Journal of Affective Disorders 150 (2013) 1188–1191

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Brief report

Cognitive function in adulthood and elderly euthymic bipolar patients: A comparison to test models of cognitive evolution

Sergio A. Strejilevich [a,b,*,1], Diego J. Martino [a,1]

[a] Bipolar Disorder Program, Neurosciences Institute, Favaloro University, Buenos Aires, Argentina
[b] Cognitive Neurology Institute (INECO), Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 31 March 2013
Accepted 3 May 2013
Available online 28 May 2013

Keywords:
Cognition
Bipolar disorder
Evolution
Staging
Progression

ABSTRACT

Objective: Neurocognitive dysfunction is considered as the main predictor of overall outcome of BD. The issue of whether neurocognitive dysfunction in BD is progressive—or not—has become critical in the effort to define staging models for these disorders. Data about cognitive dysfunction evolution are scarce and contradictory. While some studies showed a progressive pattern others have found a stable form of evolution.

Methods: Twenty four patients with BD aged 60 years or older (E-BD), 24 patients with BD aged 40 years or younger (Y-BD) and 20 healthy controls matched by the E-BD group were evaluated with traditional clinical instruments and an extensive neuropsychological battery was completed. We used ANOVA and Chi-squared for comparisons. Raw score of neurocognitive tasks was transformed to standardized Z-score from the normative data of each test to avoid the effect of age. In order to decrease the risk of type I errors, one-way multivariate analysis of variance was conducted.

Results: Despite having an illness duration that was 4 times longer, E-BD did not differ in terms of key cognitive domains compared to Y-BD. These data do not support the hypothesis of a progression of cognitive dysfunction due to illness chronicity.

1. Introduction

Bipolar disorders (BD) are prevalent genetic chronic psychiatric illnesses associated with significant functional impairment, even when appropriately treated. The clinical presentation and pattern of evolution of BD are heterogeneous. In recent years there has been a concerted effort to define staging models for BD as a starting point for rationalizing and personalizing treatment options. In this context, the issue of whether neurocognitive dysfunction in BD is progressive—or not—has become critical.

Neurocognitive dysfunction is recognized as a critical feature of BD. A growing body of data has consistently shown that almost two-thirds of middle-aged bipolar patients suffer persistent impairments in verbal memory, attention, and executive functions (Martino et al., 2008a; Reichenberg et al., 2009; Iverson et al., 2011) which have strong correlations with socio-vocational disabilities (Martino et al., 2009; Bonnín et al., 2010). Actually, cognition is considered as the main predictor of overall outcome of BD and because of that, it is one of the most important pillars over which the emergent staging models of BD are being constructed (Vieta et al., 2013).

Regarding the staging models, two prevalent hypotheses are being used to explain cognitive evolution in this context: one considers progressive neurocognitive dysfunction due to the neuro-toxic effect of mood episodes (Kauer-Sant'Anna et al., 2009; López-Jaramillo et al., 2010a; Vieta et al., 2013) and the other attributes progression to the evolution of the illness itself (Post et al., 2012) due to an allostatic-load process (McEwen, 2003). Both hypotheses imply a progressive increase in neurocognitive deviance causally associated with the number of mood episodes possibly linked to cellular-level changes (for a revision see Kapczinski et al. 2009). However, the issue of progression in neurocognitive dysfunction in BD is far from being resolved.

The best design methodology for the study of the evolution of cognitive impairment is the serial neurocognitive assessment. In two small studies, Balanzá-Martínez et al. (2005) and Mur et al. (2008) found a stable pattern of cognitive impairments over time. Another recent study reported a stable pattern of cognitive impairments across a mean follow-up period of 9 years with a slight improvement of attention and worsening of executive functioning (Torrent et al., 2012). However, these studies were restricted to working age adults. Among elderly euthymic patients with BD, a longitudinal study found a more pronounced cognitive decline in comparison to healthy controls (Gildengers et al. 2009).

* Correspondence to: Congreso 2477 Dto. D (1428) Ciudad de Buenos Aires, Argentina. Tel.: +54 11 4544 2156; fax: +54 11 4833 2424.
E-mail address: sstrejilevich@ffavaloro.org (S.A. Strejilevich).
[1] Both the authors equally contributed to this work.

0165-0327/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2013.05.012

Likewise, some epidemiological studies suggested that elderly patients with BD have increased risk of dementia (reviewed by da Silva et al., 2013). In contrast, other recent follow-up studies in euthymic elderly bipolar patients have found a non-progressive pattern of cognitive evolution (Schouws et al. 2012; Gildengers et al., 2013).

Given the scarcity and inconsistency of longitudinal studies, another indirect source of evidence on the evolution of cognitive deficits could be derived from cross-sectional studies in older adults. In fact, if neurocognitive impairments increase with chronicity one could expect a higher extension and severity of deficits among elderly patients. However, studies in elderly ethymic patients with BD tend to find the same pattern of cognitive deficits both in terms of domains affected and magnitude that were reported in younger patients suggesting, indirectly, no progression in neurocognitive impairments (Schouws et al., 2009; Martino et al., 2008b; Delaloye et al., 2009). A recent review and meta-analytic study corroborated these findings (Samamé et al., 2013).

In this study we use another approach to help understand the evolution of cognitive deficits in BD by comparing the cognitive profile of older patients with BD to their healthy counterparts and to young euthymic patients with BD. We hypothesized that if cognitive deficits were progressive then we should observe greater impairment in older than in younger patients.

2. Methods

Twenty four patients with BD aged 60 years or older (E-BD) and twenty four patients with BD aged 40 years or younger (Y-BD) were consecutively selected from the outpatient population of the Bipolar Disorder Program of the Favaloro University based on the following inclusion criteria: DSM-IV diagnosis of BDI or BDII based on the SCID (First et al., 1996); euthymic (Hamilton Depression Rating Scale≤8 and Young Mania Rating Scale≤6) for at least 8 weeks. Exclusion criteria were history of alcohol dependence or substance abuse, history of mental retardation, neurological disease, or any unstable clinical condition that could affect cognitive performance. Additionally, 20 healthy controls matched by age and years of education with the E-BD group were included if they had no personal history of neurological, psychotic or affective disorders and no family history of psychosis or affective disorders in their first-degree relatives and were not taking psychotropic medication. The study was approved by the Hospital Ethics Committee and all subjects gave written informed consent.

2.1. Clinical assessment

In addition to SCID, all subjects were evaluated with the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), and Young Mania Rating Scale (YMRS) (Young et al., 1978). Psychosocial functioning was assessed with the Global Assessment of Functioning (GAF). Additional clinical information was obtained from medical case notes and direct patients' interviews.

2.2. Neurocognitive assessment

Neurocognitive battery was selected to assess (1) pemorbid IQ: WAIS vocabulary subtest (Wechsler, 1955); (2) attention: Forward Digit Span (Wechsler, 1955); (3) verbal memory: Memory Battery of Signoret (Signoret and Whiteley, 1979); (4) language: Boston Naming Test (Kaplan et al., 1983); (5) executive functions: Wisconsin Card Sorting Test (WCST) (Heaton, 1981); phonological fluency (Benton et al., 1983); and Backward Digit Span (Wechsler, 1955).

2.3. Statistical analysis

The three groups (E-BD, Y-BD, and healthy controls) were compared on clinical and demographical variables using ANOVA and Chi-squared as appropriate. Raw scores of neurocognitive tasks were transformed to standardized Z-score from the normative data of each test to avoid the effect of age. In order to decrease the risk of type I errors because of the large number of analysis, one-way multivariate analysis of variance was conducted with all neurocognitive measures as dependent variables and group membership as factor, followed by Tukey post hoc comparison procedure when significant main effects were present. The variables with significant correlation with psychosocial functioning (GAF) were considered as possible explanatory variables in a multiple linear regression model.

3. Results

Clinical and demographical features of patients and healthy controls are shown in Table 1. There were no differences between E-BD and Y-BD in terms of exposure to any kind of medications.

A significant overall difference in neurocognitive functioning between the groups was detected with multivariate analysis of variance (Pillai´s $F=2.98$; $df=20, 112$; $P<0.001$). For 6 of 10 comparisons the differences reached statistical significance ($P<0.05$). The group means performance for each neurocognitive measure and the respective analysis of variance are presented in Table 2.

Table 1
Clinical and demographical characteristics of bipolar patients and healthy controls (values are expressed as mean; standard deviation is shown in brackets).

	E-BD (A) ($n=24$)	Y-BD (B) ($n=24$)	Controls (C) ($n=20$)	Test	Group comparison (p-value)		
					A vs. B	B vs. C	A vs. C
Age	67.46 (7.51)	34.13 (8.24)	70.50 (7.37)	$F=157.2$ $P<0.001$	<0.001	<0.001	0.401
Gender (% female)	87.5	70.83	90.0	$X^2=3.43$ $P=0.18$			
Premorbid IQ (Z-score)	0.20 (0.71)	0.48 (0.71)	0.22 (0.25)	$F=1.91$ $P=0.15$			
YMRS score	1.08 (1.61)	0.83 (1.27)	0.45 (0.51)	$F=1.40$ $P=0.27$			
HDRS score	1.63 (2.44)	2.38 (1.86)	2.23 (0.50)	$F=1.99$ $P=0.37$			
GAF score	77.18 (12.01)	78.00 (11.76)	86.25 (4.02)	$F=5.06$ $P=0.009$	0.81	0.014	0.027
Age at illness onset	29.50 (6.37)	24.26 (6.82)		$F=7.08$; $p=0.011$			
Length of illness (years)	37.75 (12.11)	9.13 (5.24)		$F=7.08$ $P=0.01$			
Previous hospitalizations	0.79 (1.69)	0.29 (0.62)		$F=1.84$ $P=0.18$			
Clinical subtype (% type II)	17 (70.83)	17 (70.83)		$X^2=0.00$ $P=1.00$			
History of psychosis, n (%)	6 (25)	7 (29.16)		$X^2=0.10$ $P=0.74$			

E-BD: elderly bipolar disorder patients; Y-BD: young bipolar disorder patients; IQ: Intelligence Quotient; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale; GAF: General Assessment of Functioning.

Table 2
Neurocognitive performance of bipolar patients and healthy controls (values are expressed as mean of Z-scores; standard deviation is shown in brackets).

	E-BD (A) ($n=24$)	Y-BD (B) ($n=24$)	Controls (C) ($n=20$)	Test	Group comparison (p-value)		
					A vs. B	B vs. C	A vs. C
Immediate recall	−1.74 (2.01)	−1.63 (1.32)	−0.37 (1.23)	$F=4.94$ $P=0.010$	0.969	0.027	0.016
Delay recall	−1.56 (1.86)	−2.13 (1.43)	−0.35 (1.03)	$F=7.87$ $P=0.001$	0.398	0.001	0.028
Serial learning	0.91 (2.25)	0.17 (1.08)	2.25 (1.62)	$F=8.08$ $P=0.001$	0.313	<0.001	0.034
Free delay recall	−0.70 (2.11)	−0.47 (1.28)	0.29 (1.54)	$F=2.01$ $P=0.14$			
Recognition	1.52 (0.71)	1.31 (0.73)	1.78 (0.41)	$F=2.86$ $P=0.064$			
Boston naming test	−0.33 (1.22)	0.003 (1.05)	−0.21 (0.67)	$F=0.75$ $P=0.47$			
Forward Digit Span	−0.80 (1.02)	−0.69 (1.41)	−0.09 (1.10)	$F=2.13$ $P=0.12$			
Backward Digit Span	0.05 (1.13)	0.01 (1.06)	1.06 (1.39)	$F=5.22$ $P=0.008$	0.995	0.020	0.014
Phonological fluency	−0.28 (0.71)	−0.25 (0.85)	0.41 (0.78)	$F=5.30$ $P=0.007$	0.993	0.017	0.014
WCST-perseverative errors	0.32 (1.30)	−0.12 (1.50)	1.30 (1.07)	$F=6.60$ $P=0.002$	0.473	0.002	0.046

E-BD: elderly bipolar disorder patients; Y-BD: young bipolar disorder patients.

In the E-BD group, GAF score was associated with executive functions measures (Backward Digit Span: $R=0.51$, $P=0.013$; and perseverative errors in WCST: $R=0.58$, $P=0.006$). When we included these variables in a linear regression model, Backward digit Span ($\beta=4.37$; $t=-2.42$; $P=0.026$) and perseverative errors ($\beta=4.54$; $t=2.54$; $P=0.013$) were independent predictors of psychosocial functioning ($F=9.01$, $df=2$, $P=0.002$). Likewise, in the Y-BD group, GAF score was associated with verbal memory (Recognition: $R=0.43$, $P=0.038$), and executive functions (Backward Digit Span: $R=0.50$, $P=0.014$). Backward Digit Span ($\beta=4.85$; $t=2.51$; $P=0.020$) was an independent predictor of psychosocial functioning ($F=6.22$, $df=2$, $P=0.008$) in a linear regression model.

4. Discussion

The main finding of this study was that, despite having an illness duration that was 4 times longer, older patients with BD did not differ in terms of key cognitive domains compared to young patients. Furthermore, both samples showed the predicted associations between cognitive deficits and overall functioning.

These findings agree with those from longitudinal (Balanzá-Martínez et al., 2005; Mur et al., 2008; Schouws et al. 2012; Gildengers et al., 2013) and cross-sectional (Schouws et al., 2009; Martino et al., 2008b; Delaloye et al., 2009) studies showing a stable pattern of cognitive impairments or minimal changes in relation to illness chronicity. In contrast, our results do not support some theoretical models suggesting cognitive decline as evidence of illness progression in BD (Kapczinski et al., 2009; Post et al., 2012). Unfortunately, we did not have a reliable measure of the number of previous episodes in our study. However, taking into account the difference in duration of illness one could assume that E-BD patients have had a higher number of episodes than Y-BD. The patient groups did not differ in number of hospitalizations although these were numerically fewer in the Y-BD group. Hospitalization is a very indirect measure of severity and our findings suggest that this was similar between patient groups. The results of this study agree with a recent research which has provided the first empirically derived staging classification of BD based on illness severity and cognitive impairments. In that study inhibitory control, previous IQ, depressive symptoms and episode density but not chronicity were related with staging classification (Reinares et al., 2013). Another recent longitudinal study does not support the hypothesis that the experience of successive episodes is related to a progressive neurocognitive decline and suggested different hypothetical models of relationship between neurocognitive impairments and episode recurrences (Martino et al., 2013a).

Although our data suggest that accelerated cognitive decline is not a general finding in BD they do not exclude the possibility that subsample of patients may show cognitive deterioration. This possibility has been suggested by populations studies that report a marginal increase in dementia in BD compared to the general population. In line with this supposition, two recent studies (Schouws et al., 2009; Martino et al., 2013b) and a meta-analysis (Samamé et al., 2013) have shown that late-onset BD may represent a subgroup susceptible to cognitive decline. Additionally this association, if it exists, could be mediated by different genetic or environmental factors (such as medical comorbidity or substance abuse) and not the core disease mechanisms involved in BD.

Our study informs about the pattern of cognitive dysfunction post-disease onset. However, it is possible that cognitive deterioration may occur around the time of syndromal onset. This possibility is suggested by studies reporting preserved or ever superior cognitive function in individuals before they develop BD (reviewed by Kumar and Frangou, 2010). Moreover, our study, as is the case for most of the relevant literature, was done on patients in treatment. Treatment may have the potential to stop cognitive deterioration. Basic and clinical data on the neuroprotective effects of lithium (Chuang and Manji, 2007) could support this hypothesis, but studies comparing cognition in euthymic patients treated and untreated are needed to test it. The only study, to our knowledge, in which euthymic patients treated with lithium and untreated patients were compared, found that both groups had the same cognitive performance (López-Jaramillo et al., 2010b).

Finally, this work has other common limitations. First, our sample was small and may have lacked the power to detect differences. Additionally we did not have a reliable measure of the number of previous episodes in our sample. However other critical factors such as premorbid IQ, clinical subtype of BD or exposure to different kind of psychopharmacological agents, were well controlled.

In summary, this study shows that cognitive deficits in patients with BD and long duration of illness are similar to those in young patients with short illness duration. From a clinical point of view, our results offer an optimistic perspective of long-term cognitive outcome in BD. At this point, it is obvious that longitudinal studies are essential for a full understanding of the problems discussed. Specifically we need more data about very long-term cognitive outcome in treated—and ideally—in non-treated bipolar patients to be able to effectively address it. Meanwhile, we should be cautious at the time to assume models of cognitive evolution in BD. An erroneous assumption could determine a pessimistic view of bipolar disorders evolution which would limit the hopes of people affected and facilitate nihilistic behaviors in the professionals involved in the management of these diseases.

Role of funding source
Governmental post-doctoral fellowship.

Conflict of interest
No conflict declared.

Authors disclosures

Sergio Strejilevich is part of the speaker bureau of the following companies: GSK, Abbott, Astra Zeneca, Janssen.

Diego Martino's work is partially supported by a fellowship from CONICET, Argentina.

Acknowledgments
Sophia Frangou.

References

Balanzá-Martínez, V., Tabarés-Seisdedos, R., Selva-Vera, G., Martínez-Arán, A., Torrent, C., Salazar-Fraile, J., Leal-Cercós, C., Vieta, E., Gómez-Beneyto, M., 2005. Persistent cognitive dysfunctions in bipolar I disorder and schizophrenic patients: a 3-year follow-up study. Psychotherapy and Psychosomatics 74 (2), 113–119.

Benton, A., Hamsher, K., Sivan, A., 1983. Multilingual Aphasia Examination, 3rd ed. AJA Associates, Iowa.

Bonnín, C.M., Martínez-Arán, A., Torrent, C., Pacchiarotti, I., Rosa, A.R., Franco, C., Murru, A., Sanchez-Moreno, J., Vieta, E., 2010. Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. Journal of Affective Disorders 121 (1–2), 156–160.

Chuang, D.M., Manji, H.K., 2007. In search of the Holy Grail for the treatment of neurodegenerative disorders: has a simple cation been overlooked? Biological Psychiatry 62 (1), 4–6.

da Silva, J., Gonçalves-Pereira, M., Xavier, M., Mukaetova-Ladinska, E.B., 2013. Affective disorders and risk of developing dementia: systematic review. British Journal of Psychiatry 202, 177–186.

Delaloye, C., Moy, G., Baudois, S., de Bilbao, F., Remund, C.D., Hofer, F., Ragno Paquier, C., Campos, L., Weber, K., Gold, G., Moussa, A., Meiler, C.C., Giannakopoulos, P., 2009. Cognitive features in euthymic bipolar patients in old age. Bipolar Disorders 11 (7), 735–743.

First, M., Spitzer, R., Gibbon, M., Williams, J., 1996. Structured Clinical Interview for DSM-IV Axis I Disorders-Clinical Version (SCID-CV). American Psychiatry Press, Washington, DC.

Gildengers, A.G., Mulsant, B.H., Begley, A., Mazumdar, S., Hyams, A.V., Reynolds Iii, C.F., Kupfer, D.J., Butters, M.A., 2009. The longitudinal course of cognition in older adults with bipolar disorder. Bipolar Disorders 11 (7), 744–752.

Gildengers, A.G., Chisholm, D., Butters, M.A., Anderson, S.J., Begley, A., Holm, M., Rogers, J.C., Reynolds, C.F., Mulsant, B.H., 2013. Two-year course of cognitive function and instrumental activities of daily living in older adults with bipolar disorder: evidence for neuroprogression? Psychological Medicine 43 (4), 801–811.

Hamilton, M., 1960. A rating scale for depression. Journal of Neurology, Neurosurgery, and Psychiatry 23, 56–62.

Heaton, R., 1981. Wisconsin Card Sorting Test. Psychological Assesment Resources, Odessa, FL.

Iverson, G.L., Brooks, B.L., Langenecker, S.A., Young, A.H., 2011. Identifying a cognitive impairment subgroup in adults with mood disorders. Journal of Affective Disorders 132 (3), 360–367.

Kapczinski, F., Dias, V.V., Kauer-Sant'Anna, M., Frey, B.N., Grassi-Oliveira, R., Colom, F., Berk, M., 2009. Clinical implications of a staging model for bipolar disorders. Expert Review of Neurotherapeutics 9 (7), 957–966.

Kaplan, F., Goodglass, H., Weintraub, S., 1983. The Boston Naming Test, 2nd ed. Leo & Febliger, Philadelphia.

Kauer-Sant'Anna, M., Kapczinski, F., Andreazza, A.C., Bond, D.J., Lam, R.W., Young, L.T., Yatham, L.N., 2009. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. International Journal of Neuropsychopharmacology 12 (4), 447–458.

Kumar, C.T., Frangou, S., 2010. Clinical implications of cognitive function in bipolar disorder. Therapeutic Advances in Chronic Disease 1 (3), 85–93.

López-Jaramillo, C., Lopera-Vásquez, J., Gallo, A., Ospina-Duque, J., Bell, V., Torrent, C., Martínez-Arán, A., Vieta, E., 2010a. Effects of recurrence on the cognitive performance of patients with bipolar I disorder: implications for relapse prevention and treatment adherence. Bipolar Disorders 12 (5), 557–567.

López-Jaramillo, C., Lopera-Vásquez, J., Ospina-Duque, J., García, J., Gallo, A., Cortez, V., Palacio, C., Torrent, C., Martínez-Arán, A., Vieta, E., 2010b. Lithium treatment effects on the neuropsychological functioning of patients with bipolar I disorder. Journal of Clinical Psychiatry 71 (8), 1055–1060.

Martino, D.J., Strejilevich, S.A., Scápola, M., Igoa, A., Marengo, E., Ais, E.D., Perinot, L., 2008a. Heterogeneity in cognitive functioning among patients with bipolar disorder. Journal of Affective Disorders 109 (1–2), 149–156.

Martino, D.J., Igoa, A., Marengo, E., Scápola, M., Ais, E., Strejilevich, S.A., 2008b. Cognitive and motor features in elderly people with bipolar disorder. Journal of Affective Disorders 105, 291–295.

Martino, D.J., Marengo, E., Igoa, A., Scápola, M., Ais, E.D., Perinot, L., Strejilevich, S.A., 2009. Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. Journal of Affective Disorders 116 (1–2), 37–42.

Martino, D.J., Strejilevich, S.A., Marengo, E., Igoa, A., Fassi, G., Teitelbaum, J., Caravotta, P., 2013a. Relationship between neurocognitive functioning and episode recurrences in bipolar disorder. Journal of Affective Disorders 147 (1–3), 345–351.

Martino, D.J., Strejilevich, S.A., Manes, F., 2013b. Neurocognitive functioning in early-onset and late-onset older patients with euthymic bipolar disorder. International Journal of Geriatric Psychiatry 28 (2), 142–148.

McEwen, B.S., 2003. Interacting mediators of allostais and allostatic load: towards an understanding of resilience in aging. Metabolism 52 (2), S10–S16, Suppl. 10.

Mur, M., Portella, M.J., Martínez-Arán, A., Pifarré, J., Vieta, E., 2008. Long-term stability of cognitive impairment in bipolar disorder: a 2-year follow-up study of lithium-treated euthymic bipolar patients. Journal of Clinical Psychiatry 69 (5), 712–719.

Post, R.M., Fleming, J., Kapczinski, F., 2012. Neurobiological correlates of illness progression in the recurrent affective disorders. Journal of Psychiatric Research 46 (5), 561–573.

Reichenberg, A., Harvey, P.D., Bowie, C.R., Mojtabai, R., Rabinowitz, J., Heaton, R.K., Bromet, E., 2009. Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. Schizophrenia Bulletin 35 (5), 1022–1029.

Reinares, M., Papachristou, E., Harvey, P., Mar Bonnín, C., Sánchez-Moreno, J., Torrent, C., Ayuso-Mateos, J.L., Ploubidis, G.B., Vieta, E., Frangou, S., 2013. Towards a clinical staging for bipolar disorder: defining patient subtypes based on functional outcome. Journal of Affective Disorders 144 (1–2), 65–71.

Samamé C., Martino D.J., Strejilevich S.A., A quantitative review of neurocognition in euthymic late-life bipolar disorder. Bipolar Disorder. 2013 May 7. doi: 10.1111/bdi.12077.

Schouws, S.N., Comijs, H.C., Stek, M.L., Dekker, J., Oostervink, F., Naarding, P., van der Velde, L., Beerkman, A.T., 2009. Cognitive impairment in early and late bipolar disorder. American Journal of Geriatric Psychiatry 17, 508–515.

Schouws, S.N., Stek, M.L., Comijs, H.C., Dols, A., Beekman, A.T., 2012. Cognitive decline in elderly bipolar disorder patients: a follow-up study. Bipolar Disorders 14 (7), 749–755.

Signoret, J., Whiteley, A., 1979. A memory battery scale. International Neuropsychological Society Bulletin l, 2–26.

Torrent, C., Martinez-Arán, A., del Mar Bonnin, C., Reinares, M., Daban, C., Solé, B., Rosa, A.R., Tabarés-Seisdedos, R., Popovic, D., Salamero, M., Vieta, E., 2012. Long-term outcome of cognitive impairment in bipolar disorder. Journal of Clinical Psychiatry 73 (7), e899–e905, http://dx.doi.org/10.4088/JCP.11m07471.

Tsai, S.Y., Lee, H.C., Chen, C.C., Huang, Y.L., 2007. Cognitive impairment in later life in patients with early-onset bipolar disorder. Bipolar Disorders 9, 868–875.

Vieta, E., Popovic, D., Rosa, A.R., Solé, B., Grande, I., Frey, B.N., Martinez-Aran, A., Sanchez-Moreno, J., Balanzá-Martínez, V., Tabarés-Seisdedos, R., Kapczinski, F., 2013. The clinical implications of cognitive impairment and allostatic load in bipolar disorder. European Psychiatry 28 (1), 21–29.

Wechsler, D., 1950. Wechsler Adult Intelligence Scale-Revised. Psychological Corporation, Cleveland.

Young, R., Biggs, J., Ziegler, V., Meyer, D., 1978. A rating scale for mania: reliability, validity and sensitivity. British Journal of Psychiatry 133, 429–435.