Journal of Affective Disorders 190 (2016) 607–615

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Screening for cognitive dysfunction in unipolar depression: Validation and evaluation of objective and subjective tools

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ARTICLE INFO

Article history:
Received 18 August 2015
Received in revised form
12 October 2015
Accepted 23 October 2015
Available online 10 November 2015

Keywords:
Cognition
Socio-occupational function
Screening
Assessment
Depression
Mood disorder

ABSTRACT

Background: Persistent cognitive dysfunction in unipolar depression (UD) contributes to socio-occupational impairment, but there are no feasible methods to screen for and monitor cognitive dysfunction in this patient group. The present study investigated the validity of two new instruments to screen for cognitive dysfunction in UD, and their associations with socio-occupational capacity.
Method: Participants ($n=53$) with UD in partial or full remission and healthy control persons ($n=103$) were assessed with two new screening instruments, the Danish translations of the Screen for Cognitive Impairment in Psychiatry (SCIP-D) and Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) and with established neuropsychological and self-assessment measures. Depression symptoms and socio-occupational function were rated with the Hamilton Depression Rating Scale and Functional Assessment Short Test respectively.
Results: The SCIP-D and COBRA were valid for detection of objective and subjective cognitive impairment, respectively. The three parallel SCIP-D forms were equivalent. A combined SCIP-D-COBRA measure showed high sensitivity and good specificity for objective cognitive impairment (91% and 70%, respectively). There was no correlation between subjective and objective measures of cognition. Subjective cognitive difficulties correlated more with socio-occupational impairment ($r=0.7$, $p<0.01$) than did objective cognitive difficulties, for which there was a weak correlation with the executive skills domain only ($r=-0.3$, $p=0.05$).
Limitations: A modest sample size.
Conclusions: The SCIP-D and COBRA are valid measures of objective and subjective cognitive impairment, respectively, and should ideally be implemented together in the screening for cognitive dysfunction in UD.

1. Introduction

Cognitive dysfunction in attention, memory and executive function occurs across a range of neuropsychiatric disorders, including schizophrenia, bipolar disorder (BD) and unipolar disorder (UD) (Bora et al., 2013; Kurtz and Gerraty, 2009; Stefanopoulou et al., 2009). Although the profile of cognitive dysfunction is similar in these disorders (Etkin et al., 2013), the degree of impairment is more severe in schizophrenia than affective disorders (Barch 2009), and greater in BD than in UD (Gualtieri and Morgan, 2008). In UD, trait-related impairments after clinical remission have small to moderate effect sizes (Bora et al., 2013; Hasselbalch et al., 2011; Rock et al., 2013), indicating that it is partially independent of mood symptoms. These trait-related cognitive deficits have been shown to impede socio-occupational capacity (Jaeger et al., 2006), and increase the risk of depressive relapse (Judd et al., 1998). Patients report that they continue to experience cognitive problems 44% of the time after remission from a depressive episode (Conradi et al., 2011), and self-reported attention

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http://dx.doi.org/10.1016/j.jad.2015.10.059
0165-0327/

and concentration difficulties mediate as much as 25% of the impact of depression on patients' psychosocial impairment (Buist-Bouwman et al., 2008). However, the association between *subjectively* reported and *objectively* measured cognitive difficulties in affective disorders remains controversial with some studies finding no association (Burdick et al., 2005; Svendsen et al., 2012) and others showing significant but weak correlations (Demant et al., 2015a; Jensen et al., 2015; Rosa et al., 2013). Correct identification of objective cognitive dysfunction is important in the clinic for monitoring treatment effects and in randomised controlled trials investigating new candidate treatments for cognitive dysfunction in UD (Martinez-Aran and Vieta, 2015; Solé et al., 2015). Specifically, inclusion of participants with subjective but no objective cognitive impairment in clinical trials could introduce ceiling effects for objective cognitive improvement (Demant et al., 2015b). Moreover, it has to be clarified whether it is objective or subjective cognitive impairment that has the greater impact on psychosocial functioning. Taken together, this highlights the need for a valid and feasible method to monitor and screen for objective cognitive dysfunction in UD patients.

The Screen for Cognitive Impairment in Psychiatry (SCIP) is a feasible neuropsychological test, and the English language SCIP, as well as the Spanish translation (SCIP-S) have demonstrated good psychometric properties in healthy controls (HCs) and in patients with BD or schizophrenia (Guilera et al., 2009; Pino et al., 2008; Purdon, 2005; Rojo et al., 2010). We recently demonstrated high validity, sensitivity and specificity of the Danish translation of the SCIP (SCIP-D) for cognitive dysfunction in BD (Jensen et al., 2015). The Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) is a newly developed self-assessment tool for subjective cognitive difficulties that also has good validity and reliability in BD (Jensen et al., 2015; Rosa et al., 2013). The present study extends the application of the SCIP-D and COBRA by investigating the validity of these instruments for detection of cognitive impairment in UD. This study was conducted in parallel with the BD study by Jensen et al. (2015) and therefore includes a partially overlapping group of HCs ($n=64/103$). In addition, we perform a sub-study of the equivalence of the three parallel SCIP-D forms based on data from the present UD study and the parallel study in BD patients.

1.1. Aims and hypotheses

The study aims to (i) assess the validity of the SCIP-D and validity and reliability of the COBRA in a sample of UD patients, (ii) determine the optimal cutoff scores on the SCIP-D and COBRA for objective cognitive impairment, and if either measure alone or a combined SCIP-D-COBRA measure has the best sensitivity and specificity for objective dysfunction, and (iii) assess the associations between objective and subjective cognitive dysfunction and socio-occupational impairment. In addition to these three primary aims, we assess the equivalence of the three parallel versions of the SCIP-D in the *combined* sample of UD and BD patients.

2. Methods

2.1. Participants

The study included 53 out-patients with an ICD-10 diagnosis of UD, who had been stable for mood symptoms for several weeks, and 103 HCs, and was conducted between January 2014 and June 2015. Patients were recruited consecutively through the outpatient Clinic for Affective Disorders, Psychiatric Centre Copenhagen, District Psychiatric Centre Copenhagen, and Psychiatric Centre Hvidovre, in the Capital Region of Denmark. HCs were recruited consecutively from the blood bank at Copenhagen University hospital, Rigshospitalet. Inclusion criteria for patients were: age 18 to 65 years, full or partial remission defined as a Hamilton Depression Rating Scale (HDRS-17; Hamilton, 1960) score of ≤ 7 and $\geq 8 - \leq 14$, respectively), general good physical health and fluency in Danish. Patients were excluded if they had a daily use of benzodiazepines > 22.5 mg oxacepam. The same eligibility criteria were applied to the BD cohort, and BD patients were additionally required to have a Young Mania Rating Scale score of ≤ 14 (Young et al., 1978).

HCs were excluded if suffering from dyslexia or if they, or their first-degree relatives, had a history of mental illness. Participants were instructed to be well rested and avoid nicotine and caffeine intake on the day of their study participation. The local ethics committee stated that their approval was not needed, as the study did not involve invasive or biomedical procedures. All participants provided informed written consent.

2.2. Procedure

Participants attended one assessment at the Psychiatric Centre Copenhagen, Rigshospitalet, lasting approximately two hours. They were given the SCIP-D and the COBRA and a set of well-established neuropsychological tests and subjective rating scales and were rated for affective symptoms and socio-occupational function. Participants were given the Danish Adult Reading Test (DART; Crawford et al., 1987) to assess verbal intelligence. Participants received a small gift certificate for their time and were reimbursed for travel expenses.

2.3. Measures

2.3.1. Measures of affective symptoms and socio-occupational function

Depressive symptoms were rated with the HDRS-17 and socio-occupational function was assessed with the Functional Assessment Short Test (FAST; Rosa et al., 2007), a 24-item interviewer-administered instrument with good validity and reliability in BD (Rosa et al., 2007) and psychotic disorders (González-Ortega et al., 2010).

2.3.2. Objective and subjective measures of cognitive function

Participants were assessed on the Danish versions of the SCIP (SCIP-D), translated by KWM using forward-translation and revised by LVK.

The SCIP has an administration time of < 20 min and there are three parallel forms, facilitating longitudinal assessments (Purdon, 2005). SCIP consists of five subtests: (1) verbal learning (VLT-I) (2) working memory (WMT) (3) verbal fluency (VFT) (4) delayed memory (VLT-D) and (5) processing speed (PST) (Purdon, 2005). Consistent with our approach in Jensen et al. (2015) the established neuropsychological tests encompassed Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 2004), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Digit Span (Randolph, 1998), verbal fluency tests with the letters S and D (Borkowski et al., 1967), the WAIS-III Digit-Letter Substitution test (Wechsler, 1997) and the Trail Making Test A (Army Individual Test Battery, 1944). There was no overlap between word lists in the SCIP-D and RAVLT.

Subjective cognitive difficulties were assessed with the COBRA, a 16-item questionnaire with good psychometric properties developed to assess cognitive difficulties in BD (Rosa et al., 2013). COBRA correlates well with some aspects of objective cognitive dysfunction in BD (Rosa et al., 2013), although Jensen et al. (2015) recently only found a trend towards a correlation between COBRA and objective cognitive measures in BD.