, they showed no difference in verbal intelligence (p>0.23). BD patients displayed more sub-syndromal depression and manic symptoms (p-values<0.01) (see Table 2).

<Please insert Table 2 around here>

Global sensitivity composite

The multiple linear regression model with patients' global sensitivity score as the dependent variable was statistically significant ($F(10,90)=7.64$, $p<0.001$, adjusted $r^2=0.40$). In this model, depressive and manic symptoms, BD type, number of hospitalisations, verbal IQ, and gender were significant predictors (all p-levels$\leq$0.04, see Table 3). Specifically, more depressive and manic symptoms, BD type II and male gender were associated with greater sensitivity, while higher verbal IQ was associated with more stoicism (for the remaining variables: illness duration, number of medications, years of education, and age, $p\geq0.21$) (see Figure 1).

<Please insert figure 1 around here>

Higher sensitivity in BD patients was associated with more socio-occupational disability (WSAS, FAST; r=0.54-0.57, $p<0.001$), greater perceived stress (Global Measure of Perceived Stress; r=0.56, $p<0.001$) and lower quality of life (WHOQOL-BREF; r=-0.45, $p<0.001$).

Domain-specific sensitivity scores

The three multiple linear regression models with patients' symptom sensitivity for each of the different cognitive domains as the dependent variable (and the above-mentioned clinical characteristics as predictor variables) were statistically significant: 'attention and processing speed', ($F(10,90)=4.74$, $p<0.001$, adjusted $r^2=0.27$), 'verbal learning and memory', ($F(10,90)=2.05$, $p=0.04$, adjusted $r^2=0.10$), and 'working memory and executive functions', ($F(10,90)=5.28$, $p<0.001$, adjusted $r^2=0.30$). For 'attention and processing speed', manic symptoms were positively associated with greater sensitivity whereas verbal IQ was negatively associated with sensitivity (all p-values$\leq$0.02, see Table 3; for the remaining variables: $p\geq0.07$). For 'verbal learning and memory', male gender was positively associated with greater sensitivity (all p-values$\leq$0.01, see Table 3; for the remaining variables: $p\geq0.06$). For 'working memory and executive functions', having BD-II, being male, and having a greater number of hospitalisations were positively associated with greater sensitivity, whereas higher verbal IQ was negatively associated with sensitivity (all p-values$\leq$0.04, see Table 3; for the remaining variables: $p\geq0.19$).

<Please insert Table 3 around here>

Comparison of domain-specific sensitivity scores

An exploratory repeated measures ANOVA revealed a significant difference in the degree of discrepancy between the cognitive domains in BD, ($F(2,200)=38.65$, $p<0.001$), which was driven

by substantially greater stoicism in 'attention and processing speed' compared with both the 'verbal learning and memory', (t=-10.29, df=100, p<0.001, Cohen's d=-1.0) and the 'working memory and executive functions' domains, (t=-6.07, df=100, p<0.001, Cohen's d=-0.6). There was also greater sensitivity for 'verbal learning and memory' compared to 'working memory and executive functions', although this difference represented only a small effect size (t=2.04, df=100, p=0.04, Cohen's d=0.2).

<Please insert figure 2 around here>

Given the unexpected impact of gender and BD type on the degree of discrepancy, we conducted post-hoc independent samples t-test comparisons to examine if this could be explained by differences between these groups in mood symptoms, number of hospitalisations and/or number of depressive episodes. This revealed no differences between men and women or patients with BD-I and BD-II in depressive ($p\geq0.21$) or manic symptoms ($p\geq0.14$), number of hospitalisations ($p\geq0.61$) or number of depressive episodes ($p\geq0.27$).

Discussion

In this study, we applied a novel methodology to examine the clinical characteristics associated with the discrepancy between objective and subjective cognitive impairment in BD. Patients with more sub-syndromal mood symptoms, more previous hospitalisations and BD type II (vs. type I) showed greater 'sensitivity' (i.e., disproportionately more subjective than objective impairment), and patients with a higher verbal IQ were more 'stoic' (i.e., tended to under-report objective cognitive deficits). In line with previous findings in other areas (Delbaere *et al.*, 2010; Robinson *et al.*, 2014), the sensitive patients displayed greater socio-occupational difficulties, more perceived

stress and lower quality of life. Similar associations between sensitivity scores and greater subsyndromal mood symptoms, BD type II, gender and verbal IQ were observed for the individual cognitive domains. Comparison of sensitivity scores between the cognitive domains revealed substantially greater 'stoicism' for 'attention and processing speed' (with large effect sizes) than the other domains. This suggests that the relationship between subjective and objective cognitive function varies by the domain of the impairment, with patients being particularly unaware of attention and speed of processing problems.

Our demonstration that more sub-syndromal mood symptoms predicted greater 'sensitivity' is consistent with prior observations that depressive symptoms are closely associated with subjective but not objective cognitive impairment in affective disorders (e.g., Burdick, Endick, & Goldberg, 2005; Demant *et al.*, 2015; Prudic, Peyser, & Sackeim, 2000; Rosa *et al.*, 2013; Svendsen *et al.*, 2012) and of a correlation between more sub-syndromal manic symptoms and greater subjective cognitive difficulties in BD patients (Miskowiak *et al.*, 2012). Interestingly, this influence of mood symptoms on 'sensitivity' could potentially explain the discrepancy between subjective and objective cognitive side-effects of electroconvulsive therapy (ECT). Specifically, it is conceivable that the symptom resolution with ECT accounts for patients' reduction in sensitivity (i.e., their *subjective* memory improvement despite observable *objective* memory decline) (Prudic, Peyser, & Sackeim, 2000).

While our study is the first to identify the role of sub-syndromal mood symptoms for the discrepancy between subjective and objective *cognition*, Delbaere *et al.* (2010) demonstrated a similar role of depressive symptoms in the discrepancy between *objective* physiological and *subjectively* perceived risk of falling in elderly people. Interestingly, higher depressive symptoms have an important impact on health related quality of life (e.g., Brown *et al.*, 2010) and generally modulate the experience of physical illness, including greater perceived neck disability in patients

with whiplash disorder (Schmitt *et al.*, 2009), mouth dryness symptoms in Sjögren's Syndrome (Anttila, Knuuttila, & Sakki, 1998) and complaints of attention difficulties in narcolepsy patients (Zamarian *et al.*, 2015). Taken together, these findings indicate that mood symptoms play a fundamental role in the discrepancy between subjective and objective disability, introducing a *negative bias* in patients' perception of their current and future problems across several domains, including cognitive impairment, dryness in the mouth, fall risk and pain.

The association between more previous hospitalisations and greater sensitivity (which was independent of current sub-syndromal mood symptoms) is not easily explained. However, it is conceivable that patients with high sensitivity to cognitive difficulties may also be more sensitive to *other* symptoms, leading them to experience more distress and to have greater need of hospital admission.

Our observation of greater sensitivity in BD-II than BD-I patients is consistent with previous observations that BD-II patients present more *subjective* cognitive complaints than BD-I patients (Pallanti *et al.*, 1999) despite evidence for equal (or even less) *objective* cognitive impairment in BD-II (Dittmann *et al.*, 2008; Simonsen *et al.*, 2011; Sole *et al.*, 2012; Sparding *et al.*, 2015).

A possible explanation is that BD-II patients show greater resemblance to patients with UD than BD-I (Bowden, 2005), in line with 'the spectrum hypothesis of affective disorders' (Angst, 2007) according to which the disorders occur along a dimensional spectrum according to the profile and degree of mood symptoms (Goodwin *et al.*, 2008). In particular, BD-II patients generally experience more depressive episodes during their course of illness than BD-I patients (Judd *et al.*, 2003) and may therefore display more *negative bias* in their self-evaluations (including self-evaluated cognitive capacity). Nevertheless, we observed no difference between our BD-I and BD-II patients in current sub-syndromal depressive or manic symptoms or in the number of previous hospitalisations or depressive episodes, suggesting that this cannot fully explain the present finding.

Interestingly, patients with a higher verbal IQ displayed more 'stoicism' with regards to cognitive impairment. Intelligence can be regarded as a proxy measure of 'cognitive reserve' (CR) (Anaya *et al*., 2016), which involves skills to make strategies and compensate for cognitive difficulties in brain-pathological and psychiatric disorders (Anaya *et al.*, 2016; Stern, 2002). In keeping with this definition, CR is positively associated with performance across all cognitive domains in remitted BD patients (Anaya *et al.*, 2016; Forcada *et al.*, 2015). Our finding that patients with a high verbal IQ tended to be more stoical could therefore reflect better ability to compensate for subtle cognitive deficits in daily life before these emerge as conscious difficulties. Notably, this finding contrasts with the notion that *subjective* measures may better capture cognitive decline in patients with *supra*-normal premorbid cognitive functioning than objective cognitive tests (for which performance is merely compared with normative means of individuals with average intelligence and may therefore not show any deficits) (Forcada *et al.*, 2015). Indeed, the present finding suggests that *objective* neuropsychological tests may be more sensitive than subjective measures to cognitive impairment in individuals with large cognitive reserve. Finally, our observation that men were somewhat more sensitive than women was surprising given the previous finding that women have greater tendency to ruminate (Johnson & Whisman, 2013), which is associated with greater risk of depression (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Notably, there were no differences between men and women in sub-syndromal mood symptoms, number of hospitalisations, or number of depressive episodes, indicating that this could not account for the gender difference.

There are several implications of the finding that patients with more sub-syndromal mood symptoms, BD-II and more hospitalisations were more sensitive. First, patients with acute mood episodes are likely to present substantial cognitive complaints relatively independent of the degree of objective deficits. Therefore, mood symptoms should ideally be treated *before* a treatment targeting cognition is initiated. In clinical trials targeting cognition, particular care should also be

taken before inclusion of patients with substantial mood symptoms. Specifically, it may be feasible to screen these patients with a short *objective* neuropsychological test battery to verify that their complaints are accompanied by measurable cognitive deficits. It may also be feasible to assess patients with BD-II and/or great illness load with objective tests to verify that their complaints **are** accompanied by measurable deficits given their greater 'sensitivity' in our study. Finally, the tendency to under-report cognitive impairment in patients with high IQ indicates that objective neuropsychological screening of patient with large cognitive reserve is warranted as part of their clinical care, particularly if they patients present vocational problems or difficulties in home and social life. For example, if patients' occupation involves high degrees of executive decisions, multi-tasking and strategic planning, patients may be able to compensate for their cognitive difficulties to a certain degree given their large cognitive reserve. However, in cases of excessive work load/demand the compensatory mechanisms may break down and lead to manic or depressive relapse. These patients may benefit from psychoeducation about cognitive difficulties, coping and stress and adjustment of their work demands to their actual cognitive capacity. More generally, our finding that patients show poor insight into their attention and processing speed capacity suggests that this cognitive domain should be more systematically evaluated with cognitive tests since attention and processing speed deficits are directly associated with socio-occupational disability in remitted BD patients (Mur *et al.*, 2009).

The present study involves secondary analysis of data from previously published/ongoing studies and the findings should therefore be regarded as preliminary. The cross-sectional design is also a limitation as this impedes any causal inferences. The study should therefore ideally be followed up with longitudinal assessments to assess the association between changes in objective and subjective cognition and mediating factors with the course of treatment.

In conclusion, this study provides novel insights into the clinical characteristics that influence the discrepancy between subjective and objective cognitive impairment in BD based on a new methodology. The findings suggest that it may be particularly warranted to assess cognition with a neuropsychological test battery in BD patients with (sub-syndromal) mood symptoms, a BD type II diagnosis and/or high IQ to further substantiate cognitive impairment.

Acknowledgements

The Lundbeck Foundation, Weimann Foundation and TrygFonden are acknowledged for their contributions to KWM's post-doctorate salary at the Psychiatric Center Copenhagen, Copenhagen University Hospital, Rigshospitalet.

Declaration of interests

KWM reports having received consultancy fees from Lundbeck and Allergan within the last 3 years. UK reports having received consultancy fee from AstraZeneca within the last three years. LVK reports having been a consultant for Lundbeck, AstraZeneca and Sunovion within the last 3 years. JZP, CVO, PG and LR report no biomedical financial interests or potential conflicts of interest.

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Figure legends

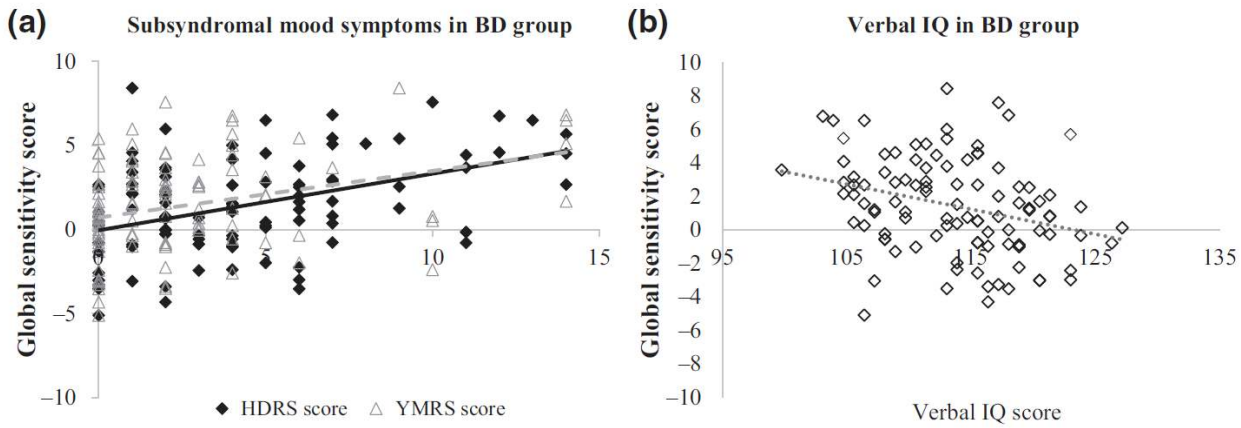

Figure 1. **(a)** Relation between subsyndromal mood symptom severity (scores on the Hamilton Depression Rating Scale-17 and the Young Mania Rating Scale, respectively) and degree of sensitivity (global composite sensitivity score) in BD. The black line shows a linear relation between changes in depression symptoms and global sensitivity score, and the dashed line shows a similar relation between changes in mania symptoms and global sensitivity score, indicating that greater mood symptom severity predicts more sensitivity in BD patients. **(b)** Relationship between intelligence (verbal IQ score) and degree of sensitivity (global composite sensitivity score) in BD. The dotted line shows a linear relation between changes in intelligence levels and global sensitivity score, revealing that higher verbal IQ is associated with less sensitivity and closer accordance between subjective and objective cognitive measures in BD patients.

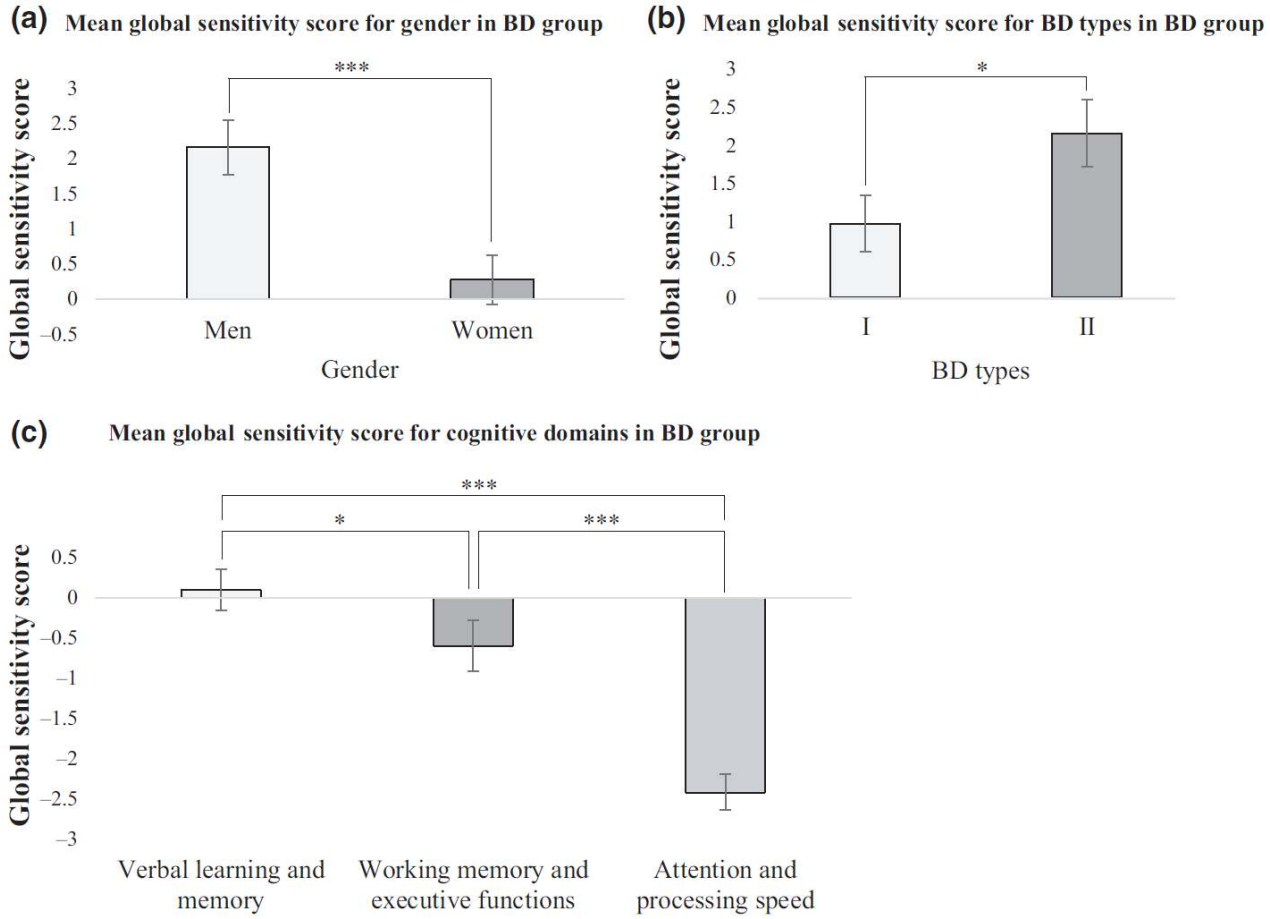

Figure 2. **(a)** Mean global composite sensitivity scores for gender in the BD group. There was a difference in the degree of 'sensitivity' between women and men, t=3.61, df=97.35, p<0.001. **(b)** Mean global composite sensitivity score for BD types revealed a difference in the degree of 'sensitivity' between patients with BD-I and BD-II, t=2.03, df=99, p=0.045. **(c)** Mean global composite sensitivity score for the three cognitive domains revealed substantially greater stoicism for 'attention and processing speed' compared with both 'verbal learning and memory' and 'working memory and executive functions', as well as greater stoicism (i.e., reduced sensitivity) for 'working memory and executive functions' compared with 'verbal learning and memory' in BD. Bars represent means and error bars represent standard error of the mean. *$p\leq$0.05, ***$p\leq$0.001.

Table 1. Grouping of objective neuropsychological tests and corresponding self-reported cognition items on the COBRA into cognitive domains

Cognitive domain	Neuropsychological tests	COBRA items
Attention and processing speed	SCIP Processing Speed Test Trail Making Test Part A	5: Do you find it hard to concentrate when reading a book or a newspaper? 12: Are you easily distracted? 14: Do you get the impression that you cannot follow a conversation? 16: Do you struggle to keep focused on a particular task for a long time?
Verbal learning and memory	RAVLT (four subtests: total recall across five learning trials (I–V), recall following interference (trial VI), and recall following 30-min delay and recognition) SCIP Immediate & Delayed Verbal Learning Test	1: Do you have difficulties to remember peoples' names? 2: Do you have difficulties to find objects of daily use (keys, glasses, wrist watch. . .)? 3: Do you find it difficult to remember situations that were important to you? 4: Is it hard for you to place important events in time? 6: Do you have problems recalling what you have read or have been told recently? 10: When people remind you of a conversation or a comment you heard, do you get the impression that it is the first time you hear it? 15: Have you noticed that you find it difficult to learn new information?
Working memory and executive functions	RBANS: Digit Span (Forward) SCIP Verbal Fluency Test SCIP Working Memory Test Verbal Fluency Test with letters S & D WAIS-III Letter-Number Sequencing	7: Do you have the feeling that you do not finish what you begin? 9: Have you ever felt disoriented in the street? 11: Is it sometimes difficult for you to find the words to express your ideas? 13: Do you find it hard to do simple mental calculations?

RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; WAIS-III, Wechsler's Adult Intelligence Scale 3rd edition; SCIP, Screening for Cognitive Impairment in Psychiatry.

Table 2 Demographical and clinical characteristics of patients with bipolar disorder (BD) and healthy controls (HC).

	BD (N=109)	HC (N=110)	*p*-value
Gender composition male/female %	60/40	57/43	0.72
Age, mean (SD)	36(10)	35 (12)	0.70
Verbal IQ[a], mean (SD)	114 (6)	115 (5)	0.23
Years of education, mean (SD)	15 (3)	16 (3)	0.04*
HDRS-17, mean (SD)	5 (4)	1 (1)	<0.01**
YMRS[1], mean (SD)	3 (3)	1 (1)	<0.01**
BD type I/II[2] (%)	60/40	-	-
Illness duration in years[3], mean (SD)	13 (11)	-	-
Number of hospitalizations[4], mean (SD)	3 (1)	-	-
Medication:			
Anticonvulsants (%)	59	-	-
Antidepressants (%)	7	-	-
Lithium (%)	61	-	-
Antipsychotics (%)	52	-	-
Benzodiazepines (%)	12	-	-
Melatonin (%)	2	-	-
Number of medications, mean (SD)	2 (1)	-	-
Frequencies of medications, 1/2/3/4/5, %	34/30/25/5/4	-	-
No medications, %	3	-	-

Abbreviations: BD: Bipolar Disorder, HC: Healthy controls, HDRS-17: Hamilton Depression Rating Scale 17-items, YMRS: Young Mania Rating Scale. [a]Estimated from the Danish Adult Reading Test (DART). [1]N=108, [2]N=108, [3]N=108, [4]N=104. *p-value ≤0.05, **p-value ≤0.01

Table 3 Multiple linear regression analyses of predictors of global and domain-specific 'sensitivity' (i.e., greater subjective than objective cognitive impairments) (n = 101). Standardized Beta-coefficients and p-values are only reported for significant predictor variables.

	Dependent variable			
Predictive variable	Global *β (p)*	Attention and processing speed *β (p)*	Verbal learning and memory *β (p)*	Working memory and executive functions *β (p)*
Age in years	-	-	-	-
Gender	0.22 (0.01)	-	0.25 (0.01)	0.26 (0.01)
Years of education	-	-	-	-
HDRS-17	0.25 (<0.01)	-	-	-
YMRS	0.21 (0.01)	0.25 (<0.01)	-	-
BD type	0.18 (0.04)	-	-	0.32 (0.001)
Number of hospitalisations	0.24 (0.01)	-	-	0.21 (0.02)
Number of medications	-	-	-	-
Illness duration	-	-	-	-
Verbal IQ	-0.28 (<0.01)	-0.23 (0.02)	-	-0.20 (0.04)

Abbreviations: HDRS-17: Hamilton Depression Rating Scale 17-items; YMRS: Young Mania Rating Scale. β: Standardized Beta-coefficient. p: p-value.