BIPOLAR DISORDERS
AN INTERNATIONAL JOURNAL OF PSYCHIATRY AND NEUROSCIENCES

Bipolar Disorders 2013

BIPOLAR DISORDERS

Review Article

A quantitative review of neurocognition in euthymic late-life bipolar disorder

Samamé C, Martino DJ, Strejilevich SA. A quantitative review of neurocognition in euthymic late-life bipolar disorder.
Bipolar Disord 2013: 00: 000–000. © 2013 John Wiley & Sons A/S.
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Objectives: A sizeable body of work has consistently documented that a number of euthymic mixed-age bipolar disorder subjects exhibit prominent impairments in a variety of cognitive domains. By contrast, knowledge about neuropsychological functioning in elderly patients is scant, despite being necessary for the adequate treatment of this population and the understanding of illness evolution. The aim of this study was to combine findings from the available literature in order to examine the pattern and extent of cognitive deficits in euthymic late-life bipolar disorder subjects.

Methods: A literature search was conducted through the online databases PubMed, ScienceDirect, EBSCO, and Wiley-Blackwell, covering the period between January 1990 and April 2012. Effect sizes reflecting patient–control differences for 10 cognitive variables were extracted from selected investigations and combined by means of meta-analytical procedures.

Results: No significant patient–control differences were found for global cognitive status as assessed with the Mini-Mental State Examination and the Clock Drawing Test. Significant overall effect sizes (Hedges' *g*) of between 0.61 and 0.88 were noted for sustained attention, digit span (forwards and backwards), delayed recall, serial learning, cognitive flexibility, and verbal fluency (phonemic and categorical).

Conclusions: The extent of cognitive dysfunction in euthymic late-life bipolar disorder subjects may be, on average, similar to that reported for remitted young adult patients. Larger effect sizes of impairment may be associated with late illness onset. Implications and future directions for research are proposed.

Cecilia Samamé, Diego J Martino and Sergio A Strejilevich

Bipolar Disorders Program, Institute of Neurosciences, Favaloro University, Buenos Aires, Argentina

doi: 10.1111/bdi.12077

Key words: bipolar disorder – cognition – elderly – euthymia – meta-analysis – neuropsychology

Received 17 April 2012, revised and accepted for publication 13 January 2013

Corresponding author:
Dr. Sergio A. Strejilevich
Bipolar Disorders Program
Institute of Neurosciences
Favaloro University
Congreso 2477 Dto. D (1428)
Ciudad Autónoma de Buenos Aires
Argentina
Fax: +54-11-4833-2424
E-mail: sstrejilevich@ffavaloro.org

It is now well documented that a number of euthymic mixed-age patients with bipolar disorder (BD) display conspicuous cognitive dysfunctions in a variety of domains, with medium to large effect sizes of impairment observed for attention/processing speed, verbal memory, and executive functions (1–4). Defective neuropsychological performance is associated with suboptimal functional outcome, as revealed by cross-sectional (5–7) and longitudinal studies (8–10).

Late-life BD is a growing public health concern; subjects aged 60 years and older could represent as much as 25% of the population with bipolar illness (11), and about half of them may exhibit cognitive dysfunctions (12, 13). Notwithstanding these considerations, there is a vast knowledge gap in the neurocognitive profile of elderly euthymic BD patients. It has been suggested that neuropsychological deficits might be more pronounced among older, relative to younger, patients (14, 15). However, this point of view has not been supported by a handful of recent investigations that provide evidence that neurocognitive impairments in older BD patients are comparable to those previously reported (16–18) in younger patients in terms of both affected functions and magnitude. Given

these mixed findings, and the fact that the available data derive from small studies with several methodological shortcomings, the extent of cognitive impairment in remitted, older BD patients is unclear.

From a practical perspective, a better description of the cognitive profile of older BD patients has critical importance, given the preliminary evidence suggesting that neuropsychological deficits are strongly associated with persistent difficulties in activities of daily living (18, 19). Likewise, a more thorough understanding of elderly BD patients' neuropsychological performance would contribute to the development of more specific treatment and rehabilitation approaches. Finally, the exploration of cognitive function in elderly patients may help to improve comprehension of the longitudinal course of neurocognition in BD. If BD presents with progressive cognitive impairment, as proposed by some studies (20–22), we should expect older patients to exhibit a more pronounced magnitude of cognitive impairment in comparison to younger ones. Therefore, the aim of this study was to pool the findings of investigations on cognitive functioning in euthymic elderly BD patients by means of meta-analytical procedures in order to obtain a more comprehensive picture of the magnitude of neuropsychological impairments in this clinical population.

Materials and methods

Search strategy and study selection criteria

A literature search was conducted through the online databases PubMed, ScienceDirect, EBSCO, and Wiley-Blackwell, covering the period between January 1990 and April 2012, using combinations of the following keywords: *bipolar disorder*, *affective disorders*, *age*, *elderly*/*geriatric*/*old*/*late-life*, *cognitive functioning*, *neuropsychology*, *cognition*, *memory*/*recall*, *language*, *executive functions*, *attention*, and *processing speed*. The reference lists of review articles on cognitive aspects of BD and the studies identified for inclusion were also cross-checked for additional relevant reports. Studies included in the meta-analysis met the following criteria: (i) included an asymptomatic patient group aged 50 years or above, with the diagnosis of BD [type I (BD-I), type II (BD-II), or not otherwise specified (NOS)] according to DSM-IV or similar criteria, (ii) included a healthy control group, (iii) euthymia was ascertained on the basis of concurrent depression/mania scores on mood rating scales, (iv) there were at least 10 subjects in each of the patient and healthy comparison groups, (v) investigated at least one neuropsychological domain that was included in a minimum of three studies, and (vi) provided data to estimate patient–control effect size differences.

Additionally, if there were studies with overlapping content based on the same patient sample, we only considered the data from the study with the highest quality, taking into account the criteria used to define euthymia, between-group matching for clinical and demographic variables, and sample size. Two studies on the same patient group were only included if they reported different cognitive measures.

Meta-analytical procedure

Meta-analyses were performed using Comprehensive Meta-Analysis software version 2.0 (23). The effect size for each cognitive measure was calculated as the mean difference between BD patients and healthy controls divided by the pooled standard deviation. We used Hedges' formula to correct for upwardly biased estimation of the effect size in small samples. Effect sizes were weighted using the inverse variance method. Whenever BD patients performed more poorly than controls, we reported between-group differences by positive effect sizes. If means and standard deviations of more than one group with euthymic BD were provided, the mean values and standard deviations were combined. The homogeneity of the resulting mean weighted effect sizes for each variable was tested using Cochran's Q. The I^2 index (24) 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 significant heterogeneity in some of the analyses performed, we chose a random effects model, which assumes that there is not 'one true effect,' but a distribution of true effect sizes. Under this model, the combined measure does not represent the common effect, but instead, the mean of the population of true effects (25). A significance level of $p < 0.05$ was used for the random effects model and homogeneity analyses.

When possible, subgroup meta-analyses were conducted in order to explore potential differences in the magnitude of cognitive impairment among BD subjects with different ages at illness onset. Also, given that two studies (26, 27) reported separate results for early- and late-onset BD subjects, pooled effect sizes were recalculated excluding the data derived from the latter BD subgroup. In

addition, sensitivity analyses were undertaken to explore heterogeneity.

Neuropsychological variables

For the purposes of the current study, the results of reports utilizing the same test or assessing approximately the same neuropsychological construct were meta-analyzed together. When different scoring systems were used for the same task across studies, we included them together under the assumption that each scoring measure reflected the same underlying process. Two distinct overall measures of global cognitive status were calculated using results of the Mini-Mental State Examination (MMSE) (28) and the Clock Drawing Test (CDT) (29). An attention summary measure was calculated by combining the scorings obtained in two sustained attention tasks: the Trail Making Test–Part A (TMT-A) (30) and variants of the Continuous Performance Test (CPT) (31). The test parameters considered were *time (in seconds) taken to conclude the task* and *latency in milliseconds*, respectively. Immediate verbal learning was assessed by means of word list learning from the California Verbal Learning Test (CVLT) (32), the Signoret Memory Battery (33), and the memory subtest of the Cambridge Cognitive Examination (CAMCOG) (34). Delayed verbal learning was assessed by combining free delayed recall measures of the CVLT, Signoret Memory Battery, and memory subtest of the CAMCOG. Verbal fluency was assessed by means of tasks requiring either the naming of words corresponding to a common category (animals) or words beginning with a certain letter (35). Meta-analyses for categorical and phonemic scores were performed separately. Overall measures for digit span were obtained by combining the results of studies utilizing the Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS) (36, 37) and the Corsi blocks from the Wechsler Memory Scale (WMS) (38). Forwards and backwards digit spans were meta-analyzed separately. A measure of cognitive flexibility was obtained by combining the results of studies using the Trail Making Test–Part B (TMT-B) (30) and the Color Trail Making Test (39). The test parameters used were *time needed to conclude the task* and *flexibility cost* [(time to complete part B – time to complete part A)/time to complete part A], respectively.

Results

Our search strategy identified 38 studies investigating cognitive functioning in older BD subjects. Twenty of them were excluded as they did not meet the inclusion criteria (BD subjects were not euthymic/mood state was not specified/did not include a healthy control group). Eighteen reports met all the inclusion criteria required for this meta-analysis. Seven of these were excluded as they were based on the same sample as used in other studies (17, 40–45). Finally, 11 reports (12, 16, 18, 19, 26, 27, 46–50) comparing the neurocognitive performance of 382 BD patients (weighted mean age = 69.2 years) with that of 363 healthy controls (weighted mean age = 69.8 years) were included in the current review (Table 1).

Meta-analytic findings

Effect size differences for cognitive variables, together with their confidence intervals, significance tests, and homogeneity statistics are reported in Table 2. With the exception of general cognitive status (MMSE and CDT) meta-analyses, BD patients performed significantly more poorly than healthy controls, with effect sizes considered in the medium to large range (0.61–0.88) according to a widely used convention for the appraisal of effect sizes (51). No significant between-group differences were found for age or years of education in any of the analyses performed. Significant effect size differences were found for depressive symptomatology in three of the analyses, namely delayed recall [Hedges' $g = 0.37$, 95% confidence interval (CI): 0.04–0.71, $p = 0.03$], sustained attention (Hedges' $g = 0.36$, 95% CI: 0.01–0.72, $p = 0.04$), and semantic fluency (Hedges' $g = 0.32$, 95% CI: 0.04–0.59, $p = 0.02$). Differences for this variable could not be assessed in the MMSE and CDT analyses, since data from controls were not available. Group differences regarding manic symptoms could only be assessed in the digit span analyses, and significant effect sizes were noted (Hedges' $g = 0.48$, 95% CI: 0.24–0.72, $p < 0.001$).

A large magnitude of impairment was found for cognitive flexibility (Hedges' $g = 0.88$, 95% CI: 0.64–1.12, $p < 0.001$), with a homogeneous distribution of effect sizes (Fig. 1). When this summary measure was recalculated after excluding the data corresponding to the late-onset subgroup from the study by Schouws et al. (27), large effect sizes were still evident (Hedges' $g = 0.83$, 95% CI: 0.56–1.10, $p < 0.001$) in the presence of homogeneity. A similar overall effect size was noted for phonemic fluency (Hedges' $g = 0.80$, 95% CI: 0.43–1.01, $p < 0.001$). Despite the null hypothesis of homogeneity not being rejected, some heterogeneity was observed in this analysis (Fig. 2). When the data from the late-onset subgroups included in the

Table 1. Characteristics of the studies included in the meta-analysis

Primary study	Subjects with BD (type)/HC	Matched	Mean age (SD), years	Criteria of euthymia	Age of illness onset, years, mean (SD)	Cognitive variables	Hedges' *g*
Brooks et al., 2009 (46)	16 (I, II)/11	Age Education	58.7 (7.5)	MADRS, YMRS cut-off scores not given	42.6 (15.2)	Delayed recall	1.10
Brooks et al., 2010 (47)	16 (I, II)/11	Age Education	58.7 (7.5)	MADRS, YMRS cut-off scores not given	42.6 (15.2)	CPT reaction time	0.53
Delaloye et al., 2009 (16)	22 (I, II)/22	Age Gender Education	68.5 (5.5)	DSM-IV (absence of symptoms for at least 2 months) + GDS < 5; YMRS < 5	38.9 (15.2)	Simple reaction time Digit span forwards Digit span backwards Color Trail Making Category fluency Phonemic fluency	0.74 0.65 0.69 0.96 0.78 0.63
Gildengers et al., 2004 (12)	18 (I, II)/45	Age Education	68.7 (8.0)	HDRS $\leq$ 10; YMRS $\leq$ 10 for at least 4 weeks	—	MMSE	0.69
Gildengers et al., 2007 (19)	20 (I, II)/40	Age Gender Race	73.6 (8.4)	HDRS $\leq$ 10; YMRS $\leq$ 10	—	CDT TMT-A TMT-B Category fluency Phonemic fluency Delayed recall	0.36 0.64 0.99 0.50 0.31 0.39
Ladeira et al., 2010 (48)	35/35	Age Education	68.1 (5.8)	—	—	CDT	0.22
Martino et al., 2008 (18)	20 (I, II)/20	Age Education	66.6 (8.2)	HDRS $\leq$ 8; YMRS $\leq$ 6 for at least 4 weeks	39.7 (13.0)	MMSE Attention (latency)	0.23 0.26
Martino et al., 2013 (26)	40 (I, II)/20	Age Education	68.0 (6.6)	HDRS $\leq$ 8; YMRS $\leq$ 6 for at least 8 weeks	34.6 (7.2)	Digit span forwards Free delayed recall Serial learning Digit span backwards Category fluency Phonemic fluency	0.68 0.81 0.85 0.84 0.56 1.02
Radanovic et al., 2008 (49)	33 (I, II)/33	Age Education	67.0 (4.5)	HDRS $\leq$ 7; YMRS $\leq$ 4 for at least 4 weeks	45.4 (18.5)	Memory (remote) Memory (learning) Category fluency	0.22 0.10 0.79
Schouws et al., 2009 (27)	119 (I, II)/78	Education	70.4 (7.2)	DSM IV + CES-D; YMRS cut off scores not given	40.8 (15.5)	MMSE CDT TMT-A TMT-B Phonemic fluency Category fluency Digit span forwards Digit span backwards Learning Delayed recall	0.00 0.15 0.66 0.83 1.07 0.68 0.59 0.77 1.28 1.07
Tsai et al., 2009 (50)	59 (I)/59	Age Education	71.1 (5.9)	HDRS < 7; YMRS < 5 for 2 months	39.6 (14.1)	MMSE	1.16

BD = bipolar disorder; CDT = Clock Drawing Test; CES-D = Centre for Epidemiologic Studies Depression Scale; CPT = Continuous Performance Test; GDS = Geriatric Depression Scale; HC = healthy controls; HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; MMSE = Mini-Mental State Examination; SD = standard deviation; TMT-A = Trail Making Test–Part A; TMT-B = Trail Making Test–Part B; YMRS = Young Mania Rating Scale.

studies by Martino et al. (26) and Schouws et al. (27) were excluded, the summary measure remained significant, but fell within the medium range (Hedges' $g = 0.72$, 95% CI: 0.43–1.01, $p < 0.001$), and the trend toward significance previously noted for the test of homogeneity disappeared (before: Q-test $p = 0.08$, $I^2 = 55\%$; after: Q-test $p = 0.28$, $I^2 = 22\%$). Pooled standardized mean differences for semantic fluency were also in the medium rage (Hedges' $g = 0.75$, 95% CI: 0.55–0.95, $p < 0.001$) (Fig. 2). After the exclusion of late-onset BD subjects' performance, the summary

Table 2. Mean weighted effect sizes of patient–control differences for neurocognitive domains

Variable	Studies (*k*)	Patients	Controls	ES[a]	95% CI	Z[b]	p-value	*Q* test (P) [c]	I^2 (%)
General cognitive status (MMSE)	4	216	202	0.52	−0.09 to 1.12	1.67	0.09	<0.001	87
General cognitive status (CDT)	3	174	153	0.20	−0.02 to 0.42	1.78	0.08	0.80	0
Sustained attention	5	197	171	0.61	0.39–0.82	5.62	<0.001	0.82	0
Serial learning	3	192	131	0.76	0.02–1.49	2.02	0.04	<0.001	88
Delayed recall	5	228	187	0.71	0.33–1.08	3.68	<0.001	0.02	64
Digit span forwards	3	181	120	0.61	0.38–0.85	5.11	<0.001	0.95	0
Digit span backwards	3	181	120	0.77	0.53–1.01	6.32	<0.001	0.88	0
Semantic fluency	5	234	193	0.75	0.55–0.95	7.40	<0.001	0.74	0
Phonemic fluency	4	201	160	0.80	0.43–1.16	4.28	<0.001	0.08	55
Cognitive flexibility (TMT-B)	3	161	140	0.88	0.64–1.12	7.12	<0.001	0.86	0

CDT = Clock Drawing Test; MMSE = Mini-Mental State Examination; TMT-B = Trail Making Test–Part B.
[a]Effect size (Hedges' *g*).
[b]Test of significance of effect size.
[c]Test of homogeneity, based on χ^2 with $k - 1$ degrees of freedom.

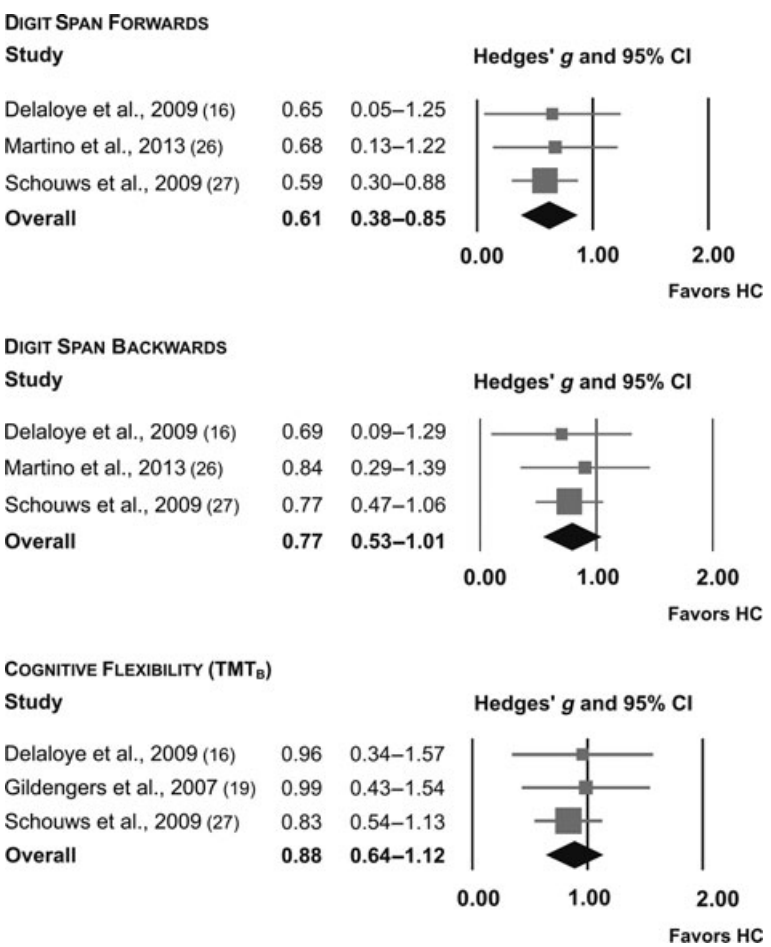

Fig. 1. Forest plots of individual and pooled patient–control standardized mean differences for cognitive flexibility (Trail Making Test–Part B) and digits forwards and digits backwards. The area of each square reflects weighting from random effects analysis. CI = confidence interval; HC = healthy controls.

effect size became Hedges' $g = 0.65$, 95% CI: 0.42–0.88, $p < 0.001$, with a homogeneous effect size distribution.

Moderate effect sizes were found for digit span forwards (Hedges' $g = 0.61$, 95% CI: 0.38–0.85, $p < 0.001$) (Fig. 1), digit span backwards (Hedges' $g = 0.77$, 95% CI: 0.53–1.01, $p < 0.001$) (Fig. 1), and sustained attention (Hedges' $g = 0.61$, 95% CI: 0.39–0.82, $p < 0.001$) in the presence of homogeneity. A recalculation of summary estimates for

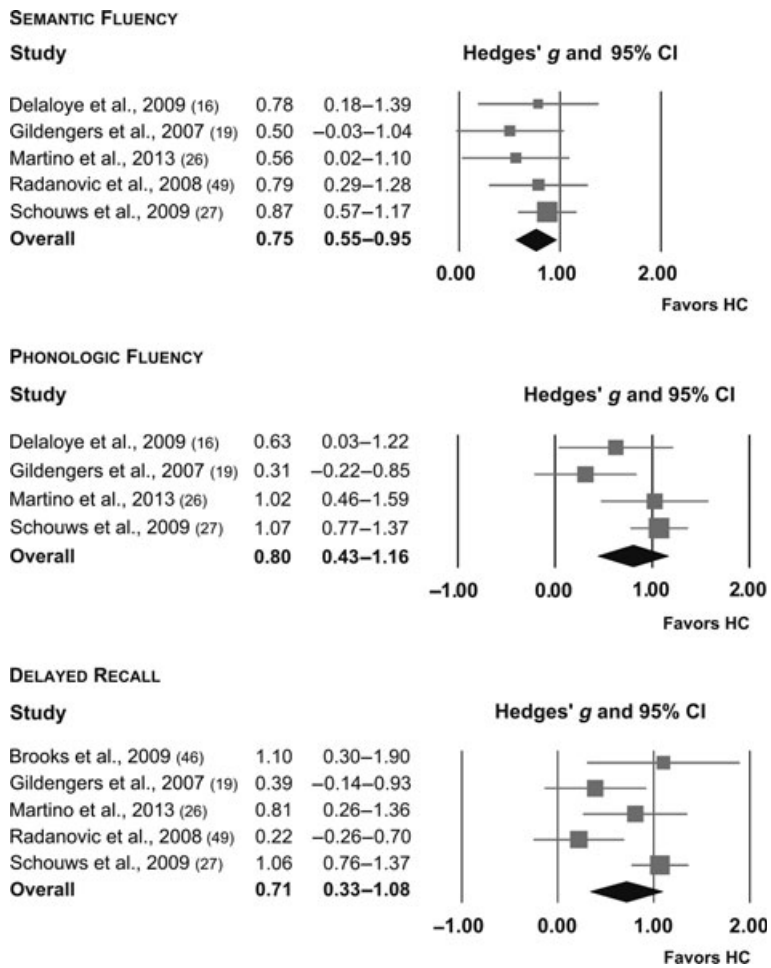

Fig. 2. Forest plots of individual and pooled patient–control standardized mean differences for verbal fluency (phonemic and categorical scores) and delayed verbal recall. The area of each square reflects weighting from random effects analysis. CI = confidence interval; HC = healthy controls.

digit span forwards (Hedges' $g = 0.52$, 95% CI: 0.25–0.79, $p < 0.001$) and backwards (Hedges' $g = 0.75$, 95% CI: 0.48–1.02, $p < 0.001$) was performed by excluding the data corresponding to the late-onset BD patients (26, 27). Similarly, the overall sustained attention effect size was recalculated (Hedges' $g = 0.57$, 95% CI: 0.34–0.80, $p < 0.001$) excluding late-onset BD subjects' performance reported by Schouws et al. (27).

As for delayed recall (Hedges' $g = 0.71$, 95% CI: 0.33–1.08, $p < 0.001$) (Fig. 2) and serial learning (Hedges' $g = 0.76$, 95% CI: 0.02–1.49, $p = 0.04$), moderate impairments were noted. However, effect size distributions were heterogeneous. Delayed recall summary measure was recalculated excluding the data for late-onset BD subjects (Hedges' $g = 0.68$, 95% CI: 0.27–1.08, $p = 0.001$). However, the distribution of effect sizes remained highly heterogeneous. When two studies were excluded (27, 47), this heterogeneity disappeared (before: Q-test $p = 0.001$, $I^2 = 64\%$; after: Q-test $p = 0.67$, $I^2 = 0\%$), and effect sizes were in the small range (Hedges' $g = 0.37$, 95% CI: 0.05–0.68, $p = 0.02$). As for serial learning, when the summary measure was recalculated after the exclusion of late-onset subgroups, the summary effect size became non-significant (Hedges' $g = 0.66$, 95% CI: −0.04 to 1.35, $p = 0.06$). However, the distribution of effect sizes was highly heterogeneous.

On the other hand, patient–control differences for MMSE and CDT failed to reach statistical significance. A highly heterogeneous distribution of effect sizes was observed in the former analysis, whereas homogeneity was found in the latter. In the MMSE analysis, the study by Tsai et al. (50) stood out as a source of heterogeneity. When this study was removed, the trend toward significance of effect sizes previously observed largely disappeared (Hedges' $g = 0.26$, 95% CI: −0.16 to 0.67, $p = 0.23$) and heterogeneity diminished (before: Q-test $p < 0.001$, $I^2 = 87\%$; after: Q-test $p = 0.1$, $I^2 = 57\%$).

Finally, subgroup analyses of the studies by Martino et al. (26) and Schouws et al. (27) revealed larger effect sizes of neuropsychological deficits in late-onset BD subjects when compared to early-onset patients (Fig. 3).

Discussion

To the best of our knowledge, this is the first study to provide a meta-analysis of the results of available reports on the cognitive performance of elderly patients with euthymic BD in order to quantify the magnitude of neuropychological deficits. Pooled standardized patient–control differences were calculated for 10 cognitive variables: global cognitive status (as assessed with two distinct but complementary widespread instruments), phonemic fluency, category fluency, delayed recall, serial learning, digit span forwards, digit span backwards, sustained attention, and cognitive flexibility. No significant patient–control differences were found for BD subjects' performance on screening tests for dementia, namely the MMSE and the CDT. However, the distribution of effect sizes was highly heterogeneous in the former analysis. Significant differences of medium magnitude were noted for category fluency, delayed recall, serial learning, digit span forwards, digit span backwards, and sustained attention. Large effect sizes were found for cognitive flexibility and phonemic fluency. Hence, on average, the cognitive performance of elderly BD subjects may be between 0.6 and 0.9 standard deviations below that of healthy subjects. Nonetheless, significant heterogeneity was found for verbal recall and serial learning meta-analyses, indicating that these overall effect sizes should be interpreted cautiously. Two studies included in this meta-analysis specifically compared the cognitive performances of both early- and late-onset BD subjects (26, 27) and noted that the latter displayed a more severely impaired neuropsychological performance, as shown in the subgroup meta-analyses. In addition, summary measures were recalculated considering, when possible, only the data corresponding to early-onset patients. When the available data from late-onset subjects were excluded, all of the mean effect sizes fell within the medium range, except cognitive flexibility, which barely reached the large range.

The findings of this meta-analysis have important clinical and theoretical implications. First, screening tools might not be sensitive enough to capture behavioral variance associated with faulty cognitive functioning in elderly BD patients, thus reinforcing the importance of utilizing an extensive neuropsychological battery for the adequate assessment of this population in daily clinical practice. Moreover, if further studies support the preliminary evidence of a relationship between cognitive deficits and functional outcome in elderly BD subjects (18, 19), neuropsychological impairments may be acknowledged as rational targets for treatment. Secondly, the findings of worse neurocognitive performance in late- compared to early-onset patients are in keeping with the proposal of including age at onset as a subtype marker of BD (52, 53) and the hypothesis of different etiological mechanisms involved in the emergence of BD symptoms in late-onset patients. In fact, research studies documented that the presence of vascular risk factors, subcortical hyperintensities, decreased cerebral blood flow, and silent cerebral infarcts is frequently associated with late-onset bipolar illness (54–57). Indeed, a study by Tamashiro et al. (58) compared structural brain differences between early- and late-onset BD subjects using magnetic resonance imaging, and documented a greater prevalence of white matter hyperintensities in the latter subgroup, thus providing evidence in support of the notion that vascular-related mechanisms may be involved in the emergence of late-onset BD. Longitudinal studies comparing structural and functional neuroimaging features and behavioral measures between early- and late-onset BD subjects could aid in the identification of subtypes associated with different prognoses. Likewise, these differences must be considered in the design of biological and therapeutic studies in elderly BD patients.

On the other hand, the findings of this meta-analysis indirectly shed light on the longitudinal course of neurocognition in BD. Previous studies have suggested that cognitive deficits may worsen with illness progression (14, 21, 22, 59) as a result of the interplay between genetic vulnerability and prolonged exposure to a number of variables, such as comorbid conditions, neurotoxicity related to acute episodes, and treatment effects. Conversely, our preliminary finding that euthymic elderly patients with BD exhibit effect sizes of impairment similar to those reported for younger patients does not appear to support the hypothesis of a progressively evolving nature of cognitive dysfunction in BD subjects. Longitudinal studies on cognitive function in BD subjects have yielded discrepant results so far. To our knowledge, there have been nine published studies addressing this issue, and only five of these focused on older adults. In a pioneering study, Dhingra and Rabins (60) used the MMSE to follow older patients for five to seven years after hospitalization for mania. They

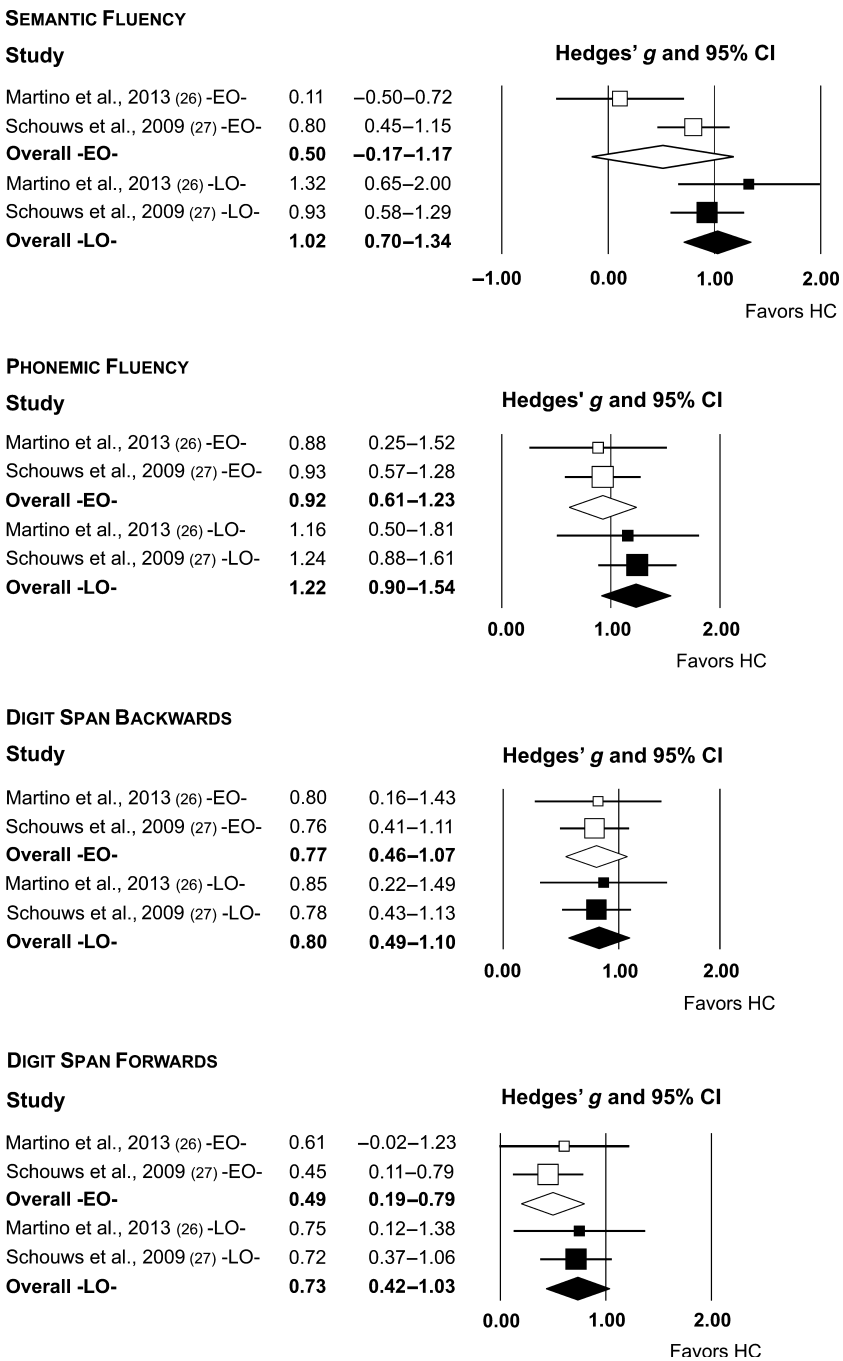

Fig. 3. Forest plots of individual and pooled effect sizes for verbal fluency (phonemic and categorical scores) and digit span (backwards and forwards) in two subgroups of elderly bipolar disorder patients: early onset (EO) and late onset (LO). The area of each square reflects weighting from random effects analysis. CI = confidence interval; HC = healthy controls.

found that eight (32%) of the 25 BD individuals included in the study experienced a decline in this test to a score below 24, indicating possible dementia. However, no control group was included. Similarly, in a study conducted by Gildengers et al. (59), 33 euthymic BD subjects underwent cognitive assessment with the Dementia Rating Scale. The authors concluded that elderly adults with BD exhibited worse cognitive function and more rapid cognitive decline than expected given their age and education. Another study conducted by Depp et al. (61) examined the short-term course of neurocognitive abilities in middle-aged and older adults with BD. They assessed 35 BD patients with a battery of neurocognitive tests, repeated once (one to three years after baseline), and compared

their performance with that of demographically matched healthy comparison subjects and patients with schizophrenia. The authors observed that BD individuals did not differ from healthy controls or patients with schizophrenia in the mean trajectory of change between time-points, but that the BD group displayed more intra-individual variability over time than either comparison group. Similarly, Delaloye et al. (41) reported that euthymic BD patients did not differ from controls in the mean trajectory of cognitive changes during a two-year follow-up period. Moreover, they documented that longitudinal gray matter and white matter changes did not differ between BD patients and controls. Finally, Schouws et al. (62) found that, although euthymic elderly BD patients had worse cognitive function than normal controls, there was no significant group-by-time interaction between the patients and the comparison group. This mixed picture of stability or decline of BD subjects' cognitive abilities in the long run may be related to the fact that elderly BD subjects are heterogeneous with respect to age at illness onset, as mentioned above. On the other hand, preliminary evidence from studies in middle-aged adults supports the hypothesis that cognitive impairments may be stable. The studies by Engelsmann et al. (63) and Balanzá-Martínez et al. (64) in middle-aged subjects showed that impairments in cognitive function were present in memory and overall cognitive function. Nevertheless, no significant decline was evident over the three to six years of follow-up. Consistent with this finding, when patients were assessed in euthymic states, Mur et al. (65) observed stable cognitive deficits in executive function and information processing speed over two years of follow-up in patients treated with lithium as their primary mood stabilizer. Moreover, a recent study by Torrent et al. (66) revealed that cognitive deficits remained stable across a follow-up period of nine years, except for a worsening of executive measures found to be associated with the duration of illness and subdepressive symptoms. However, further longitudinal studies with longer follow-up periods and controlling for potential confounders are needed to elucidate the static or progressive nature of neurocognitive dysfunction in euthymic BD.

Certain methodological characteristics of our study should be taken into account. First, since primary reports excluded patients with a clinical diagnosis of dementia, a potential selection bias may have been introduced by not including BD patients with a more severe cognitive decline. Likewise, in contrast to previous meta-analyses, which focused on BD-I (3, 4), almost all the reports reviewed in this study included mixed samples of BD-I and BD-II, which could have led to an underestimation of the overall effect sizes. For instance, the heterogeneity caused by one of the studies (50) in the MMSE analysis could be partly explained by differences in sample constitution (100% BD-I). Unfortunately, the small number of studies included in this meta-analysis prevented us from performing meta-regression analysis including the proportion of BD-I patients as a covariate. However, a recent meta-analysis concluded that, with the exception of mild differences in verbal memory and verbal fluency, cognitive impairment in BD-II is as severe as in BD-I (67). Another limitation is that, with the exception of two research reports (26, 27), the studies considered for this meta-analysis did not distinguish between early and late onset, and included subjects with a weighted mean age at illness onset of 41.1 years, thus indicating that late-onset patients were included, possibly leading to an overestimation of the effect sizes. Furthermore, the generalizability of the results is limited by the small sample of primary studies included, and the presence of heterogeneity in some of the analyses. Finally, medication variables could have influenced the results of this review. Indeed, it has been proposed that lithium may have a protective effect on the risk of cognitive decline (68, 69). This agent has been associated with neurotrophic properties in BD and in other neuropsychiatric disorders (70). By contrast, other psychotropic drugs, such as antipsychotics, might have deleterious effects on cognition (71, 72). It is worth noting that in the MMSE analysis, the study causing heterogeneity by reporting large effect sizes (50) was based on a sample in which 37% of patients were on typical antipsychotics. Unfortunately, the small number of studies included prevented us from performing meta-regression analysis to assess the possible effect of pharmacological variables on the observed effect sizes.

On the other hand, it is also noteworthy that most overall effect sizes were based on four reports (16, 19, 26, 27). However, in these investigations all of the patients included were aged 60 years or above, with a mean age of 70 years. Besides, two studies included separate information for early- and late-onset BD patients, which enabled a recalculation of overall effect sizes considering subjects mainly with very long illness duration. Unfortunately, the study by Gildengers et al. (19) did not report age at illness onset and included patients with a significantly higher level of education when compared to healthy controls. The latter issue, together with the fact that different assessment

approaches were used across the primary studies, could explain the heterogeneity observed in the serial learning analysis.

In conclusion, our study provides preliminary evidence that elderly remitted BD patients have an extent of cognitive impairment that, on average, is similar to that widely reported for young adult patients (3, 4) and may be more pronounced in those who experienced late illness onset. A number of methodologies should be integrated in order to explore these hypotheses and further elucidate the underlying mechanisms of elderly BD patients. Additionally, the possible negative impact of medication, number of mood episodes, history of psychotic symptoms, and other clinical variables on cognition deserve to be further investigated, as well as the preventative efficacy of drugs like lithium for the risk of dementia.

Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

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