European Psychiatry 39 (2017) 17–26

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Review

Are major depression and bipolar disorder neuropsychologically distinct? A meta-analysis of comparative studies

C. Samamé [a,b,c], A.G. Szmulewicz [a,d], M.P. Valerio [b,d], D.J. Martino [a,b], S.A. Strejilevich [a,e,*]

[a] Bipolar Disorder Program, Institute of Neurosciences, Favaloro University, Buenos Aires, Argentina
[b] National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina
[c] School of Psychology, University of Buenos Aires, Buenos Aires, Argentina
[d] Psychiatric Emergencies Hospital Torcuato de Alvear, Buenos Aires, Argentina
[e] Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 9 May 2016
Received in revised form 18 June 2016
Accepted 20 June 2016
Available online

Keywords:
Major depressive disorder
Bipolar disorder
Cognitive functioning
Meta-analysis

ABSTRACT

Background: Neuropsychological deficits are present in both major depression and bipolar disorder. So far, however, reports directly comparing these mood disorders with regard to cognitive outcomes have been scant and yielded inconsistent results. This work aims to combine the findings of comparative studies of cognition in major depression and bipolar disorder in order to explore whether these neuropsychiatric conditions present with distinct cognitive features.
Methods: The main online databases were extensively searched to retrieve reports assessing neurocognitive functioning in two groups of mood disorder patients, one with major depressive disorder and another with bipolar disorder, both in the same phase of illness. Between-group effect sizes for cognitive variables were obtained from selected studies and pooled by means of meta-analytic procedures.
Results: During euthymia, a significant overall effect size (Hedges'$g = 0.64$, $P < 0.001$) favoring major depressive disorder was found for verbal memory as assessed with list learning tests, whereas no significant between-group differences were found for the remaining variables analyzed. During depressive episodes, similar cognitive outcomes were observed between groups.
Conclusion: At present, it is not possible to postulate specific neuropsychological profiles for major depression and bipolar disorder in light of available evidence. It remains to be ascertained whether the differences found for verbal memory constitute an expression of distinct underlying mechanisms or whether they are best explained by sample characteristics or differential exposure to variables with a negative impact on cognition.

1. Introduction

The current nosological distinction between bipolar disorder (BD) and major depressive disorder (MDD) dates back to the 1960s, when the proposal made by Kleist and Leonhard gained support from the evidence yielded by a number of clinical and epidemiological investigations [1,2]. However, the strongest support for that division may have actually come from the differential response to pharmacological treatment of these disorders. While antidepressants have significant efficacy for the management of acute episodes and prophylaxis in MDD, they may have limited efficacy in the treatment of BD and could even worsen the course of illness [3,4]. Such outcomes not only compel clinicians to make a differential diagnosis in order to prescribe the correct pharmacological treatment but also support the idea that BD and MDD may have their own physiopathology. This division has gained official acceptance in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), which places these entities in different chapters. However, there are no clinical or physiopathological models supporting this division. Furthermore, diagnostic criteria for bipolar and unipolar depression remain unchanged and there is no adequate explanation about why MDD and BD have different evolution and response to treatment. In recent years, a series of studies by means of neuroimaging techniques have found differences in brain structure [5,6] and patterns of neural activity [7,8] between these disorders. It is therefore possible that such differences become evident at a neuropsychological level.

* Corresponding author. Gurruchaga, 2463, 1° C (1425), Ciudad Autónoma de Buenos Aires, Argentina. Tel.: +5411 4833 2424; fax: +5411 4833 2424.
E-mail address: sstreji@gmail.com (S.A. Strejilevich).

http://dx.doi.org/10.1016/j.eurpsy.2016.06.002
0924-9338/

At present, converging pieces of evidence have revealed that BD subjects display neuropsychological abnormalities that persist during euthymia and involve the domains of memory, attention, and executive functions [9–11]. Similar, though milder, deficits have been found in remitted MDD patients [12,13]. Moreover, cognitive dysfunction has consistently been shown to be a strong predictor of functional outcome in both disorders [14–18].

Currently, however, studies directly comparing MDD and BD with regard to neuropsychological functioning are scant and yield inconsistent results. A number of reports show different cognitive outcomes favoring one or the other disorder [19–22], whereas some investigations suggest that performance on neurocognitive tasks does not differentiate one condition from the other [23–26]. Such discrepancies may be explained, at least partly, by the fact that most studies were conducted on small samples, assessed different neuropsychological domains, and included subjects in different phases of illness. Hence, it is not clear whether the cognitive profiles and magnitude of impairment exhibited by MDD and BD are similar or not. If MDD and BD were found to present with distinct neuropsychological features, this would assist in distinguishing between two diagnostic entities whose boundaries are still fuzzy. Furthermore, ascertaining the existence of neuropsychological differences between BD and MDD could contribute to better understanding the neurobiology of these disorders and to the development of specific interventions targeted at preventing or arresting cognitive impairment and poor functional outcome [27,28].

The aim of the present study was to combine, by means of meta-analytic procedures, the findings of reports comparing neuropsychological functioning between BD and MDD in order to explore whether these mood disorders could be distinguishable by virtue of their neuropsychological features.

2. Material and methods

2.1. Search strategy and study selection criteria

MOOSE guidelines [29] were followed to conduct this study. PubMed/PsycINFO databases were extensively searched, covering the period from January 1980 to April 2016, using combinations of the following keywords: *mood disorders, affective disorders, major depressive disorder, bipolar disorder, mania, depression, affective psychoses, cognition, neuropsychology, memory, executive, and attention*. The same search was performed using Google Scholar in order to identify unpublished material (theses, congress presentations) and reports written in languages other than English or published in journals not indexed in the aforementioned electronic databases. Moreover, the reference lists of retrieved studies and systematic reviews on cognitive aspects of affective disorders were cross-checked for further relevant investigations.

Reports were included in this review if they met the following criteria:

- were available in English, Spanish, Portuguese, French, or Italian;
- assessed neuropsychological domains in two groups of mood disorder patients: one with MDD and another with BD, both in the same phase of illness (euthymia or depression);
- ascertained diagnosis using structured criteria;
- patients within each group were in the same phase of illness;
- ascertained mood state on the basis of standardized measures;
- reported separate behavioral results for each mood disorder group;
- included more than ten subjects in each group;
- provided data to estimate between-group effect sizes for cognitive domains;
- explored a neuropsychological domain assessed in a minimum of three studies.

Additionally, if there were studies with overlapping content based on the same patient sample, only the data from the study with the largest sample were considered.

2.2. Data analysis

Meta-analyses were performed using Comprehensive Meta-Analysis software version 2.0 [30]. Data from depressed and euthymic patients were meta-analyzed separately. Hence, summary measures for both the euthymic and depressive phases of mood disorders were obtained. The effect size for each neuropsychological variable was calculated as the mean difference between groups divided by the pooled standard deviation. Hedges' formula [31] was applied to correct for upwardly biased estimation of the effect size in small samples. Effect sizes were weighted using the inverse variance method. Whenever patients with BD underperformed those with MDD, between-group differences were reported by positive effect sizes. When means and standard deviations of more than one group of euthymic/depressed BD or MDD patients were given, the mean values and standard deviations were combined. The homogeneity of the resulting mean weighted effect sizes for each variable was examined using the *Q*-statistic. The I^2 index [32] was calculated to describe the percentage of total variation across reports due to heterogeneity rather than chance. I^2 values of 25, 50, and 75% indicate low, moderate, and high heterogeneity, respectively. Based on the small sample sizes and the presence of heterogeneity in most analyses, a random-effects model was chosen. A significance level of $P < 0.05$ was set for the random-effects model and homogeneity analyses.

2.3. Neuropsychological variables

For the purposes of this study, the results of reports utilizing the same test or assessing approximately the same neuropsychological construct were pooled together. Summary measures were obtained for twelve different variables, namely TMT_A, TMT_B, processing speed, forward digit span, backward digit span, digit symbol coding, list learning, spatial span, response inhibition, planning, phonological fluency, and cognitive flexibility, thus reflecting the domains of attention/processing speed, verbal memory, and executive functions (Table 1).

3. Results

The initial search through PubMed and PsycInfo resulted in 1905 potentially relevant abstracts, which were assessed for suitability. Furthermore, a search using Google Scholar enabled the identification of 75 additional records corresponding to studies written in languages other than English, unpublished material, and articles published in journals not indexed in major bibliographic databases. Of this initial pool of 1980 records, only 56 studies assessed neuropsychological functioning in both BD and MDD, and their full texts were retrieved for detailed evaluation. Finally, 23 reports fully met eligibility criteria and were included in the current review (Fig. 1, Table 2). Ten of the selected studies compared the neuropsychological performance of 338 MDD patients with that of 402 BD patients during euthymia (Table 2) and were considered for the meta-analysis of remitted mood disorder subjects. Two studies by Clark et al. [46,47] were included as they explored different cognitive domains. The study by Xu et al. [48], in which the same patients were assessed during depression and remission, was only considered for the analysis of euthymic

Table 1
Neuropsychological domains analyzed.

Cognitive measure	Outcome measure
Attention/processing speed	
Digit-symbol coding [33]	Number of items correctly coded
Trail Making Test, part A (TMT_A) [34]	Time to complete the task
Processing speed	Reaction time
Variants of the Continuous Performance Test [35]	
Forward span [33]	Maximum number of items recalled in the correct order
Verbal memory	
List learning (California Verbal Learning Test (CVLT) [36]; Rey Auditory Verbal Learning Test (RAVLT) [37]; Auditory Verbal Learning Test (AVLT) [38]; Word List Learning Memory Task from the CERAD Neuropsychological Battery [39])	Immediate recall scores (sum of trials 1–5/total words recalled on the last trial)
Executive functions	
Trail Making Test, part B (TMT_B) [34]	Time to complete the task
Backward span [33]	Maximum number of items recalled in the correct order
Cognitive flexibility (Wisconsin Card Sorting Test (WCST) [40]; Intra-Dimensional Extra Dimensional Set Shifting (ID/ED) from the CANTAB [41])	Total errors/perseverative errors/extradimensional errors
Planning (Stockings of Cambridge (SoC) from the CANTAB [41]; Tower of Hanoi [ToH] [42])	Problems solved/total score
Phonological fluency [43]	Number of words beginning with a certain letter recalled in a minute
Response inhibition Stroop color-word interference test [44]	Color-word interference scores
Spatial span (Spatial span subtests from the CANTAB [41] and the WMS [45])	Maximum number of items remembered in the correct order

CANTAB: Cambridge Neuropsychological Test Automated Battery; WMS: Wechsler Memory Scale; CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

patients as it was based on the same sample as another study included in the meta-analysis of depressed subjects [49]. Thirteen reports assessing the cognitive performance of at least 462 BD patients and 665 MDD patients were considered for the meta-analysis of depressed mood disorder subjects. The reports by Maalouf et al. [50] and Taylor Tavares et al. [51] were based on overlapping samples but they explored different cognitive domains, so they were both included.

3.1. Findings in euthymia

No significant between-group differences were found for age in the total sample of studies included in the analysis. Summary measures were calculated for seven cognitive variables (Table 3). A significant overall effect size in the medium range favoring MDD was found for verbal memory as assessed with list learning tests (Hedges'g = 0.64, CI = 0.31 to 0.97, $P < 0.001$), with homogeneously distributed effect sizes. As for the remaining variables, no significant differences were observed. However, high levels of homogeneity were evident only in the cognitive flexibility analysis.

3.2. Findings in depression

No significant between-group differences were found for severity of depressive symptomatology or age in the total sample of studies included in the analysis. Summary measures were calculated for eleven cognitive domains (Table 3). Similar neuropsychological outcomes were observed between MDD and BD across all the variables analyzed. However, effect size distributions were highly heterogeneous for most cognitive measures.

4. Discussion

To the best of our knowledge, this is the first meta-analysis to compare cognitive functioning between BD and MDD. Twenty-three studies assessing neuropsychological performance in BD and MDD patients during the same phase of illness were reviewed. Seven overall effect sizes were obtained for euthymic mood disorder subjects, whereas eleven summary measures were calculated for depressed patients. The results of this study showed that, during depressive states, both mood disorder groups displayed similar cognitive performance. During euthymia, a significant overall effect size favoring MDD was found for list learning in the presence of high levels of homogeneity. Consequently, the same summary measure could be obtained using either a fixed or a random-effects model, supporting the robustness of this result. As for the remaining variables, no significant between-group differences were observed during remission.

One of the strengths of this meta-analysis was the assessment and inclusion of unpublished material (theses, congress presentations) and studies available in languages other than English. This approach minimizes publication-related biases, given that studies with non-significant findings are less likely to be published than studies with positive results, particularly in high-impact English-language journals. Another strength of this review was that the groups of mood disorder subjects were compared during the same phase of illness, and mood state was similar in all the subjects within each group, which is generally not the case in meta-analyses of mood disorder patients.

Overall, the findings of the current study suggest that cognitive deficits as assessed with traditional neuropsychological tests are present among both MDD and BD subjects, and that they may not assist in distinguishing between these disorders during depressive episodes. However, it is possible that, during euthymia, bipolar patients exhibit worse verbal memory performance than MDD subjects. This is in keeping with one of the largest studies of euthymic mood disorder patients [20], which could not be included in the present meta-analysis on account of not providing individual test scores. Nevertheless, several limitations should be considered when interpreting the findings of this review. First, heterogeneity was observed in many of the analyses performed and it could be related to the fact that most primary studies were based on small samples. Second, it was not possible to assess

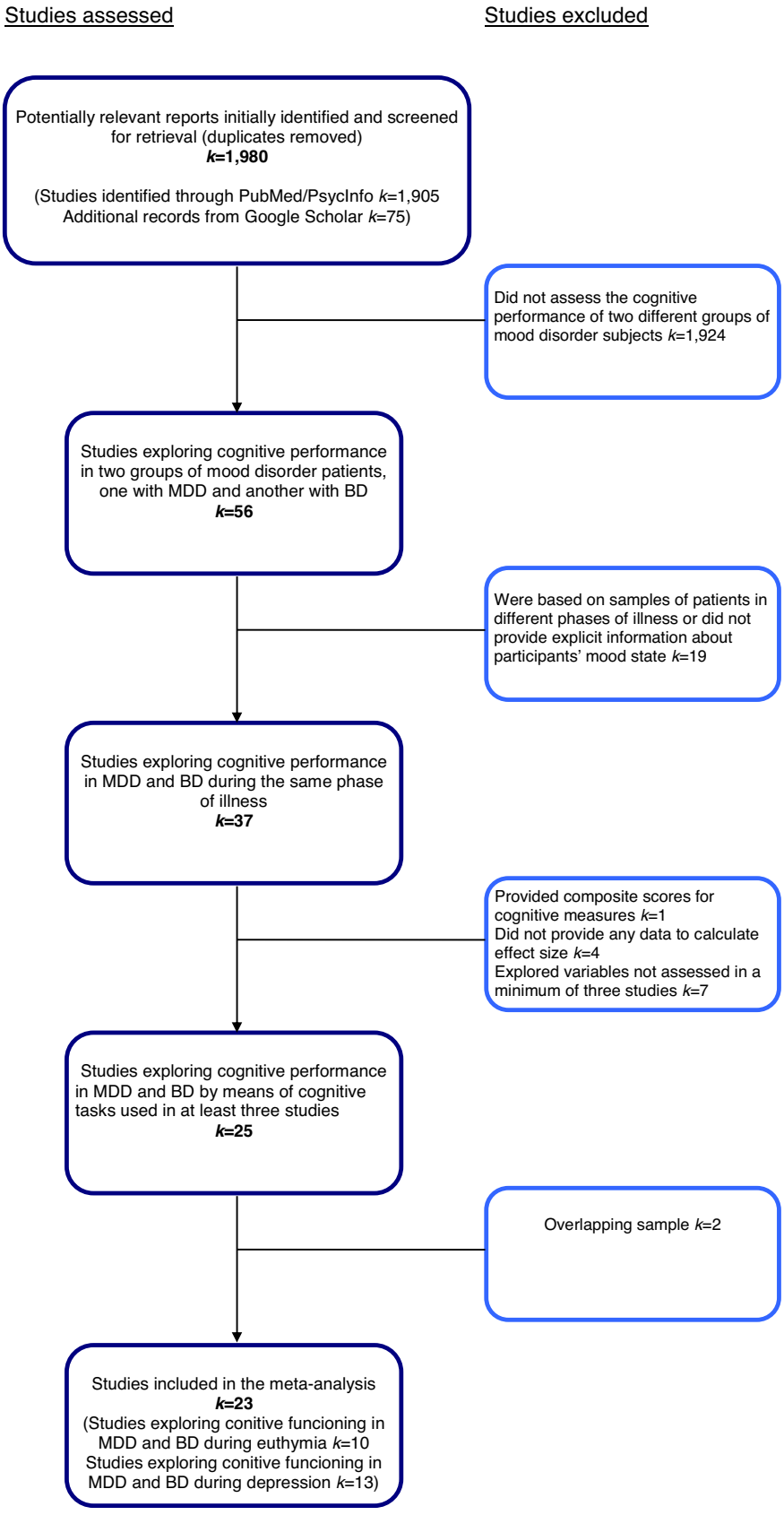

Fig. 1. Study selection flow chart (BD: bipolar disorder; MDD: major depressive disorder).

Table 2
Studies included in the meta-analysis.

Primary study	Sample[a] BD (type)/ MDD	Patients' mean age	Criteria of euthymia	Matched[b]	Medication			Cognitive variable	Hedges'*g*
					AP	AD	MS		
Remission									
Canuto et al., 2010 [52]	22(I–II)/36	66.7	GDS < 5 YMRS < 5	Education General physical status	32% BD 0% MDD	23% BD 47% MDD	73% BD 0% MDD	Processing speed List learning Response inhibition	0.61 0.90 0.21
Clark et al., 2005 [46]	13(I)/15	41.5	HDRS < 9 YMRS < 9	Age Crystallized IQ Severity of depressive symptoms Severity of manic symptoms % of patients on AD	20% BD 0% MDD	33% BD 40% MDD	73% BD 0% MDD	Processing speed	0.36
Clark et al., 2005 [47]	13(I)/15	41.5	HDRS < 9 YMRS < 9	Age Crystallized IQ Severity of depressive symptoms Severity of manic symptoms % of patients on AD	20% BD 0% MDD	33% BD 40% MDD	73% BD 0% MDD	List learning Cognitive flexibility	0.34 −0.15
Daniel et al., 2013 [25]	25(I)/25	46.7	HDRS < 8 YMRS < 5	Age Sex Education Severity of depressive symptoms % of patients on AX	60% BD 17% MDD	8% BD 91% MDD	100% BD 13% MDD	TMTB Cognitive flexibility Digit symbol	0.49 0.15 0.60
Di Paolo, 2008 [53]	141(I–II)/58	47.9	HDRS < 8 YMRS < 8	Age Sex Education Duration of illness Number of depressive episodes History of psychotic symptoms	NA	NA	NA	Processing speed	−0.10
Jaracz et al., 2008 [54]	31(NA)/14	NA	BDI (Cut-off scores NA)	Age Severity of depressive symptoms	NA	NA	NA	TMTA TMTB Response inhibition	−0.14 −0.32 −0.27
Paradiso et al., 1997 [19]	11(I)/20	56.3	HDRS < 15 MBRS < 17	Age Sex Education General cognitive status (MMSE) Severity of depressive symptoms Duration of illness Remission time % of patients on AX and AP	18% BD 5% MDD	36% BD 86% MDD	100% BD 43% MDD	TMTA TMTB Response inhibition Digit symbol	−0.04 −1.04 −0.31 −0.15
Robertson et al., 2003 [55]	44(I)/28	19.0	BDI < 13	Sex % of patients on AX % of patients with comorbid ADHD	25% BD 0% MDD	7% BD 53% MDD	93% BD 3% MDD	Processing speed	−0.39
Smith et al., 2006 [21]	21(BSD)/42	21.7	HDRS < 9	Age Sex Crystallized IQ Severity of depressive symptoms Age at onset Number of depressive episodes History of deliberate self-harm % of patients on MS-only, AD, and AP	0% BD 0% MDD	81% BD 88% MDD AD-only: 62% BD 83% MDD	38% BD 14% MDD MS-only: 19% BD 10% MDD	TMTA TMTB List learning Response inhibition	0.39 0.61 0.58 0.48

Table 2 (*Continued*)

Primary study	Sample[a] BD (type)/ MDD	Patients' mean age	Criteria of euthymia	Matched[b]	Medication			Cognitive variable	Hedges'g
					AP	AD	MS		
Xu et al., 2012 [48] [c]	94(I–II)/100	NA	HDRS < 8 YMRS < 6	NA	NA	NA	NA	TMTA TMTB Cognitive flexibility Digit symbol	−0.08 −0.21 0.13 0.05
Depression									
Borkowska and Rybakowski, 2001 [56]	15(I–II)/30	40.0		Age Education Overall and crystallized IQ Severity of depressive symptoms Duration of illness Number of depressive episodes	0% BD 0% MDD	0% BD 0% MDD	0% BD 0% MDD	TMTA TMTB Phonemic fluency Cognitive flexibility Response inhibition	1.16 2.35 1.50 2.66 1.76
Fossati et al., 2004 [57]	18(NA)/51	41.9		Age Education Severity of depressive symptoms Age at onset % of patients on AP, AD, and AX	50% BD 47% MDD	89% BD 94% MDD	72% BD 6% MDD	Forward digit span Backwards digit span	0.43 0.09
Gallagher et al., 2015 [58]	33(I–II)/39	39.0		Crystallized IQ Severity of depressive symptoms Age at onset	47% BD 0% MDD	81% BD 0% MDD	84% BD 0% MDD	Processing speed	0.32
Godard et al., 2011 [59]	14(I–II)/16	47.6		Age Education Severity of depressive symptoms Severity of manic symptoms Severity of anxiety symptoms Psychotic features Age at onset Duration of illness Number of depressive episodes Number of hospitalizations Suicide attempts Duration of current episode % of patients on AP and AX % of patients with comorbid ADHD, personality, anxiety, or eating disorders	21% BD 19% MDD	0% BD 25% MDD	71% BD 25% MDD	Processing speed Reponse inhibition List learning Phonemic fluency Planning	0.43 0.66 0.11 −0.08 0.10
Gruber et al., 2007 [60]	22(I–II)/30	46.7		Age Education Duration of illness Age at onset	55% BD 10% MDD	64% BD 93% MDD	77% BD 27% MDD	List learning Cognitive flexibility	0.02 0.21
Hermens et al., 2010 [61]	20(I–II)/20	20.7		Age Sex Education Severity of depressive symptoms Crystallized IQ Number of depressive episodes	60% BD 30% MDD	60% BD 60% MDD	30% BD 15% MDD	TMTA TMTB List learning	−0.26 −0.18 −0.26
Hori et al., 2012 [62]	41(II)/131	41.6		Age Sex Education Severity of depressive symptoms Number of hospitalizations % of patients on AX	54% BD 28% MDD	54% BD 73% MDD	27% BD 10% MDD	Forward digit span Backwards digit span Cognitive flexibility Spatial span	0.15 0.14 0.47 0.05

Table 2 (*Continued*)

Primary study	Sample[a] BD (type)/ MDD	Patients' mean age	Criteria of euthymia	Matched[b]	Medication			Cognitive variable	Hedges'g
					AP	AD	MS		
Kerr et al., 2005 [63]	13(I)/17	45.8		Age Sex Crystallized IQ General cognitive status (MMSE) Severity of depressive symptoms Duration of illness	? BD ? MDD	? BD ? MDD	100% BD ? MDD	Response inhibition	−0.36
Lin et al., 2014 [49] [d]	236(I–II)/219	33.7		Severity of depressive symptoms	0% BD 0% MDD	0% BD 0% MDD	0% BD 0% MDD	TMTA TMTB Forward digit span Backward digit span Cognitive flexibility Planning	−0.21 −0.07 −0.10 −0.15 −0.02 0.01
Maalouf et al., 2010 [50]	14(I)/20	36.5		Age Sex Overall IQ Severity of depressive symptoms Severity of manic symptoms Age at onset Duration of illness	NA	NA	NA	Processing speed Planning	0.39 0.37
Sweeney et al., 2000 [64]	21(NA)/58	32.2		Age Overall IQ Psychotic features % of patients on AX	33% BD 7% MDD	52% BD 79% MDD	67% BD 10% MDD	Processing speed Cognitive flexibility Spatial span Planning	0.05 −0.17 0.38 0.27
Taylor Tavares et al., 2007 [51]	17(II)/22	36.0		Age Sex Overall IQ Severity of depressive symptoms Severity of manic symptoms Age at onset Severity of anxiety symptoms Ruminative thoughts Anhedonia scores Time off medication Socio-economic status Impulsivity scores	0% BD 0% MDD	0% BD 0% MDD	0% BD 0% MDD	Cognitive flexibility Spatial span	−0.40 −0.09
Wolfe et al., 1987 [65]	12(I)/20	46.7		Age Education Severity of depressive symptoms	0% BD 0% MDD	0% BD 0% MDD	0% BD 0% MDD	List learning Phonemic fluency	0.85 0.76

AP: antipsychotics; AD: antidepressants; MS: mood stabilizers; AX: anxiolytics; BD: bipolar disorder patients; MDD: major depressive disorder patients; BSD: bipolar spectrum disorder; ADHD: attention-deficit/hyperactivity disorder; MMSE: Mini Mental State Examination; TMT: Trail Making Test; GDS: Geriatric Depression Scale; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; MBRS: Manic Behavior Rating Scale; BDI: Beck Depression Inventory; NA: not available;?: unclear.

[a] Only mood disorder patients undergoing cognitive assessment during the same phase of illness were considered in the current synthesis.

[b] Matching on clinical and demographic variables involves exclusively the two mood disorder groups compared in the meta-analysis.

[c] Clinical and demographic data for the sample of mood disorder subjects at baseline are available from Xu et al. [48]. No data on these variables are available for the subgroup of subjects achieving remission after follow-up.

[d] Only the data corresponding to 'strict MDD' were included to estimate effect sizes from the study by Lin et al. [49].

overall between-group differences for years of education or premorbid IQ given that many of the studies reviewed did not provide mean scores for these variables. Neither was it possible to explore between-group differences for subclinical symptoms in the meta-analysis of euthymic patients, although all the primary studies, except for Jaracz et al. [54], focused exclusively on subjects scoring below given cut-off values on mood rating scales. Third, despite the utilization of standardized methods to ascertain euthymia and the fact that similar levels of depressive symptomatology were found between patient groups during acute mood episodes, adequate matching on other clinical variables with a possible effect on cognitive outcomes was hardly accomplished. In many studies, data on duration of illness, age at onset, number of affective episodes, severity of illness, and psychotic features were missing. This issue is particularly relevant as the clinical and neuropsychological features of mood disorders are not uniform across affected subjects. Rather, there may be subgroups within these disorders presenting with distinct cognitive characteristics [12,66]. For instance, more deficient cognitive performance has been shown to be present in MDD subjects with psychotic features in comparison to their nonpsychotic counterparts [67] and BD patients with more recurrent relapses have been found to be more

Table 3
Mean weighted effect sizes of MDD-BD differences for neuropsychological domains during euthymia and depression.

Variable	K[a]	BD	MDD	ES[b]	95% CI	Z[c]	P	Q test (P)[d]	I^2 (%)[e]
Euthymia									
TMT_A	4	157	176	0.00	−0.22 to 0.22	0.28	0.99	0.45	0.00
TMT_B	5	182	201	−0.06	−0.55 to 0.43	−0.23	0.82	0.001	78.00
Processing speed	4	220	137	0.08	−0.34 to 0.49	0.36	0.72	0.03	66.41
Digit-symbol coding	3	130	145	0.16	−0.22 to 0.54	0.84	0.40	0.16	44.64
List learning	3	56	93	0.65	0.31 to 0.98	3.77	<0.001	0.45	0.00
Response inhibition	4	85	112	0.08	−0.30 to 0.45	0.39	0.69	0.18	37.92
Cognitive flexibility	3	134	140	0.10	−0.13 to 0.34	0.85	0.39	0.76	0.00
Depression									
TMT_A	3	271	269	0.19	−0.58 to 0.97	0.49	0.63	<0.001	87.33
TMT_B	3	271	269	0.65	−0.59 to 1.90	1.03	0.30	<0.001	94.40
Processing speed	4	82	133	0.27	−0.01 to 0.54	1.88	0.06	0.77	0.00
List learning	4	67	84	0.15	−0.28 to 0.58	0.67	0.50	0.14	44.58
Response inhibition	3	42	63	0.69	−0.59 to 1.89	1.12	0.26	<0.001	88.34
Cognitive flexibility	6	351	475	0.39	−0.15 to 0.92	1.41	0.16	<0.001	89.35
Forward digit span	3	294	386	0.07	−0.20 to 0.35	0.52	0.60	0.13	51.20
Backward digit span	3	294	386	−0.05	−0.24 to 0.13	−0.56	0.57	0.31	15.26
Planning	4	285	313	0.06	−0.10 to 0.22	0.73	0.46	0.61	0.00
Phonological fluency	3	41	66	0.73	−0.18 to 1.64	1.58	0.12	0.007	80.14
Spatial span	3	79	199	0.11	−0.15 to 0.37	0.85	0.40	0.45	0.00

BD: bipolar disorder patients; MDD: major depressive disorder patients; CI: confidence interval.
[a] Number of primary studies.
[b] Effect size (Hedges' *g*).
[c] Test of significance of effect size.
[d] Test of homogeneity, based on X^2 with *k*–1 degrees of freedom.
[e] Heterogeneity Index.

impaired in terms of neuropsychological functioning than those with a more stable course [66,68]. Furthermore, it has been reported that both late-onset MDD and BD present with more severe cognitive impairment and that they could be etiologically distinct from mood disorders developing in early adulthood [12,69]. Such heterogeneity may obscure the interpretation of neuropsychological findings and, therefore, studying subgroups of patients with comparable clinical features could be a more valid approach. In addition, the results of this meta-analysis may have been obscured by the differential pharmacological treatment regimens assigned to MDD and BD patients, being the latter remarkably more prone to receiving mood stabilizers and antipsychotics, which have been shown to have deleterious effects on cognition [70–74]. Unfortunately, it was not feasible to study the effect of medication on the reported effect sizes by means of meta-analytic procedures. However, this variable alone may not explain the between-group differences found for verbal memory or the heterogeneity observed in some analyses. For instance, a study of antipsychotic-free mood disorder subjects closely matched on pharmacological variables revealed that bipolar spectrum disorder patients displayed poorer verbal memory performance than 'strict MDD' patients, with a medium effect size [21]. Contrarily, in another study [19], the bipolar group displayed much better outcomes across a number of cognitive variables despite the percentage of patients on antipsychotics and mood stabilizers being higher than that in the MDD group. Furthermore, the fact that polypharmacy is highly prevalent among bipolar subjects, as was the case in most of the reports reviewed, should not be overlooked when interpreting our preliminary findings. Although at present there are no studies addressing the relationship between polypharmacy and cognitive outcomes, it is possible that the combination of drugs of different psychotropic classes or their cumulative effects exert a negative impact on neuropsychological functioning.

Another limitation involves the lack of data to compare different memory variables between BD and MDD. If significant differences were found for such cognitive characteristics in future studies, that would bring further support to our preliminary finding of verbal memory being more impaired in BD subjects. Furthermore, it is of note that the results of the current study are limited to those cognitive functions more commonly explored during neuropsychological assessment, and true differences between mood disorder groups could eventually exist for other cognitive domains. It is also possible that neurocognitive differences emerge with the use of more sensitive assessment techniques. In addition, our results are limited by the small number of reports included in each meta-analysis. Nonetheless, the finding of better verbal memory performance in euthymic MDD is in keeping with the results of three meta-analyses showing minimal or non-significant differences between patients with major depression and healthy controls with regard to this variable [12,13] and an extensive literature revealing significant large deficits in verbal memory as assessed with list learning tasks among euthymic BD subjects [9–11]. Hence, the evidence available at present indicates that memory may be the only variable that could assist in distinguishing between MDD and BD during euthymia. Moreover, it is worth noting that, among MDD samples, a number of patients may be bipolar in nature [75,76], thus confounding the findings reported for this disorder. The mixture of bipolar I and II disorder in many primary studies and in this meta-analysis could also be a confounding factor. However, preliminary meta-analytic findings have shown that these disorders may be similar with regard to the severity of cognitive impairment, except for verbal memory, on which BD II subjects were found to be less impaired [77]. But again, it is not clear whether that finding is best explained by the fact that BD I subjects are more prone to being exposed to several variables with a negative effect on cognition. Finally, comorbidity with anxiety disorders, substance abuse, or attention-deficit/hyperactivity disorder could have moderated the findings of this meta-analysis. Given that very few studies provided information about comorbidities, it was not possible to explore the impact of such variables on the overall effect sizes.

In summary, during depressive episodes, BD and MDD may not be distinguishable by virtue of their cognitive features as evaluated with a set of tests commonly used in neuropsychological assessment. Even though remitted BD subjects could display more severe neuropsychological impairment than MDD subjects in terms of affected domains and magnitude, it is not possible to

postulate any specificity of BD profile of cognitive dysfunction with respect to MDD until larger studies with better-matched mood disorder samples replicate our findings. In addition, in order to arrive at more robust and useful conclusions, it is important that researchers agree on a consistent approach to studying this issue, for instance, by establishing a consensus battery and better specifying the characteristics of the mood disorder samples. Forthcoming research should be aimed at clarifying whether the differences in verbal memory observed between euthymic MDD and BD reflect distinct underlying mechanisms or whether they are best explained by a differential exposure to a number of variables with a negative effect on cognition.

Role of the funding source

The funding source had no role in the writing of this report, interpretation of data, or in the decision to submit the study for publication.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgement

This study was partially supported by grants from the Scientific and Technical Research Council of Argentina (CONICET) awarded to C.S., M.P.V. and D.J.M.

References

[1] Angst J. Historical aspects of the dichotomy between manic-depressive disorders and schizophrenia. Schizophr Res 2002;57:5–13.
[2] Perris C. A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. Acta Psychiatr Scand Suppl 1966;194:9–14.
[3] Salvadore G, Quiroz JA, Machado-Vieira R, Henter ID, Manji HK, Zarate Jr CA. The neurobiology of the switch process in bipolar disorder: a review. J Clin Psychiatry 2010;71:1488–501.
[4] Strejilevich SA, Martino DJ, Marengo E, Igoa A, Fassi G, Whitham EA, et al. Long-term worsening of bipolar disorder related with frequency of antidepressant exposure. Ann Clin Psychiatry 2011;23:186–92.
[5] Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, Frangou S, et al. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry 2011;68:675–90.
[6] Redlich R, Almeida JJ, Grotegerd D, et al. Brain morphometric biomarkers distinguishing unipolar and bipolar depression. A voxel-based morphometry-pattern classification approach. JAMA Psychiatry 2014;71:1222–30.
[7] Mourão-Miranda J, Almeida JR, Hassel S, et al. Pattern recognition analyses of brain activation elicited by happy and neutral faces in unipolar and bipolar depression. Bipolar Disord 2012;14:451–60.
[8] Diler RS, Pan LA, Segreti A, et al. Differential anterior cingulate activity during response inhibition in depressed adolescents with bipolar and unipolar major depressive disorder. J Can Acad Child Adolesc Psychiatry 2014;23:10–9.
[9] Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatr Scand 2007;116:17–26.
[10] Arts B, Jabben N, Krabbendam L, van Os J. Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. Psychol Med 2008;38:771–85.
[11] Mann-Wrobel MC, Carreno JT, Dickinson D. Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. Bipolar Disord 2011;13:334–42.
[12] Bora E, Harrison BJ, Yücel M, Pantelis C. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. Psychol Med 2013;43:2017–26.
[13] Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med 2014;44:2029–40.
[14] Fennig S, Mottes A, Ricter-Levin G, Treves I, Levkovitz Y. Everyday memory and laboratory memory tests: general function predictors in schizophrenia and remitted depression. J Nerv Ment Dis 2002;190:677–82.
[15] Martino DJ, Strejilevich SA, Scápola M, Igoa A, Marengo E, Ais ED, et al. Heterogeneity in cognitive functioning among patients with bipolar disorder. J Affect Disord 2008;109:149–56.
[16] Yen YC, Rebok GW, Gallo JJ, Jones RN, Tennstedt SL. Depressive symptoms impair everyday problem-solving ability through cognitive abilities in late life. Am J Geriatr Psychiatry 2011;19:142–50.
[17] Mackala SA, Torres IJ, Kozicky J, Michalak EE, Yatham LN. Cognitive performance and quality of life early in the course of bipolar disorder. J Affect Disord 2014;168:119–24.
[18] Baune BT, Malhi GS. A review on the impact of cognitive dysfunction on social, occupational, and general functional outcomes in bipolar disorder. Bipolar Disord 2015;17(Suppl. 2):41–55.
[19] Paradiso S, Lamberty GJ, Garbey MJ, Robinson RG. Cognitive impairment in the euthymic phase of chronic unipolar depression. J Nerv Ment Dis 1997;185:748–54.
[20] Gildengers AG, Butters MA, Chisholm D, et al. Cognition in older adults with bipolar disorder versus major depressive disorder. Bipolar Disord 2012;14:198–205.
[21] Smith DJ, Muir WJ, Blackwood DH. Neurocognitive impairment in euthymic young adults with bipolar spectrum disorder and recurrent major depressive disorder. Bipolar Disord 2006;8:40–6.
[22] Cotrena C, Branco LD, Shansis FM, Fonseca RP. Executive function impairments in depression and bipolar disorder: association with functional impairment and quality of life. J Affect Disord 2015;190:744–53.
[23] Albus M, Hubmann W, Wahlheim C, Sobizack N, Franz U, Mohr F. Contrasts in neuropsychological test profile between patients with first-episode schizophrenia and first-episode affective disorders. Acta Psychiatr Scand 1996;94:87–93.
[24] Bearden CE, Glahn DC, Monkul ES, Barrett J, Najt P, Villarreal V, et al. Patterns of memory impairment in bipolar disorder and unipolar major depression. Psychiatry Res 2006;142:139–50.
[25] Daniel BD, Montali A, Gerra ML, Innamorati M, Girardi P, Pompili M, et al. Cognitive impairment and its associations with the path of illness in affective disorders: a comparison between patients with bipolar and unipolar depression in remission. J Psychiatr Pract 2013;19:275–87.
[26] Scott EM, Hermens DF, Naismith SL, et al. Distinguishing young people with emerging bipolar disorders from those with unipolar depression. J Affect Disord 2013;144:208–15.
[27] Cardoso de Almeida JR, Phillips ML. Distinguishing between unipolar depression and bipolar depression: current and future clinical and neuroimaging perspectives. Biol Psychiatry 2013;73:111–8.
[28] Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. Lancet 2013;381:1663–71.
[29] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[30] Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-Analysis (Version 2). Biostat: Englewood, NJ; 2005.
[31] Hedges L, Olkin I. Statistical Methods for Meta-Analysis. London: Academic Press; 1985.
[32] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[33] Wechsler D. Wechsler Adult Intelligence Scale-Revised. Cleveland, OH: Psychological Corporation; 1981.
[34] Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills 1958;8:271–6.
[35] Conners CK. MHS Staff. Conners' Continuous Performance Test II (CPT II). Toronto, ON: MHS; 2000.
[36] Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test: adult version. San Antonio, TX: The Psychological Corporation; 1987.
[37] Rey A. Psychological examination in cases of traumatic encephalopathy: problems [in French]. Arch Psychol (Geneve) 1941;28:215–85.
[38] Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. J Gen Psychol 1985;112:201–10.
[39] Morris JC, Mohs RC, Rogers H, Fillenbaum G, Heyman A. Consortium to establish a registry for Alzheimer's disease (CERAD): clinical and neuropsychological assessment of Alzheimer's disease. Psychopharmacol Bull 1988;21:641–4.
[40] Heaton RK. A Manual for the Wisconsin Card Sorting Test. Odessa, FL: Psychological Assessment Resources; 1981.
[41] Sahakian BJ, Morris RG, Evenden JL, Heald AL, Raymond PM, Robbins TW. A Comparative Study of Visuospatial Memory and Learning in Alzheimer-Type Dementia and Parkinson's Disease. Brain 1988;111:695–718.
[42] Welsh MC, Satterlee-Cartmell T, Stine M. Towers of Hanoi and London: contribution of working memory and inhibition to performance. Brain Cogn 1999;41:231–42.
[43] Benton AL, Hamsher K. Multilingual Aphasia Examination Manual-Revised. Iowa City, IA: University of Iowa; 1978.
[44] Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643–62.
[45] Wechsler D. Wechsler Memory Scale Manual-Revised. San Antonio, TX: Psychological Corporation; 1978.
[46] Clark L, Kempton MJ, Scarnà A, Grasby PM, Goodwin GM. Sustained attention-deficit confirmed in euthymic bipolar disorder but not in first-degree relatives of bipolar patients or euthymic unipolar depression. Biol Psychiatry 2005;57:183–7.
[47] Clark L, Sarna A, Goodwin GM. Impairment of executive function but not memory in first-degree relatives of patients with bipolar I disorder and in euthymic patients with unipolar depression. Am J Psychiatry 2005;162:1980–2.
[48] Xu G, Lin K, Rao D, et al. Neuropsychological performance in bipolar I, bipolar II and unipolar depression patients: a longitudinal, naturalistic study. J Affect Disord 2012;136:328–39.
[49] Lin K, Xu G, Lu W, et al. Neuropsychological performance of patients with soft bipolar spectrum disorders. Bipolar Disord 2015;17:194–204.

[50] Maalouf FT, Klein C, Clark L, et al. Impaired sustained attention and executive dysfunction: bipolar disorder versus depression-specific markers of affective disorders. Neuropsychologia 2010;48:1862–8.
[51] Taylor Tavares JV, Clark L, Cannon DM, Erickson K, Drevets WC, Sahakian BJ. Distinct profiles of neurocognitive function in unmedicated unipolar depression and bipolar II depression. Biol Psychiatry 2007;62:917–24.
[52] Canuto A, Giannakopoulos P, Moy G, et al. Neurocognitive deficits and personality traits among euthymic patients with mood disorders in late life. J Neurol Sci 2010;299:24–9.
[53] Di Paolo L. Caratterizzazione Neuropsicologica dei Disturbi dell'Umore. Tesi di laurea specialistica. Università de Pisa; 2008 [https://etd.adm.unipi.it/t/etd-10062008-101751/accessed 20 November 2015].
[54] Jaracz M, Tomaszewska M, Wilkosc M, Jaracz J, Cierpialkowska L, Borkowska A.In: Working memory and executive functions in remitted bipolar and unipolar subjects: A controlled study; 2008/02.
[55] Robertson HA, Kutcher SP, Lagace DC. No evidence of attentional deficits in stabilized bipolar youth relative to unipolar and control comparators. Bipolar Disord 2003;5:330–9.
[56] Borkowska A, Rybakowski JK. Neuropsychological frontal lobe tests indicate that bipolar depressed patients are more impaired than unipolar. Bipolar Disord 2001;3:88–94.
[57] Fossati P, Harvey PO, Le Bastard G, Ergis AM, Jouvent R, Allilaire JF. Verbal memory performance of patients with a first depressive episode and patients with unipolar and bipolar recurrent depression. J Psychiatr Res 2004;38:137–44.
[58] Gallagher P, Nilsson J, Finkelmeyer A, et al. Neurocognitive intra-individual variability in mood disorders: effects on attentional response time distributions. Psychol Medicine 2015;45:2985–97.
[59] Godard J, Grondin S, Baruch P, Lafleur MF. Psychosocial and neurocognitive profiles in depressed patients with major depressive disorder and bipolar disorder. Psychiatry Res 2011;190:244–52.
[60] Gruber S, Rathgeber K, Bräunig P, Gauggel S. Stability and course of neuropsychological deficits in manic and depressed bipolar patients compared to patients with major depression. J Affect Disord 2007;104:61–71.
[61] Hermens DF, Naismith SL, Redoblado Hodge MA, Scott EM, Hickie IB. Impaired verbal memory in young adults with unipolar and bipolar depression. Early Interv Psychiatry 2010;4:227–33.
[62] Hori H, Matsuo J, Teraishi T, et al. Schizotypy and genetic loading for schizophrenia impact upon neuropsychological status in bipolar II and unipolar major depressive disorders. J Affect Disord 2012;142:225–32.
[63] Kerr N, Scott J, Phillips ML. Patterns of attentional deficits and emotional bias in bipolar and major depressive disorder. Br J Clin Psychol 2005;44:343–56.
[64] Sweeney JA, Kmiec JA, Kupfer DJ. Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. Biol Psychiatry 2000;48:674–84.
[65] Wolfe J, Granholm E, Butters N, Saunders E, Janowsky D. Verbal memory deficits associated with major affective disorders: a comparison of unipolar and bipolar patients. J Affect Disord 1987;13:83–92.
[66] Martino DJ, Strejilevich SA, Marengo E, Igoa A, Fassi G, Teitelbaum J, et al. Relationship between neurocognitive functioning and episode recurrences in bipolar disorder. J Affect Disord 2013;147:345–51.
[67] Zaninotto L, Guglielmo R, Calati R, et al. Cognitive markers of psychotic unipolar depression: a meta-analytic study. J Affect Disord 2015;174:580–8.
[68] López-Jaramillo C, Lopera-Vásquez J, Gallo A, et al. Effects of recurrence on the cognitive performance of patients with bipolar I disorder: implications for relapse prevention and treatment adherence. Bipolar Disord 2010;12:557–67.
[69] Samamé C, Martino DJ, Strejilevich SA. A quantitative review of neurocognition in euthymic late-life bipolar disorder. Bipolar Disord 2013;15:633–44.
[70] Donaldson S, Goldstein LH, Landau S, Raymont V, Frangou S. The Maudsley Bipolar Disorder Project: the effect of medication, family history, and duration of illness on IQ and memory in bipolar I disorder. J Clin Psychiatry 2003;64:86–93.
[71] Frangou S, Donaldson S, Hadjulis M, Landau S, Goldstein LH. The Maudsley Bipolar Disorder Project: executive dysfunction in bipolar disorder I and its clinical correlates. Biol Psychiatry 2005;58:859–64.
[72] Jamrozinski K, Gruber O, Kemmer C, Falkai P, Scherk H. Neurocognitive functions in euthymic bipolar patients. Acta Psychiatr Scand 2009;119:365–74.
[73] Goldberg JF, Burdick KE. Cognitive side effects of anticonvulsants. J Clin Psychiatry 2001;62:27–33.
[74] Wingo AP, Wingo TS, Harvey PD, Baldessarini RJ. Effects of lithium on cognitive performance: a meta-analysis. J Clin Psychiatry 2009;70:1588–90.
[75] Angst J, Cui L, Swendsen J, Rothen S, Cravchik A, Kessler RC, et al. Major depressive disorder with subthreshold bipolarity in the National Comorbidity Survey Replication. Am J Psychiatry 2010;167:1194–200.
[76] Zimmermann P, Brückl T, Nocon A, Pfister H, Lieb R, Wittchen HU, et al. Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. Arch Gen Psychiatry 2009;66:1341–50.
[77] Bora E, Yücel M, Pantelis C, Berk M. Meta-analytic review of neurocognition in bipolar II disorder. Acta Psychiatr Scand 2011;123:165–74.