Association of neurocognitive function with psychiatric hospitalization and socio-demographic conditions in individuals with bipolar and major depressive disorders

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Summary

Background Neurocognitive impairments are associated with poor clinical and employment outcomes in individuals with affective disorders. However, little is known about their associations with long-term clinical outcomes such as psychiatric hospitalizations, and with socio-demographic indicators other than employment. In the largest longitudinal study of neurocognition in affective disorders to date, we investigate the role of neurocognitive impairments on psychiatric hospitalizations and socio-demographic conditions.

Methods The study included 518 individuals with bipolar or major depressive disorder. Neurocognitive assessments covered executive function and verbal memory domains. Longitudinal data on psychiatric hospitalization and socio-demographic conditions (employment, cohabitation, and marital status) for up to 11 years were obtained using National population-based registers. The primary and secondary outcomes were psychiatric hospitalizations (n = 398) and worsening of socio-demographic conditions (n = 518), in the follow-up period since study inclusion, respectively. Cox regression models were used to examine the association of neurocognition with future psychiatric hospitalizations and the worsening of socio-demographic conditions.

Findings Clinically significant impairment in verbal memory (z-score ≤ -1; defined by the ISBD Cognition Task Force), but not in executive function, was associated with a higher risk of future hospitalization, when adjusted for age, sex, hospitalization in the year preceding inclusion, depression severity, diagnosis, and type of clinical trial (HR = 1.84, 95% CI:1.05–3.25, p = 0.034; n = 398). The results remained significant even after accounting for illness duration. Neurocognitive impairments were not associated with the worsening of socio-demographic conditions ($p \geq 0.17$; n = 518).

Interpretation Promoting neurocognitive function, especially verbal memory, may mitigate the risk of future psychiatric hospitalization in individuals with affective disorders.

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Keywords: Bipolar disorder; Major depressive disorder; Cognition; Hospitalization; Socio-demographic status; Survival analysis

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Research in context

Evidence before this study

Studies investigating the association between cognition and psychiatric hospitalization were identified through searches of English language manuscripts published in PubMed, Medline, and Embase from 1 January 1990 to 1 August 2022 using the search terms: (cognition OR cognitive OR neurocognitive OR memory OR executive function OR attention OR processing) and (depess* OR bipolar* OR manic OR mania) and (hospital* OR admission). There is substantial literature on the influence of cognitive impairments on clinical outcomes such as illness duration, and treatment response. However, studies of the association between cognition and debilitating, longer-term outcomes such as psychiatric hospitalizations have been few and limited to older adults. Furthermore, these studies have largely examined whether hospitalization contributes to cognitive decline and not the reverse association. We found no study that examined cognitive impairment related risk of future psychiatric hospital readmission in a single large cohort of adults with major depressive and bipolar disorders. As a secondary outcome, this study also examined whether cognitive impairments were associated with the worsening of socio-demographic conditions in this sample.

Added value of this study

We present the largest single-site longitudinal study to date investigating the role of neurocognitive impairments on future psychiatric hospitalizations and socio-demographic function in individuals with affective disorders (n = 518). We showed for the first time that neurocognitive impairments are associated with an increased risk of future hospitalization across affective disorders in adults. Prior hospitalization is a clinically robust indicator of risk of future hospitalization, and our study showed that clinically significant impairment in neurocognition, particularly, verbal memory was a statistically significant additional indicator of future risk of hospitalization, beyond the risk associated with prior hospitalization. To test the robustness of the study findings, the analysis models included a comprehensive array of clinical confounders such as illness duration, depression severity, diagnosis, and prior hospitalization. Where applicable, subtype of bipolar disorder and history of psychotropic medication classes were also included. Furthermore, to improve the clinical applicability of the study findings, evidence-based cut-offs for 'clinically significant' impairment in cognitive domains (as defined by z score $\leq$ -1), defined by the ISBD Cognition Task Force, was used.

The study did not find compelling evidence for cognitive impairments to be associated with a risk of worsening of socio-demographic conditions; however, they were associated with lower odds of achieving the highest education levels, an index of cognitive reserve.

Implications of all the available evidence

The study findings have tremendous clinical implications. The findings suggest that promoting cognitive function in individuals with affective disorders with clinically significant impairments could help in mitigating psychiatric hospitalizations.

Introduction

Bipolar disorder (BD) and major depressive disorder (MDD) are chronic affective disorders that are characterized by poor clinical and psychosocial outcomes such as frequent hospitalizations,[1] and marked impairment in socio-demographic functioning.[2] For instance, 68% of individuals with BD have been admitted to a psychiatric hospital at least once in their life,[3] and individuals with affective disorders are far less likely to achieve high educational levels, cohabit, or be employed relative to the general population.[2] The majority of research has focused on investigating the associations of clinical characteristics such as symptom severity, age of illness onset, duration of illness, and the number of affective episodes on future adverse clinical and socio-demographic outcomes.[4] Whilst the study of the above clinical characteristics is important for improving outcomes in individuals with affective disorders, neurocognitive function is also a major contributor to poor outcomes,[5] but has until recently received very little attention.

While impairments in neurocognition have historically been recognized as highly relevant in schizophrenia, they are now also increasingly recognized as core features of BD and MDD.[6,7] Approximately, 12%–45% of individuals with affective disorders present with global neurocognitive impairments across multiple domains[8] while another 18%–45% show selective deficits particularly in executive function and verbal memory.[8] Executive function is a multifaceted construct that describes higher-order cognitive processes necessary for purposeful and goal-directed behavior such as problem-solving, planning, and decision-making.[9] Verbal memory, on the other hand, involves cognitive processes important for encoding and remembering verbally delivered information. Impairments in neurocognitive function may arise before the onset of an affective disorder,[10] and often persist long after the resolution of the mood episode,[11] indicating a gap between clinical recovery and *functional* recovery.

An in-depth study of neurocognitive impairments in BD and MDD is warranted as they are associated with poor clinical and employment outcomes. For instance, impairments in executive function and verbal memory are associated with a longer duration of illness,[12] longer time to recovery,[13] and relapse in

individuals with affective disorders,[14] as well as subsequent illness onset in high-risk individuals.[15] Prior investigations have focused on the associations between neurocognition and hospitalization, however, neurocognitive function has been studied in relation to past hospitalizations.[12,16,17] Furthermore, these studies were performed predominantly in older adults (50 years and older) without affective disorders.[16,17] A study in adults with bipolar disorder, albeit in a small sample of 40 euthymic individuals, showed that impairments in verbal memory, in particular, were associated with more past hospitalizations.[12] Whether cognitive impairments are associated with future risk of admissions to psychiatric hospitals (hereafter referred to as psychiatric hospitalizations) in individuals with affective disorders has not yet been examined. This is of importance given the high rate of psychiatric hospitalizations in individuals with affective disorders. We speculate that difficulty with acquiring and recalling new information impedes daily life functioning and increases stress, which in turn may trigger new mood episodes and increase the risk of (re)hospitalization. Results from a recent meta-analysis revealed that cognition function, in particular, executive function and verbal memory are predictors of employment outcomes in individuals with affective disorders.[18] Together, these findings highlight the importance of addressing executive function and verbal memory for the successful clinical management of affective disorders, and for improving socio-demographic function in individuals with BD and MDD.

The paucity of long-term longitudinal studies examining the association between neurocognitive function and patient outcomes has left key questions unanswered, including the impact of neurocognitive impairments on longer-term outcomes such as future psychiatric hospital admissions. Further in-depth investigations are also required to examine the influence of neurocognitive impairments on areas of socio-demographic functioning other than employment, known to be affected in those with affective disorders, such as educational achievements, cohabitation, and marital status. We recently showed in a nationwide population-based Danish study that bipolar disorder is associated with decreased socio-demographic functioning within these areas.[2]

Thus, we present the largest single-site longitudinal study to date investigating the role of neurocognitive impairments on future hospitalizations (n = 398) and socio-demographic function (n = 518). In the present study, individuals with BD and MDD, who had neurocognitive assessments were subsequently followed up for up to 11 years using Danish National Register data. We hypothesized that impairments in executive function and verbal memory would be associated with an increased risk of psychiatric hospitalization. Secondly, this study aimed to provide a more in-depth exploration of the relationship between neurocognitive impairments and measures of socio-demographic function beyond employment such as education, cohabitation, and marital status.

Methods

The present study ('BrainDrugs' work-package 3) involves conducting Danish-register based follow-up studies on already acquired data (https://braindrugs.nru.dk/index.php/research).

Participants

The study included 518 individuals [ages 17–65 years, mean age±standard deviation (SD) = 35.0 ± 10.6 years; 65% female; Table 1] who met criteria for either BD (n = 438; ages 17–65 years, mean age±SD = 34.1 ± 10.0 years; 65% female) or MDD (n = 80; ages 19–65 years, mean age±SD = 40.1 ± 12.3 years; 67.5% female) according to the International Classification of Disorders (ICD-10) as assessed using the Schedule for Clinical Assessment in neuropsychiatry (SCAN) structured clinical interview.[19] Information on subtype of BD (i.e., BD type I/II) was available for 93% of the individuals with BD group and 39% of them were diagnosed with BD type I. Individuals with affective disorders were recruited between 2009 and 2020 from the Copenhagen Affective Disorder Clinic, community psychiatric centers, private clinics, and general practices as part of seven different clinical trials, of which six were intervention trials (NCT01457235 (n = 51); NCT03339596 (n = 74); NCT03315897 (n = 57); NCT03295305 (n = 48); NCT00916552 (n = 32); ECT-trial (n = 2)). In three of the intervention trials, individuals with BD and MDD were treated with erythropoietin (EPO; NCT03339596; NCT03315897; NCT00916552); on two of the intervention trials, individuals with BD were offered psychological therapy (cognitive remediation therapy in NCT01457235; action-based cognitive remediation therapy in NCT03295305); and the sixth intervention trial (ECT-trial (n = 2)) was a study assessing brain functional and cognitive changes in individuals with treatment-resistant depression who were scheduled to receive electroconvulsive therapy as part of their clinical care at the Psychiatric Research Center, Copenhagen. The seventh clinical trial (NCT02888262 (n = 254)) included individuals with BD who underwent repeated neuroimaging, blood-based, and cognitive assessments. Neurocognitive function was assessed in individuals in all seven trials. Only baseline neurocognitive data from all seven trials were used for this study to investigate the association of neurocognitive function with future psychiatric hospitalizations and the worsening of socio-demographic conditions.

Of the 80 individuals with MDD, 43.75% met criteria for treatment resistance depression based on an assessment of their medical treatment history with the Treatment Response to Antidepressants Questionnaire

	Sample (n = 518)
Baseline demographic information	
Age (mean ± SD)	35.0 ± 10.6
Gender (% Female)	65%
Baseline socio-demographic information	
Employed (including pension, student or other) (N)	346
Cohabiting (N)	256
Married (N)	108
High Education Level (≥13 years of education)	430
Clinical information	
BD/MDD (N)	438/80
[a]HDRS-17 (mean ± SD)	8.0 ± 7.4
[b]YMRS (mean ± SD)	2.5 ± 3.0
[c]Future psychiatric hospitalizations (N)	66
[c]Psychiatric hospitalizations in the year preceding inclusion (N)	90

Data reported in the table represents demographic, socio-demographic, and clinical information at baseline. Employment status was dichotomized as 'unemployed or disability' *vs.* 'employed, pension, student or other'. Cohabitation status was dichotomized as 'living with someone' *vs.* 'living alone'. Marital status was dichotomized as 'married' *vs.* 'not-married, divorced or widowed'. The highest education achieved at baseline was assessed as a categorical variable with five ordered categories: 'low'- primary education [0–9 years of education), 'elementary'- high school [9–12 years), 'intermediate'- [12–13 years), 'high'- [13–14 years) and 'academic'- polytechnics and university (≥14 years of education). The number of individuals who completed at least 13 years of education at baseline is presented here. Abbreviations: HDRS-17: Hamilton Depression Rating Scale 17 items; YMRS: Young Mania Rating Scale (YMRS); BD: Individuals with bipolar disorder; MDD: Individuals with major depressive disorder; N: total number; %: percentage; SD: standard deviation. [a]HDRS-17 scores were available for 513 (of 518) individuals. [b]YMRS was administered only on individuals with BD, and scores were available for 389 (of 438) individuals with BD. [c]Hospitalizations records were available only until 2019, therefore the numbers are based on 398 individuals with BD or MDD.

Table 1: **Demographic, socio-demographic, and clinical information in individuals with bipolar or major depressive disorders.**

(TRAQ). Briefly, treatment resistance was established when remission was not obtained after a minimum of two adequate antidepressant treatments with two different classes of antidepressant drugs in previous or current mood episodes. An adequate antidepressant trial was defined as treatment with an antidepressant drug for a minimum of 4 weeks in a sufficient dosage (corresponding to a score of 3 or above on the Antidepressant Treatment History Form (ATHF) and with >85% compliance (corresponding to a score of 4 on the TRAQ). Exclusion criteria for all individuals with BD or MDD across the seven trials were a diagnosis of schizophrenia or schizoaffective disorder, current (i.e., within the past three months of inclusion) alcohol or substance use disorder, and acute suicidal risk (score on suicide item of HDRS-17 > 2). Additional exclusion criteria were applied to a sub-population of individuals with affective disorders (n = 163) who were recruited to participate in the erythropoietin trials conducted in our lab (NCT03339596; NCT03315897; NCT00916552). These included significant medical conditions (diabetes, renal failure, epilepsy, hypertension, present or past malignancies, and thromboses), pregnancy or breast-feeding, contraceptive medication, smoking, BMI >30 kg/m2, and body weight <45 or >95 kg.

Written informed consent was obtained from all participants before their inclusion in the respective clinical trials, and letters were sent to their general practitioners to rule out a history of significant medical conditions. The procedures of the different original studies were in accordance with the ethical standards of the Danish Research Ethics Committee for the Capital Region (approval no. H-1-2010-039; H-16038506; H-16043370; H-16043480; H-7-2014-007; H-C-2008-092: H-3-2009-074), and Danish Data Protection Agency (2010-41-4710; RHP-2017-023; RHP-2017-020; 2012-58-0004; RHP-2015-023: 2008-41-2711; 2009-41-3676).

The Danish National registers

We obtained information on psychiatric hospitalization and socio-demographic conditions in participants from the seven clinical trials using the Danish National Registers. Briefly, the relevant demographic, clinical, and neuropsychological data obtained on inclusion from the participants in the seven clinical trials were linked to Danish population-based registry data using the unique personal identification number assigned to all persons living in Denmark since 1968. This ensures accurate linkage of information between data sources regardless of changes in personal information such as name or address. The Danish National Registers are centrally maintained and cover nearly all residents, with information on the date of birth, sex, death, migration, somatic and psychiatric diagnoses, hospitalizations, education, employment, and civil status recorded at regular intervals. Data for each participant was anonymized by the data controllers at Statistics Denmark and linked between the Danish Civil Registration System, the Danish National Patient Register, the Danish Psychiatric Central Research Register, and the Danish National Prescription Registry. The Danish National Patient Register and Danish Psychiatric Central Research Register contain data on diagnoses according to the ICD classification, psychiatric admissions, discharge dates, and treatments; and the National Prescription Registry contains records of any prescription drugs including the Anatomical Therapeutic Classification (ATC) code, dispensing date, dosage, and quantity dispensed. Information on death was available from the Danish Register of Causes of Death. Data were also available for migration, and socio-demographic measures: education, employment, cohabitation, and marital status from the General Population Registry.

The present study ('BrainDrugs' work-package 3) was approved by the Danish Data Protection Agency (Capital Region protocol number 2012-58-0004 [local journal number P-2021-110]).

Procedure

Cognitive measures

Neurocognition was assessed on the day of inclusion, using a broad battery of neuropsychological tests, from which composite z scores were calculated for the individual test batteries based on the mean and standard deviations of test scores from age and sex-matched healthy controls. For each participant, the z scores from the available individual test batteries were then averaged to get a mean composite z score separately for the executive function and verbal memory cognitive domains (i.e., domain-specific z-scores). The domain-specific z scores are considered more reliable than the individual test scores due to reductions in measurement error. The individual test batteries that were used to assess executive function and verbal memory are listed in Table S1 in the Supplement. Briefly, the neuropsychological tests that were used to assess executive function in the participants were the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Digit Span, verbal fluency letter "D" and "S", Screening for Cognitive Impairment in Psychiatry (SCIP) verbal fluency and working memory tests, Wechsler's Adult Intelligence Scale third edition (WAIS-III) Letter-Number Sequencing. The neuropsychological tests that were used to assess verbal memory were the SCIP immediate and delayed verbal learning test, and the Rey Auditory Verbal Learning Test (RAVLT). The individual test batteries were chosen based on three criteria: (a) sensitivity to cognitive impairments in affective disorders (b) availability of parallel versions of the tests for repeated testing in the longitudinal clinical trials, and (c) availability in the Danish language. The neuropsychological tests were administered by fully trained clinical psychologists with training in conducting neuropsychological tests or by research assistants who were trained and supervised by the neuropsychologist in the study.

For all the analyses performed herein, both executive function and verbal memory scores were dichotomized at z = −1, based on the International Society for Bipolar Disorders (ISBD) Targeting Cognition Task Force's definition of "clinically significant" cognitive impairment.[20] Further information on the recommended thresholds is detailed in eMethods1 in the Supplement.

Mood ratings

Mood symptom severity was assessed on the day of inclusion using the Hamilton Depression Rating Scale 17 items (HDRS-17)[21] for all individuals with either BD or MDD, and additionally using the Young Mania Rating Scale (YMRS)[22] for individuals with BD.

Primary outcome measure and statistical analysis

The primary outcome was psychiatric hospitalization in the follow-up period since inclusion in the study (i.e., evaluation of neurocognition). Information on psychiatric hospitalization was available from Danish National Registers. Psychiatric hospitalization is defined as contact with psychiatric hospitals as inpatients (patients admitted during daytime or overnight to a psychiatric hospital) with at least one main diagnosis of MDD, mania, or BD (ICD-10 codes F30, F31, F32, F33, F34, F38, and F39). Hospitalization records were available until 2019, which marked the end of the follow-up period. Therefore, the primary analysis of the association between neurocognition and psychiatric hospitalization was only performed in a subset of the population (n = 398) recruited prior to the end of the follow-up period. Individuals recruited to the clinical trial after this period were excluded as we did not have information on psychiatric hospitalization records subsequent to their date of assessment of neurocognition.

The primary analysis of the relationship between neurocognition (i.e., executive function and verbal memory) and psychiatric hospitalization was modeled using cause-specific Cox regression, with the event being psychiatric hospitalization, and censoring on death, emigration, or end of the follow-up period, whichever came first (eMethods2 in the Supplement).

The Cox regression model was adjusted for age, sex, hospitalization in the year preceding inclusion, HDRS-17 scores, diagnosis (i.e., BD vs MDD), and the clinical trial from which the participant was recruited. Smoothed splines were included in all the models to account for any non-linear relationship between age and neurocognitive function.

Duration of illness, an index for illness chronicity, is associated with future psychiatric hospitalization.[23] Therefore, in a subset of the sample for whom data on the duration of illness was available from clinical interviews (n = 273), this variable was incorporated into the cause-specific Cox regression models as an additional covariate. The risk of hospitalization was estimated using the Aalen-Johansen estimator.[24]

We did not investigate the effect of neurocognition on death, because death was rare in this sample (n < 5), so the associated hazard could be neglected. Thus, there is a (nearly) monotone relationship between the hazard ratio and relative risk. Individuals with BD were either euthymic or in a depressive episode and had low scores on the YMRS as detailed below, and therefore YMRS scores were not included in the model.

Post-hoc analysis was performed in the sample of individuals for whom additional clinical information such as subtype of BD (i.e. BD type I/II) and the use of psychotropic medication (presence/absence of antidepressants, antipsychotics, anticonvulsants, and Lithium) was available.

Secondary outcome measures and statistical analyses

Secondary outcome variables were employment status, cohabitation status, marital status, and the highest education achieved. Data for secondary outcome variables

were available until 2020, and that marked the end of the follow-up period. Therefore, secondary analyses on the association between neurocognition and socio-demographic variables were performed in the entire sample (n = 518).

Employment: employment status at the time of inclusion was dichotomized as 'unemployed or disability' *vs.* 'employed, pension, student or other' (other category includes early retirement pension, and business income < DKK 58,600). Information on unpaid and honorary work was not available.
Cohabitation: cohabitation status at the time of inclusion was dichotomized as 'living with someone' *vs.* 'living alone'.
Marital status: marital status at the time of inclusion was dichotomized as 'married' *vs.* 'not-married, divorced or widowed'. For the purposes of this study, civil partnerships (available in Denmark from 1989 to 2012, at which point same-sex marriage was legalized) were considered the same as marriage.
Education: the highest education achieved at the time of inclusion was assessed as a categorical variable with five ordered categories: 'low'- primary education [0–9 years of education), 'elementary'- high school [9–12 years), 'intermediate'- [12–13 years), 'high'- [13–14 years) and 'academic'- polytechnics and university (≥14 years of education). These categories were in accordance with a previously published study.[2]

The association between neurocognition and changes in employment, cohabitation, and marital status during the follow-up period since inclusion was analyzed within the subgroup of individuals who were classified as employed (including students, and on pension), living with someone, or married at the time of inclusion. Separate Cause-specific Cox regression models were used to model these associations, with the event being unemployment/living alone/divorced or widowed, and censoring on death, emigration, or end of the follow-up period, whichever came first.

Lastly, exploratory analyses were conducted on the association between neurocognition and baseline socio-demographic measures using logistic (employment status, cohabitation status, and marital status) and ordinal logistic (education) models.

All the models were adjusted for age, sex, and diagnosis. Smoothed splines were included in all the models to account for any non-linear relationship between age and socio-demographic function.

Role of funding source

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Results

Clinical and neurocognitive information

Individuals with BD (n = 438) were either euthymic or in a depressive episode at inclusion (HDRS-17 mean ± SD: 6.4 ± 5.5), and thus had low scores on the YMRS (mean ± SD: 2.5 ± 3.0). Individuals with MDD (n = 80) were in a depressive episode at inclusion (HDRS-17 mean ± SD: 17.6 ± 9.4). Consistent with the literature, 43.2% had clinically impaired executive function or verbal memory, or both.

Primary analysis of the association between neurocognitive function and future psychiatric hospitalizations

Data on psychiatric hospitalization was available only until 2019, and the median follow-up time was 58.40 months. The primary analysis was performed on 398 individuals with affective disorders, who were recruited prior to the end of the follow-up period, and had information on age, sex, past and future hospitalizations, HDRS-17, and diagnosis. There was no significant difference in age, sex, HDRS-17, executive function, or verbal memory scores between this sample (n = 398) and the sample of individuals excluded from the analysis (n = 120; $p \geq 0.17$). Sixty-six individuals had at least one record of future psychiatric hospitalization. Fig. S1 in the Supplement illustrates the proportion of individuals with low verbal memory scores (i.e., clinically significant impaired verbal memory as defined by $z \leq -1$) in the hospitalized (44%) and the non-hospitalized categories (28%). The 1-year, 5-year, and 9-year risk rates were 11%, 25%, and 39% respectively (Fig. 1). The results indicated that low verbal memory was associated with a higher risk of future hospitalization (HR = 1.84, 95% CI:1.05–3.25, p = 0.034). In contrast, low executive function was not significantly associated with a higher risk of future hospitalization (p = 0.68; Table 2). As expected, hospitalization in the year preceding inclusion was associated with a heightened risk for subsequent hospitalization (HR = 4.05, 95% CI:2.35–6.99, $p < 0.001$), while age, sex, HDRS-17 scores, diagnosis, or type of clinical trial were not associated with increased risk ($p \geq 0.13$). When the duration of illness was included in the model (n = 273), low verbal memory (HR = 3.52, 95% CI:1.57–7.92, p = 0.002), and hospitalization in the year preceding inclusion (HR = 5.02, 95% CI:2.23–11.33, $p < 0.001$) continued to be significantly associated with a higher risk of future hospitalization. No other variables were significantly associated with a higher risk of future hospitalization ($p \geq 0.26$). Post-hoc analyses revealed that neither subtype of BD nor the use of psychotropic medication

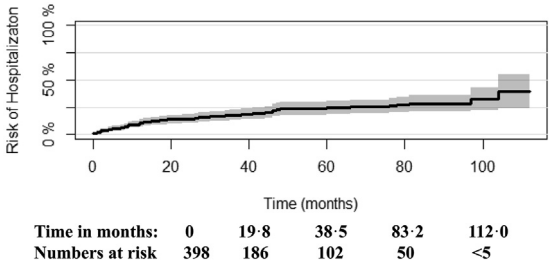

Fig. 1: **Cumulative incidence plot illustrating the probability of getting hospitalized in individuals with bipolar disorder or major depressive disorder.** The cumulative incidence plot illustrates the probability of getting hospitalized in individuals with bipolar disorder or major depressive disorder. The risk of hospitalization was estimated using Aalen-Johansen estimator. The y-axis represents the risk of hospitalization and the x-axis represents follow-up time in months. The cumulative incidence plot is estimated on a sample of 398 individuals with bipolar disorder or major depressive disorder. The 1-year, 5-year, and 9-year rates for the risk of hospitalizations were 11%, 25%, and 39% respectively. The number of individuals at risk at each time point is as follows: start of follow-up (n = 398), 19.8 months (n = 186), 38.5 months (n = 102), 83.2 months (n = 50), 112 months (n < 5).

was associated with a higher risk of hospitalization (eResults1 in the Supplement).

Secondary analyses of the association between neurocognitive function and socio-demographic outcomes

Data on socio-demographic measures until 2020 were available for 518 individuals with BD or MDD. Of the 518 individuals, 256 were cohabiting, 108 were married, and 346 were employed, at baseline. Secondary analysis indicated that neither impairments in executive function nor verbal memory were associated with the worsening of socio-demographic measures, namely employment, cohabitation, or marital status (all $p \geq 0.17$).

Exploratory analysis, however, indicated that low executive function was associated with decreased odds of having achieved the highest education levels (OR = 0.49, 95% CI:0.32–0.74, $p < 0.001$). The associations between neurocognitive impairments and baseline socio-demographic measures are tabulated in Table S2 in the Supplement. Analysis of covariates showed that the diagnosis of BD was significantly associated with decreased odds of having achieved the highest educational levels ($p = 0.006$). In addition, age was significantly associated with increased odds of having achieved the highest educational levels, cohabiting, and being married (all $p < 0.001$), but with decreased odds of being employed ($p < 0.001$). Likewise, being female was associated with decreased odds of being employed ($p = 0.003$) and being married ($p = 0.04$).

Discussion

In the largest longitudinal study of neurocognition to date in affective disorders, comprising 518 individuals with either BD or MDD, we found novel associations between neurocognitive function and long-term prognosis in individuals with BD or MDD. In particular, we found that clinically significant impairment in verbal memory (as defined by a z-score ≤ -1) was associated with a higher risk of future psychiatric hospitalization when adjusted for age, sex, hospitalization in the year preceding inclusion, HDRS-17 scores, diagnosis, and the clinical trial from which the individuals were recruited (n = 398). The findings remained the same when the model was adjusted additionally for illness

	Unadjusted HR	Adjusted HR	95% CI	p val
Association between neurocognition and future psychiatric hospitalization				
Executive Function	1.13	0.89	0.51–1.55	0.68
Verbal Memory	1.45	1.84	1.05–3.25	0.034
Association between neurocognition and change in employment status				
Executive Function	0.96	0.94	0.69–1.28	0.71
Verbal Memory	0.78	0.83	0.66–1.13	0.24
Association between neurocognition and change in cohabitation status				
Executive Function	0.80	0.78	0.55–1.11	0.17
Verbal Memory	0.85	0.85	0.60–1.20	0.34
Association between neurocognition and change in marital status				
Executive Function	0.83	0.78	0.44–1.38	0.40
Verbal Memory	0.71	0.69	0.41–1.17	0.17

The primary analysis of the relationship between neurocognition and psychiatric hospitalization was modeled using cause-specific Cox regression. The model was adjusted for age, sex, hospitalization in the year preceding inclusion, HDRS-17 scores, diagnosis (i.e., BD vs MDD), and the clinical trial from which the participant was recruited. Separate Cause-specific Cox regression models were used to model these associations between neurocognition and changes in employment, cohabitation and marital status. All models were adjusted for age, sex, and diagnosis. Abbreviations: HR: Hazard Ratio, CI: confidence Interval, p val: p value. 95% CI and p-values are based on adjusted HR. Unadjusted HR represents hazard ratio associated with executive function and verbal memory without adjusting for any covariates.

Table 2: **Association of neurocognition with future psychiatric hospitalization and socio-demographic measures.**

duration in a sub-sample for whom this data was available (n = 273). In contrast, clinically significant impairment in executive function was not associated with a higher risk of future hospitalization. Secondary analyses did not support an association between neurocognitive impairments and worsening of socio-demographic conditions. However, clinically significant impairment in executive function (as defined by a z-score ≤ -1) was associated with decreased odds of having achieved the highest educational levels.

Prior investigations have focused on the associations between neurocognition and hospitalization, however, they have been predominantly studied in older adults.[16,17,25] Furthermore, these studies have largely examined whether hospitalization contributes to cognitive decline and not the reverse association. Limited evidence, from studies performed in older adults, suggests that although hospitalization is associated with cognitive decline,[16] a decline in cognitive function is also associated with an increased risk of future hospitalization.[25] Moreover, the decline may be steeper prior to the hospitalization rather than after.[17] These findings from the literature, albeit in older adults, suggest that the relationship between cognitive impairments and hospitalization is bidirectional, however, the impairment may predominantly occur prior to hospitalization and may be an early indicator of subsequent hospitalization.

Impairments in neurocognition, in particular verbal memory, are associated with longer illness duration, higher number of mood episodes, and instances of past hospitalizations[12]— all factors that contribute to increased risk of future psychiatric hospitalization. In our study, we found an association between impaired verbal memory and future psychiatric hospitalization even when accounted for mood symptom severity, illness duration, and hospitalization in the year preceding inclusion. Impairment in verbal memory is one of the strongest indicators of pharmacological treatment non-compliance in bipolar disorder, more so than impairments in executive function.[26] In line with clinical observations, we speculate that memory impairments may lead to challenges with treatment compliance when trying to keep up with the demands of daily life, difficulties adhering to complex medication regimens and remembering dosing instructions, problems recalling important information acquired during therapy sessions and difficulty in remembering follow-up doctor and therapist appointments. Therapeutic non-compliance exacerbates mood symptoms and may increase suicide risk—a predominant cause for psychiatric hospital admissions in individuals with BD or MDD. The growing evidence for the association of verbal memory, in comparison to executive function, with clinical factors and treatment non-compliance may explain why the current study did not find a significant association between executive function and increased risk of future psychiatric hospitalization.

Our results showed that low verbal memory was a statistically significant additional indicator of future risk of hospitalization, beyond the risk associated with hospitalization in the year preceding inclusion. This finding has important clinical implications, as it suggests that including strategies to improve verbal memory impairments in the treatment program early on could reduce the risk of psychiatric hospitalizations in individuals with affective disorders. Furthermore, verbal memory tests are relatively inexpensive and do not require extensive training to administer, increasing their potential to be routinely used in clinical settings. For instance, on average the SCIP and the RAVLT test batteries in the verbal memory domain take 15 min each to complete. It is recommended that these brief and easy-to-administer tests be used in clinics to identify early on those individuals who could benefit from interventions to improve verbal memory deficits and in turn their clinical and functional outcomes.[27]

The present study did not show a statistically significant association between neurocognitive impairments and the worsening of socio-demographic measures. A reason could be that the study may not have been adequately powered to detect a more subtle effect. Individuals recruited for the research studies usually have more mild-moderate impairments in cognitive function and have some level of psychosocial functioning. The worsening of socio-demographic function would likely be more apparent in individuals with more severe cognitive impairments. Exploratory analysis, however, indicated that clinically significant impairment in executive function was associated with decreased odds of having achieved high educational levels. Executive functions include problem-solving, planning, and decision-making.[9] Difficulties in implementing problem-solving strategies or engaging in goal-directed behavior at school could impede educational achievement, and vice versa. Education level is considered a proxy measure of cognitive reserve, a theoretical concept based on the brain's plasticity, and regarded as a protective factor against clinical symptomology. Cognitive reserve refers to the brain's ability to optimize one's cognitive performance to adapt to neuropathological changes and minimize clinical consequences. Our finding is consistent with that from an earlier study that also showed an association between executive function and cognitive reserve in euthymic individuals with BD.[28] They additionally found an association between verbal memory and cognitive reserve which we failed to replicate. This may be due to methodological inconsistencies in measuring cognitive reserve, as we only used educational attainment as a proxy measure of cognitive reserve, while Anaya et al.[28] used an average score of three proxy measures, namely premorbid IQ, highest educational achievement, and occupational attainment, to calculate a composite cognitive reserve score.[28] Notwithstanding, these results suggest that

neurocognitive function has a role to play in cognitive reserve, and further support previous findings that strategies to improve executive function could have positive effects on cognitive reserve perhaps particularly so if implemented early on in treatment.[29]

Interventions shown to promote neurocognitive functioning in individuals with affective disorders include vortioxetine, erythropoietin, transcranial direct current stimulation, cognitive remediation, and exercise (detailed in systematic review: Miskowiak et al.[30]). Improvements in neurocognitive functioning could be assessed by clinicians using self-report questionnaires (eg., the 16-item Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA)). Individuals with affective disorders should also be encouraged to build cognitive reserve as it could have beneficial effects on their clinical, functional, and psychosocial outcomes.[27] Short, and well-validated questionnaires assessing subjective cognitive impairments are less burdensome, have more ecological validity, and are more relevant for tracking progress with cognition-targeted treatments, relative to objective measures.[27]

The findings of this study must be considered in the context of its limitations. As hospitalizations records were available only until 2019, we could not include all the 518 individuals with affective disorders in the analysis of the association between neurocognition and psychiatric hospitalization. Although the cause-specific Cox regression was performed only in a portion of the sample (n = 398) who were recruited prior to the end of the follow-up period, we do not think the exclusion of individuals is a concern for potential bias. Clinical factors such as psychotropic medications and psychiatric comorbidities influence the risk of future hospitalization. We did not have sufficient cross-sectional or longitudinal data on these clinical variables to systematically control for in our analysis. However, we were able to control for clinical factors that have been shown to most predict psychiatric hospitalization, namely prior hospitalization, mood symptom severity, and illness duration. Moreover, in a sample of individuals for whom data on psychotropic medication use and BD subtype were available, clinically significant impairment in verbal memory was still associated with a higher risk of future hospitalization. None of the individuals with BD were in an elevated mood state, and none of the individuals with MDD were euthymic. All our analyses were adjusted for diagnosis and HDRS-17 scores; however, the results may not be generalizable across mood states of BD and MDD. We also did not have information on factors such as childhood adversity and interpersonal functioning that may additionally influence the risk for psychiatric hospitalizations. Another limitation is that only 15% of the individuals in this cohort had MDD. Although diagnostic status was not associated with differential risk for future hospitalization, further investigations in proportionately large MDD samples are necessary to confirm our findings. Lastly, as done in our previous studies, we examined the association of neurocognition only with the worsening of socio-demographic conditions,[2] and not with improvements in socio-demographic conditions.

In conclusion, in the largest longitudinal study of neurocognition in affective disorders, we show for the first time that clinically significant verbal memory impairment is associated with an increased risk of future psychiatric hospitalization in those diagnosed with BD or MDD. However, there is no evidence to indicate that neurocognitive impairments are associated with the worsening of socio-demographic conditions. Future studies performed in individuals with affective disorders without a history of psychiatric hospitalizations would help ascertain whether verbal memory impairments occur prior to psychiatric hospitalizations and are predictive of first hospital admission. Nonetheless, findings from the present study suggest that promoting neurocognitive functioning in individuals with affective disorders as early in their disease trajectory as possible could mitigate the risk of future psychiatric hospitalization.

Contributors

Dr. Sankar made substantial contributions to the curation and analysis of data, literature search, interpretation of study findings, drafting of the manuscript, and revising it critically for intellectual content. Mr. Ziersen and Dr. Ozenne provided statistical experitise for the analyses performed herein, and substantially contributed to the interpretation of findings, drafting of the manuscript, and revising it critically for intellectual content. Ms. Beaman and Dr. Dam made substantial contributions to data curation, and critical revisions of the manuscript. Drs. Fisher, Knudsen, Kessing, and Frokjaer substantially contributed to the interpretation of findings, and critical revisions of the manuscript. Dr. Miskowiak made substantial contributions to the conception and design of the study, curation and analysis of data, interpretation of findings, and critical revisions of the manuscript.

Data sharing statement

The authors agree to make relevant de-identified data, corresponding data dictionary and relevant code used in the analyses presented in the paper available upon reasonable request. Access to information on psychiatric hospitalization and socio-demographic status is available from the National Registers.

Declaration of interests

Dr. Knudsen has received honoraria as expert advisor for Sage Therapeutics, and Sanos, and as expert supervisor for Onsero, and Gilgamesh. Dr. Frokjaer has served as consultant for SAGE therapeutics, H. Lundbeck and Janssen-Cilag. Dr. Miskowiak has received consultancy fees from Lundbeck, Janssen and Angelini Pharma in the past three years. All other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101927.

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