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Research paper

Cognition in older age bipolar disorder: An analysis of archival data across the globe

Federica Klaus [a,b,*], Hui Xin Ng [a], Izabela G. Barbosa [c], Alexandra Beunders [d,e], Farren Briggs [f], Katherine E. Burdick [g], Annemieke Dols [h,i], Orestes Forlenza [j], Ariel Gildengers [k], Caitlin Millett [l], Benoit H. Mulsant [m], Melis Orhan [n], Tarek K. Rajji [m], Soham Rej [o], Martha Sajatovic [p], Kaylee Sarna [p], Sigfried Schouws [q], Ashley Sutherland [a,b], Antonio L. Teixeira [r,s], Joy A. Yala [p], Lisa T. Eyler [a,b], on behalf of GAGE-BD Investigators

[a] Department of Psychiatry, University of California San Diego, San Diego, CA, USA
[b] Desert-Pacific Mental Illness Research Education and Clinical Center, VA San Diego Healthcare System, San Diego, CA, USA
[c] Departamento de Psiquiatria, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
[d] GGZ inGeest Specialized Mental Health Care, Department of Old Age Psychiatry, Amsterdam, the Netherlands
[e] Amsterdam UMC, Amsterdam Public Health research institute, Amsterdam, the Netherlands
[f] Department of Public Health Sciences, Miller School of Medicine, University of Miami, Miami, FL, USA
[g] Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[h] Amsterdam UMC, Amsterdam Neuroscience, Mood, Anxiety, Psychosis, Sleep & Stress Program, Amsterdam, the Netherlands
[i] Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands
[j] Laboratory of Neuroscience (LIM-27), Department and Institute of Psychiatry, HCFMUSP, Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil
[k] Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Hospital, USA
[l] Institute of Behavioral Science, The Feinstein Institutes of Medical Research, New York, USA
[m] Department of Psychiatry, Center for Addiction & Mental Health, University of Toronto, Toronto, Canada
[n] Institute of Clinical Psychology, Leiden University, Leiden, the Netherlands
[o] Department of Psychiatry, Jewish General Hospital/Lady Davis Institute, McGill University, Montreal, Canada
[p] Case Western Reserve University School of Medicine (MS), University Hospitals Cleveland Medical Center, Cleveland, OH, USA
[q] GZZ inGeest Specialized Mental Health Care, Department of Old Age Psychiatry, Amsterdam, the Netherlands
[r] Department of Psychiatry and Behavioral Sciences, University of Texas/McGovern Medical School, Houston, TX, USA
[s] Faculdade Santa Casa BH, Belo Horizonte, Minas Gerais, Brazil

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ABSTRACT

Background: Cognitive deficits in bipolar disorder (BD) impact functioning and are main contributors to disability in older age BD (OABD). We investigated the difference between OABD and age-comparable healthy comparison (HC) participants and, among those with BD, the associations between age, global cognitive performance, symptom severity and functioning using a large, cross-sectional, archival dataset harmonized from 7 international OABD studies.

Methods: Data from the Global Aging and Geriatric Experiments in Bipolar Disorder (GAGE-BD) database, spanning various standardized measures of cognition, functioning and clinical characteristics, were analyzed. The sample included 662 euthymic to mildly symptomatic participants aged minimum 50 years (509 BD, 153 HC), able to undergo extensive cognitive testing. Linear mixed models estimated associations between diagnosis and global cognitive performance (g-score, harmonized across studies), and within OABD between g-score and severity of mania and depressive symptoms, duration of illness and lithium use and of global functioning.

Results: After adjustment for study cohort, age, gender and employment status, there was no significant difference in g-score between OABD and HC, while a significant interaction emerged between employment status and diagnostic group (better global cognition associated with working) in BD. Within OABD, better g-scores were associated with fewer manic symptoms, higher education and better functioning.

Limitations: Cross-sectional design and loss of granularity due to harmonization.

* Corresponding author at: Department of Psychiatry, University of California San Diego, 9500 Gilman Dr, La Jolla, CA 92093, USA.
E-mail address: fklaus@ucsd.edu (F. Klaus).

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Conclusion: More research is needed to understand heterogenous longitudinal patterns of cognitive change in BD and understand whether particular cognitive domains might be affected in OABD in order to develop new therapeutic efforts for cognitive dysfunction OABD.

1. Background

The population worldwide is rapidly growing older (Population Division, Department of Economic and Social Affairs; United Nations, 2015), but there is a sparsity of research about the aging process in bipolar disorder (BD), a disease with a prevalence of 1–2.5 % (Merikangas et al., 2011; Whiteford et al., 2013). The evolution of symptoms and daily functioning in BD across the life span is incompletely understood, with cognitive impairment being an important contributor to disability (Montejo et al., 2023; Sajatovic et al., 2019).

Among the most persistent symptoms of BD are cognitive deficits, especially in attention, verbal learning, and executive function (Bora et al., 2009). These deficits are main contributors to impaired clinical and functional outcomes and quality of life (Bonnín et al., 2019; Sanchez-Moreno et al., 2009) and contribute substantially to disability in Older Age Bipolar Disorder (OABD; Depp et al., 2006; Gildengers et al., 2013), with cognitive impairment being associated with lower psychosocial functioning in older adults (Montejo et al., 2022a; Paans et al., 2022). According to meta-analyses, older people with BD exhibit poor performance in memory, attention, information processing speed, verbal fluency and executive function as compared to healthy comparison (HC) participants of similar age (Montejo et al., 2022c; Samamé et al., 2013).

The severity of cognitive deficits seen in the literature among BD is mixed, which might be due to high heterogeneity within samples of people with BD (Burdick et al., 2014; Montejo et al., 2022a). Several clinical characteristics, i.e. history of mania and psychotic mood episodes, have been proposed as moderators of cognitive dysfunction in a meta-analysis of adult BD (Bora, 2018). Additionally, sex differences might contribute to cognitive performance heterogeneity in BD (Barrett et al., 2008; Carrus et al., 2010) and, as a pro-cognitive moderator, lithium has been associated with better cognitive performance, also specifically in BD patients of older age (D'Souza et al., 2011). However, findings on the relationship of disease course and clinical variables with cognition in BD are mixed (Bora and Özerdem, 2017; Van Rheenen et al., 2020).

Specifically in OABD, more years of education and higher estimated IQ were found to be associated with better cognitive functioning in some studies (Belvederi Murri et al., 2019; Montejo et al., 2022a), while another study observed poorer cognitive performance in the attention domain with increasing age in BD vs HC, and poorer cognitive performance in OABD with more manic episodes in attention and verbal memory (Montejo et al., 2022b). In contrast, a different study found that OABD had worse cognitive functioning than HC, regardless of current or recurrent mood episodes (Schouws et al., 2020).

Yet another study observed that worse cognition in OABD vs HC could not be fully explained by current depressive symptoms (Orhan et al., 2023). Longer duration of illness, more psychiatric hospitalizations, use of benzodiazepines, reduced psychosocial functioning, and less employment were demonstrated to be associated with cognitive impairment with BD in some studies of older adults specifically and among adults of all ages (Beunders et al., 2021; Gilbert and Marwaha, 2013; Montejo et al., 2022a; Paans et al., 2022). However, a meta-regression estimating the association of clinical and socio-demographic variables with cognition in OABD found history of psychosis and a lower IQ to be associated on a trend-level with lower cognitive performance, and no associations with illness duration and educational level (Montejo et al., 2022b).

Most studies in OABD have been small individual studies or meta-analyses, which have large sample sizes but can only examine associations between clinical and cognitive data at the study level; this makes it difficult to understand the relationship between measures and to detect small effects. These methodological challenges and the mixed findings from these studies highlight the need for mega-analyses using large sample sizes to investigate the relationship of cognition and clinical features in OABD specifically.

We therefore aimed to investigate the associations between cognitive functioning and clinical features in OABD using a global, integrated database: the Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD) (Sajatovic et al., 2019), which comprises data from studies of adults with BD with a specific focus on older adults >50 years, conducted by different sites worldwide. Using individual, pooled cognitive and clinical data in a mega-regression approach increases generalizability and power. This international approach aims to generate findings that are generalizable to all patients with OABD, irrespective of variations in study sites.

We first investigated among older people (>50 years) whether there were differences in global cognition between OABD and HC participants. Then, we investigated, within OABD patients, which clinical characteristics were related to poorer global cognitive performance, if a potential relationship between cognitive performance and functioning existed, and if yes, if this relationship persisted after controlling for any of the relevant clinical characteristics.

We hypothesized that 1) global cognitive performance would be lower in OABD compared to HC, that 2) within OABD, a) more severe current clinical symptoms (more mania, more depression) and longer duration of illness would be associated with poorer global cognitive performance and current lithium use would be associated with better cognitive function and that b) poorer global cognition would be associated with poorer daily functioning and the relationship would persist even when controlling for clinical characteristics, i.e. mania and depression severity, duration of illness and lithium use.

2. Methods

2.1. Study population

This is an analysis of data from a large archival set of baseline, cross-sectional, observational data on adults with BD and HCs, the GAGE-BD project. The GAGE-BD database includes pooled and harmonized international data from >1300 individuals with BD. For the current analyses, data from Wave 1 and 2 (as of March 2023) were used. Detailed information on the GAGE-BD project, sample characteristics, and metadata of contributing studies can be found elsewhere (Sajatovic et al., 2022, 2019). Datasets from individual sites were included in GAGE-BD if they contained >30 % of data from participants aged ≥50 years. Participants were included in the current analysis if they were aged ≥50 years and if data on global cognition (see below for details) was available. The term OABD refers to patients diagnosed as having bipolar disorder who are ages 50 and older. This age cutoff is recommended by the International Society for Bipolar Disorders (ISBD) Task Force on Older-Age Bipolar Disorder (Sajatovic et al., 2015) and is motivated by the fact that patients with serious mental illness, such as bipolar disorder, have a reduced life expectancy of 10–20 years (Kessing et al., 2015), and their biological age may precede their chronological age (Dols et al., 2023; Rizzo et al., 2014).

A total of 7 sites contributed to the current analyses of which 3 sites also provided HC data (Table S1). Approval to contribute data or a determination of IRB oversight exemption was obtained by each site's institutional review board or ethics committees and by the GAGE-BD

coordinating center (Case Western Reserve University School of Medicine, Cleveland, Ohio, USA). Table S3 shows the inclusion/exclusion criteria for the contributing studies.

2.2. Sociodemographic and clinical characteristics

Demographic variables (age, gender, education level, employment status) and clinical variables (depression severity, lithium use due to its pro-cognitive effects, and illness duration) were harmonized across studies (Sajatovic et al., 2022). In all contributing studies, current mania severity was measured with the Young Mania Rating Scale (YMRS) (Young et al., 1978). As current depressive symptoms were measured with the Hamilton Depression Rating Scale (HAM—D) (Hamilton, 1960), Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), or the Center for Epidemiologic Studies Depression Scale (CES—D) (Radloff, 2016) in different samples, these data were transformed into one categorical depression severity variable with three categories: 0 = No depression (HAM-D $\leq$ 7; MADRS $\leq$6; CES-D $\leq$ 15), 1 = Mild or moderate depression (HAM-D 8–23; MADRS 7–34; CES-D 16–27), and 2 = Severe depression (HAM-D $\geq$ 24; MADRS $\geq$35; CES-D $\geq$ 28) (Orhan et al., 2022). General functioning was measured with the continuous Global Assessment of Functioning (GAF) scale, ranging from 0 to 100 (best functioning) (Spitzer et al., 1992).

2.3. Global cognitive performance

The outcome variable was global cognitive performance. Given the heterogeneity between neuropsychological instruments across individual studies, the GAGE-BD project harmonized the available cognitive data for each participant into a general cognitive ability "g" score. This method has been used before and has advantages for consortium analyses, as it allows all participants with cognitive data to be included regardless of the different batteries used across sites (Burdick et al., 2019). The method is based on findings that show that an overall g-score derived from different test batteries ranks patients almost identically, as indicated by very high correlations between the g-scores derived from three different test batteries (Johnson et al., 2004).

Briefly, neuropsychological tests within each contributing study were classified based on the predominant cognitive domain tested based on the relevant literature that developed these standardized tests, and tests in the domains of speed of processing, verbal learning, non-verbal learning, verbal ability, working memory, and reasoning and problem solving were selected to contribute to the g-score (See Table S4 for the final selection of tests), similar to previous studies (Beunders et al., 2022). A minimum of one and a maximum of two tests per domain and no more than one variable from each test were included; at least three different domains were required (Burdick et al., 2019). Some tests were not selected due to a small study sample size (<10 participants per one variable). These requirements ensured a variety of domains were represented, that none was over-represented in calculation of the g-score, and that there was sufficient power for the factor analysis. For each participant, a z-score was calculated for their included test scores and these were entered into an unrotated principal component analysis (PCA) which was performed on a group and study-by-study basis. The first factor of the PCA was then used to calculate a factor score for each individual - their cognitive g-score. A negative g-score represents cognitive performance worse than average, whereas a positive g-score indicates cognitive performance above average. See Beunders et al. (2022) for more details.

The concept of a g-score is widely accepted as a measure of global cognitive ability (Neisser et al., 1996; Snyderman and Rothman, 1987) and is based on the significant covariance, or phenotypic overlap, of a number of different cognitive processes, such as memory, spatial ability and verbal ability (Plomin, 1999). In other words, an individual who performs well on a measure of spatial ability is also likely to perform well on a range of other cognitive tasks, with a large proportion of variation in ability being accounted for by g-score (Burdick et al., 2006).

2.4. Statistical analysis

All variables were examined for distributional characteristics using the Kolmogorov-Smirnov test. Descriptive statistics were conducted using *t*-tests, chi-square (χ^2), and Mann-Whitney *U* tests as appropriate. For linear mixed models, dependent variables were transformed in the whole dataset if needed to meet normality assumptions using an inverse rank normal score transformation with the Rankit method (Soloman and Sawilowsky, 2009; applicable to GAF). Linear mixed models were used with site as a random effect and age, employment status and gender were used as covariates based on differences between sites (gender, employment status) and potential age-associated effects (age) in all models.

The estimate of variance used was the standard deviation (SD). A two-sided alpha of 0.05 was considered statistically significant. Estimates of effect sizes for one-sample t-tests are given as Cohen's d and for linear mixed models as partial eta squared (partial η^2). Because of the lack of clarity in the field on how to calculate effect sizes in linear mixed models, partial η^2 was calculated using general linear models with the same parameters as the linear mixed models and site as an additional fixed effect covariate (instead of a random effect). The results did not differ between the two model approaches.

1) Linear mixed models were used with global cognitive performance as dependent variable (DV) in the whole dataset, i.e. OABD and HC, and diagnostic group as independent variable (IV) in addition to age, gender and employment status to compare global cognitive performance between diagnostic groups. To follow-up, moderating effects of site, gender, age and employment status were explored, using the respective variable*group interactions.
2) Within the OABD patient group, linear mixed models were used with **2a**) global cognitive performance as DV and clinical characteristics (i.e. education, depression severity, mania severity, duration of illness, current lithium use) as IVs in separate models, False Discovery Rate (FDR)-correction was applied; and **2b**) functioning as DV and global cognitive performance as IV. To this linear mixed model, significant clinical characteristics as found in 2a) (i.e. mania severity and years of education) were added as additional independent variables of interest. In the case of significant main or interaction effects, post hoc testing was conducted using the Bonferroni test.

3. Results

3.1. Descriptive statistics

In total, 509 OABD patients and 153 HC aged 50 or older were analyzed (Table 1). Most of the study participants with OABD were not highly symptomatic when assessed (low average YMRS total score ($\leq$ 12) and on average 5.4 % with severe depression). At the time of assessment, 95 % of OABD participants had no to moderate severity of depression (based on harmonized depression measures) and 62 % had no mania (YMRS of 12 or less). Within OABD, the mean age was 65.9 years (SD 7.7), 52.5 % were female, participants received on average 13.5 years of education (SD 3.3), 22 % were currently working, average GAF was 53.6 (SD 16.1) and 36 % were current lithium users.

3.2. Global cognitive performance

3.2.1. Group comparison of global cognition

While controlling for site, gender, age and employment, there was no significant difference in g-score between participants with OABD and HC ($F(1,132) = 2.22$, $p = .14$, *partial* $\eta^2 = 0.002$; Fig. 1). Results remained unchanged if employment status was removed from the models ($F(1,596) = 2.35$, $p = .13$, *partial* $\eta^2 = 0.005$). Also, there was

Table 1
Sample characteristics.

	Total sample		Healthy comparisons		Bipolar disorder		Group difference
	N Max 662	M (SD) or % (N)	N Max 153	M (SD) or % (N)	N Max 509	M (SD) or % (N)	Test statistic (Mann-Whitney U or Chi-square test), *p*-value
Age (in years)	662	65.9 (8.2)	153	65.9 (9.8)	509	65.9 (7.7)	U = 37,749, $p = .57$
Gender	662		153		509		
Female		45.0 % (364)		63.4 % (97)		52.5 % (267)	
Male		55.0 % (298)		36.6 % (56)		47.5 % (242)	$\chi^2 = 5.7$, **p = .02**
Education level (in years)[a]	655	13.5 (3.2)	153	13.6 (3.1)	502	13.5 (3.3)	U = 37,857, $p = .78$
Employment status	408		66		342		
Working		27.7 % (113)		59.1 % (39)		21.6 % (74)	
Not working		72.3 % (295)		40.9 % (27)		78.4 % (268)	$\chi^2 = 38.8$, **p < .001**
Global cognition (g-score)[b]	662	−0.08 (0.99)	153	−0.019 (0.98)	509	−0.043 (0.995)	U = 35,376, p = .09
Duration since start illness or BD diagnosis (in years)	–	–	–	–	472	34.6 (1489)	–
Depression severity[a]	–	–	–	–	499		–
No depression						52.7 % (263)	
Mild to moderate depression						41.9 % (209)	
Severe depression						5.4 % (27)	
Manic symptoms (YMRS)	–	–	–	–	499	10.8 (12.0)	–
Euthymic state	–		–	–	492		–
Yes						40 % (198)	
No						60 % (294)	
Lithium use (current)	–	–	–	–	509		–
Yes						35.6 % (181)	
No						64.4 % (328)	
Global functioning (GAF-score)	–	–	–	–	344	53.6 (16.1)	–

Notes: M = mean; SD = standard deviation; BD = bipolar disorder; CES-D = Center for Epidemiologic Studies Depression Scale; GAF = Global Assessment of Functioning; HAMD = Hamilton Depression Rating Scale; MDRS = Montgomery-Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale. Values in bold indicate statistical significance (p<0.05).

[a] The depression severity band was harmonized from MDRS, HAMD, and CES-D, see text for cut-offs.

[b] Cognitive g-score: a continuous z-score scaling metric, see text for procedure.

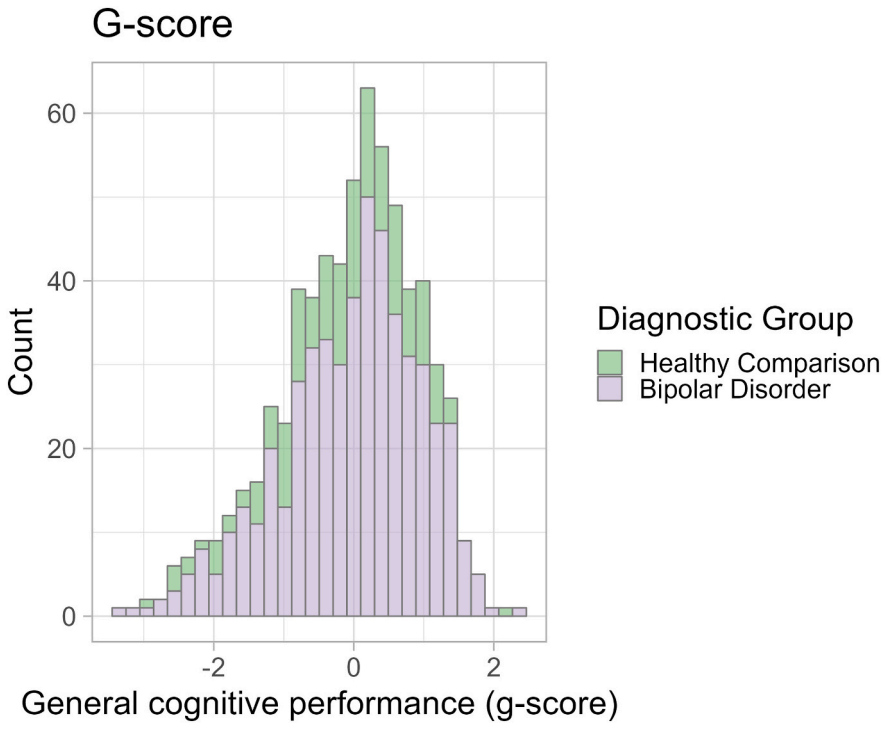

Fig. 1. Distribution of general cognitive performance (g-score) in OABD and healthy comparison participants of comparable age.

still no significant difference in global cognition between participants with OABD and HC in a model that only controlled for site ($F(1,172) = 0.62$, $p = .43$).

To follow-up on the absence of overall group differences in global cognition between HC and OABD, we added a site*group interaction to the model to investigate potential moderating effects of different study sites, which revealed no interaction effect ($F(1,398) = 1.31$, $p = .29$, *partial* $\eta^2 = 0.04$). Further, no interaction of group with gender (F

(1,398) = 2.9, $p = .09$, *partial* $\eta^2 = 0.002$) or age (F(1,380) < 0.0001, $p = .998$, *partial* $\eta^2 = 0.001$) was present. A significant interaction of employment status with group (F(1,398) = 4.1, $p = .04$, *partial* $\eta^2 = 0.001$) revealed group differences in cognition among those who were employed, with lower g-scores for HC than OABD, but no significant group differences among those who were unemployed (Supplementary Fig. S1).

3.2.2. Predictors of global cognition among older adults with bipolar disorder

When controlling for age, gender and employment status, there was no statistically-significant association of global cognition with depression severity (F(2,314) = 0.62, $p = .54$, *partial* $\eta^2 = 0.003$), duration of illness (F(1,299) = 0.02, $p = .88$, *partial* $\eta^2 = 0.0002$) or current lithium use (F(1,325) = 0.06 $p = .81$, *partial* $\eta^2 = 0.001$). Better global cognition was associated with fewer manic symptoms (F(1,175) = 5.96, $p = .02$, FDR adj. p = .04 *partial* $\eta^2 = 0.023$), and more years of education (F(1,330) = 10.4, $p \leq 0.001$, FDR adj. $p = .005$, *partial* $\eta^2 = 0.104$); both results remained significant after correction for multiple comparisons.

These results remain unchanged if removing employment status from the model, except for the significant effect of manic symptoms being reduced to trend-level (F(1,160) = 3.4, $p = .066$).

3.2.3. Global cognition as a predictor of functioning among older adults with bipolar disorder

In a model that included mania severity and years of education, due to their observed small to medium associations with global cognition, a significant association of better global cognition with better functioning was observed (F(1,315) = 10.7, $p = .001$, *partial* $\eta^2 = 0.03$), and similar results were observed when not including mania severity and education level in the model (F(1,39) = 18.71, $p < .001$, *partial* $\eta^2 = 0.06$).

These results remained unchanged if employment status was removed from the model.

4. Discussion

The overall objective of this project was to contribute to improved personalized diagnostic and treatment options, such as cognitive rehabilitation or pro-cognitive treatments for patients with BD across the life span from diverse regions with a focus on cognitive impairment, as understanding which factors might be impacting overall cognitive performance and functioning could identify those most at risk with the possibility of early intervention to mitigate long-term challenges.

4.1. Global cognition between older adults with and without BD

In contrast to our initial hypothesis and the literature on cognition in BD (Bora et al., 2009), we found no group differences in global cognition between HC and OABD. Our mega-analytic results are also in contrast to a previous meta-analysis which found consistently worse cognitive performance in OABD compared to healthy comparison participants across studies (Montejo et al., 2022b). This finding might be due to the fact that our sample included people who were not highly symptomatic and that those participants with BD who were able to participate in research studies at an older age might be those who are in a better general state of health. Further, these findings could be explained by the presence of cognitive subgroups within OABD, leading to cognitive heterogeneity (Montejo et al., 2022a). We used data from 7 different studies with varying inclusion and exclusion criteria, and it could be that our samples contained more high-ability OABD subgroups compared to other samples analyzed in the literature. Relatedly, since only 3 studies contributed HC data, it could be that those comparison participants had lower cognitive ability levels compared to HC groups in the previous literature. The covariates that we controlled for may have differed from those used in other studies, although we still observed no difference in g-score using simplified models without most covariates. It is also possible that our failure to observe cognitive performance deficits in OABD was due to our use of the g-score as our measure of global cognitive ability. While derived from individual tests that have shown deficits in previous OABD studies, the g-score is measuring the "common denominator" across these tests which might reflect more stable, trait-like cognitive abilities (Kremen et al., 2023). The g-score may have removed some variance in cognitive performance due to state factors, such as anxiety and sleep disturbances (Giannouli, 2017), that would normally lead to findings of poorer performance among OABD. In an examination of whether there were any subgroups of OABD that did show worse global ability than age-matched HC, we surprisingly found that, among employed people, OABD had *higher* g-scores than healthy comparison participants, while g-score was comparable between OABD and HC among unemployed people. This could be because an additional cognitive capacity is needed for employed OABD to remain working due to disease-related symptoms while this is not the case for employed HC. We were not able to distinguish between reasons for unemployment in our integrated dataset. Still, this finding suggests that OABD who maintain employment into middle and late life may do so because they have relatively preserved global cognitive ability (Montejo et al., 2022b).

4.2. Predictors of global cognition in OABD

Based on previous findings from the literature in adult BD, we expected to observe a relationship of education, depression and mania severity, and lithium use with global cognition (Belvederi Murri et al., 2019; Gilbert and Marwaha, 2013; Montejo et al., 2022a). We observed a significant relationship of worse global cognition with more severe mania, but not depression, scores, a finding that became non-significant once employment status was removed from the model. This finding could be due to concurrent mania symptoms, including impulsivity and inattention, potentially interfering with global cognitive performance. However, our sample had relatively low levels of mania severity, and the g-score, as mentioned above, should be relatively insensitive to state factors. A previous study in OABD found no difference in cognition between hypomanic, depressed and euthymic patients, but observed that, during a mood episode, patients exhibited worse cognitive performance compared to their performance when in an euthymic state (Schouws et al., 2020), while another study observed lower global cognition in OABD with mania vs HC while no association of mania severity with cognitive performance was found (Young et al., 2006). Differences might arise from differences in inclusion criteria (e.g., mania score cut off levels) and from within- vs between-subject analyses. Although we did not have data on number of manic episodes, those with greater current mania may have had a more severe history of manic episodes, as indirectly suggested by the association of number of mood episodes with worse clinical characteristics, such as likelihood of hospitalizations and suicide attempts (Peters et al., 2016). A higher number of mood episodes and hospitalizations have been associated with reduced cognitive ability (Beunders et al., 2021; Denicoff et al., 1999; Montejo et al., 2022b), although we lacked the ability to test this directly in the integrated dataset.

The presence of a relationship between global cognition and education, is inconsistent with a recent meta-regression in OABD, which found no associations of cognition with educational level (Montejo et al., 2022b). Our mega-analysis may be more sensitive to this relationship as it is testing associations at the individual, not study, level. More years of education could be related to better test-taking ability and more use of strategies, which could then be reflected in the g-score. Like the meta-regression (Montejo et al., 2022b), we also did not see a relationship of illness duration to cognitive ability. Although lithium use sometimes is found to be beneficial for cognition, in this OABD sample, whether or not lithium is used may be related more to cognitively-independent aspects of the patient's clinical condition and compliance that influence prescribing patterns (Shulman, 2010).

4.3. Global cognition as a predictor of functioning in OABD

Consistent with our hypothesis based on the literature (Montejo et al., 2022a), we observed that OABD with better global cognitive ability also had better everyday functioning and this held with or without accounting for mania symptom severity. This suggests that cognition could be an independent treatment target in OABD which, if improved, could result in better quality of life for people living and aging with the disorder.

4.4. Strength and limitations

Limitations of this study are the loss of granularity due to the harmonization of data as a trade-off when pooling already-collected data from multiple sources. While the g-score is not specific to a single cognitive domain, it allows us to combine datasets that could otherwise not be analyzed together, significantly increasing sample size and power which is a major strength of our study. The g-score captures a large range of global cognitive abilities suited for this project's aim to investigate the association of age with cognition and the potential contributors to this relationship, irrespective of differences in g-score between HC and BD. As it combines across multiple cognitive domains, use of the g-score could disguise areas of relative strength or relative weakness that cancel each other out. Future work with commonly administered tests of single domains that could be harmonized across large samples or collected prospectively (Lavin et al., 2023) are needed. Further, while we have controlled for site effects in all analyses, it must be noted that the comparison sample was derived from only 3 sites, based on availability of data. An additional potential limitation is that different g-scores derived from different sites might capture slightly different cognitive constructs. Further, the comparison groups did not undergo a clinical interview, assessing e.g. depressive symptoms in detail. An additional limitation is the use of GAF as a measurement of functioning, which, while often used to assess functioning, is not specific for OABD (Tyler et al., 2022), but provided the most data for harmonization in our dataset. While the international nature of our dataset should enhance generalizability, it also increases sample heterogeneity which could make it more difficult to detect differences. Because of meta-data differences between contributing studies, including differing inclusion and exclusion criteria, site was controlled for in all analyses.

Lastly, our study is cross-sectional and future studies will have to focus on longitudinal assessments to draw conclusions on causal relationships between predictors and moderators of age-associated cognitive performance in OABD.

5. Conclusion

To conclude, we observed no overall evidence of lower global cognitive ability in OABD compared to older people without BD, and, in fact, OABD who were employed showed *better* global cognitive ability than those without BD who were employed. Within OABD, better g-scores were associated with fewer manic symptoms, higher education and better functioning. These findings have implications for the development of new personalized prevention efforts and treatments for cognitive dysfunction and associated clinical outcome in BD. The absence of age interaction effects suggests that the cognitive trajectory in OABD is not steeper than that seen in healthy aging with the implication to clinical practice that decline in global cognition in OABD patients might be due to other causes. Small cognitive declines might likely be due to BD-unrelated aging processes, for which the regular prevention for neurocognitive disorder (e.g., smoking cessation, decreased cardiovascular risk, socialization, physical and intellectual activities, prevention/treatment of mood episodes and reduction of polypharmacy) can be recommended. Future work should focus on investigating cognitive domains and how the patterns across domains differ between participant groups, especially in longitudinal studies across the lifespan, which could avoid an overrepresentation of cognitively high-functioning participants with BD in later stages of life. Such research will help to design specific, personalized cognitive pharmacological and non-pharmacological treatments in subgroups of patients who would benefit specifically from disease-modifying effects.

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CRediT authorship contribution statement

Federica Klaus: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Hui Xin Ng:** Data curation, Writing – review & editing. **Izabela G. Barbosa:** Data curation, Writing – review & editing. **Alexandra Beunders:** Data curation, Writing – review & editing. **Farren Briggs:** Methodology, Writing – review & editing. **Katherine E. Burdick:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Annemieke Dols:** Conceptualization, Data curation, Writing – review & editing. **Orestes Forlenza:** Conceptualization, Data curation, Writing – review & editing. **Ariel Gildengers:** Data curation, Writing – review & editing. **Caitlin Millett:** Writing – review & editing. **Benoit H. Mulsant:** Conceptualization, Data curation, Writing – review & editing. **Melis Orhan:** Writing – review & editing. **Tarek K. Rajji:** Conceptualization, Data curation. **Soham Rej:** Conceptualization, Writing – review & editing. **Martha Sajatovic:** Conceptualization, Data curation, Writing – review & editing. **Kaylee Sarna:** Data curation, Methodology. **Sigfried Schouws:** Data curation, Writing – review & editing. **Ashley Sutherland:** Data curation, Writing – review & editing. **Antonio L. Teixeira:** Data curation, Writing – review & editing. **Joy A. Yala:** Data curation. **Lisa T. Eyler:** Conceptualization, Data curation, Writing – review & editing.

Declaration of competing interest

FK reports no conflict of interest.

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Data availability statement

Data are available as part of the GAGE- BD project and subject to the completion of appropriate data use agreements. Qualified scientists who wish to access the data should contact the study lead author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.03.126.

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