Predictors of Functional Impairment in Bipolar Disorder: Results from 13 Cohorts from Seven Countries by The Global Bipolar Cohort Collaborative

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Abstract

Objectives: Persistent functional impairment is common in bipolar disorder (BD) and is influenced by a number of demographic, clinical, and cognitive features. The goal of this project was to estimate and compare the influence of key factors on community function in multiple cohorts of well-characterized samples of individuals with BD.

Methods: Thirteen cohorts from 7 countries included n=5,882 individuals with BD across multiple sites. The statistical approach consisted of a systematic uniform application of analyses across sites. Each site performed a logistic regression analysis with empirically derived "higher versus lower function" as the dependent variable and selected clinical and demographic variables as predictors.

Results: We found high rates of functional impairment, ranging from 41–75%. Lower community functioning was associated with depressive symptoms in 10 of 12 of the cohorts that included this variable in the analysis. Lower levels of education, a greater number of prior mood episodes, presence of a comorbid substance use disorder, and a greater total number of psychotropic medications were also associated with low functioning.

Conclusions: The bipolar clinical research community is poised to work together to characterize the multi-dimensional contributors to impairment and address the barriers that impede patients' complete recovery. We must also identify the core features which enable many to thrive and live successfully with BD. A large-scale, worldwide, prospective longitudinal study focused squarely on BD and its heterogeneous presentations will serve as a platform for discovery and promote major advances toward optimizing outcomes for every individual with this illness.

Introduction

Bipolar disorder (BD) is one of the most impairing mental health conditions worldwide[1]. A meta-analysis by Léda-Rêgo (2020) focused on community function in BD, as measured by the Functional Assessment Short Test (FAST) indicated that 65.6% of people with euthymic BD experience work-related impairment (e.g., unable to maintain a job and reduced efficiency performing tasks). The same study reported that 49.2% of patients had cognitive impairments on the FAST (e.g., difficulty in concentrating, performing mental calculations and solving problems), 42.6% had impairments on autonomy, and 42.1% reported impairment in maintaining interpersonal relationships.

The BD-related factors that contribute to functional impairment are not fully understood but include: primary affective symptoms, both syndromal and subsyndromal[2], high rates of comorbid psychiatric[3] and medical disorders[4–6], substance misuse[7], sleep quality deficits[8], and cognitive impairment (deficits in attention, memory and executive functioning)[9], among other factors. An enhanced understanding of the key predictors of functional impairment in

individuals with BD would chart a clearer path to interventions that promote full recovery for every individual.

The field has embraced a mandate to improve the lives of individuals suffering from this disease; many challenges and hurdles impede progress, yet offer opportunities to deepen the knowledge base behind this complex disorder: 1) *BD is heterogeneous*. This contributes to a high rate of partial treatment response, and in many individuals, treatment resistance. This heterogeneity has also confounded our ability to identify pathophysiological mechanisms that drive disease, and limited the development of novel, more effective treatments. Heterogeneity in BD exists at the level of diagnosis, stage, clinical profile and course, cognitive capacity[10–12] and everyday functioning[13]; 2) *BD is a highly comorbid disease.* As noted above, common mental health conditions (e.g. substance use disorders, personality disorder, anxiety disorders) and environmental influences (e.g. lifestyle risks, early life exposure to trauma) add to the complexity of illness presentation and comorbid chronic cardiometabolic conditions[14] lead to a shortened life span[15]. While there may be risk factors that are shared among all individuals diagnosed with BD, each patient has a unique combination that complicates the illness trajectory and related outcomes; 3) *BD is a dynamic illness*. After diagnosis, the average BD patient is symptomatic 50% of the time with changes in symptom status approximately 6 times/year, and switches in polarity about 3 times/year[16–19]. Few longitudinal studies of representative first-episode cohorts have been conducted and thus that our knowledge about the course of BD is still limited. Alongside the episodic mood state changes that define the illness are impairments in sleep, cognitive capacity, substance use, motivation, and energy. There are intermittent stressors in social support systems and socio-economic health. There is evidence of cumulative burden of illness recurrence, with effects on the brain (e.g., grey matter abnormalities, cognitive decline)[20–22] that contribute to the high rates of functional impairment in individuals with BD. There are also indications of improvement in cognitive function after the first manic episode in those who do not relapse[23]; 4) Finally, beyond challenges inherent to the illness and its care, *resources for BD research remain insufficient*. Research focused on individuals with BD has consistently been, and remains, underfunded relative to other serious psychiatric disorders[24], despite the exceptionally high rates of disability and societal costs. Splitting of existing funds across smaller and shorter cohort studies[25] that are generally underpowered to examine the clinical variability inhibits our ability to truly parse the dynamics of illness course. This has wide ranging implications that include the support for ongoing research and the challenges of attracting early career researchers to the field, all of which contribute to the slow pace at which new discoveries are made.

The recent progress in the field has been largely due to collaborative efforts of prescient researchers with a shared vision. A better, albeit very much incomplete, understanding of the underlying genetic architecture of BD has been mustered through massive data sharing efforts. Genotype data from tens of thousands of individuals with BD have been merged in a common platform for genome-wide association studies through the Psychiatric Genomics Consortium, and replicable risk loci have successfully been identified[26]. The collective energy of the ENIGMA neuroimaging consortium further exemplifies a highly collaborative international network which has made major contributions to the knowledge of the neurobiology of the disorder. Cognitive impairment, previously considered more relevant

to schizophrenia, is now known to be a core component of BD[22], and a key contributor to the noted functional disability[1,27]. This has led to efforts in BD to target cognition with specific treatment[28]. Finally, more recent collaborative studies have begun to elucidate biological mechanisms that drive the disease, including evidence from neuroimaging paradigms, immune biomarkers, and epigenetics. Inducible pluripotent stem cells and other cutting-edge methodologies are now being applied in BD. It is an exciting time in the field, but more coordinated efforts are needed if we are to gain a full understanding of this highly complex and disabling condition.

The primary goal of the current study was to pool resources from multiple international groups in a capacity building exercise to define the current state of collaborative research opportunities and identify the barriers that need to be lifted to realize a common vision that includes optimal outcomes for every single person living with BD. With a common mission, an international group of investigators leveraged the added value from combining existing BD data to investigate core predictors of functional outcome, independent of treatment organization or societal differences. The present work, as well as our continued collaboration, will allow for us to disentangle core bipolar disorder features from secondary phenomena which is not possible in small, one-site studies. Ultimately, we plan to launch a worldwide prospective longitudinal study of BD to more rapidly advance progress via large-scale collaborations.

Methods

Participants:

Initially, 11 groups were identified via ongoing collaborative relationships. These groups do not represent all ongoing BD research worldwide, rather a starting point and an outline of an iterative process. There are many investigators worldwide conducting high quality BD research in cohorts of variable sizes. As is illustrated in Table 1, thirteen independent BD cohorts are included, with two sites contributing 2 cohorts (Mass General Hospital, MGH; and King's College London, KCL) and two cohorts representing consortium-based samples that were collected at multiple different sites (FondaMental Advanced Centers of Expertise for Bipolar Disorder, (FACE-BD, Fondation FondaMental, France[29]) and Global Aging and Geriatric Experiments in Bipolar Disorder, GAGE-BD[30]). Each of the other 7 sites contributed data from a single cohort.

Measures:

The approach was planned as purposefully simplistic with a focus on one question via systematic uniform application of analyses across sites. Because the existing data at each site are highly variable, we allowed for substantial flexibility in the measures that were included from each site. First, each site was asked to empirically identify how they defined "high versus low functioning" in their BD cohort. This was kept purposefully coarse in its definition, as some sites use detailed questionnaires (e.g., WHO Disability Adjustment Schedule (DAS)[31], Work and Social Adjustment Scale[32], Functional Assessment Short Test (FAST)[33] etc.), while others may only have documented employment status, or some other high-level indicator of everyday functionality. Sites were required to dichotomize whatever

measure was chosen for defining function in their study, such that individuals with BD were described as having either higher or lower functional status. The way in which the variable was dichotomized was also up to the investigator, based upon the measure used at each site (e.g., some scales have recognized cutoffs, some used median splits, etc.), and are defined in Table 1.

Each site was then asked to provide detailed characteristics on their cohort(s), including demographics, diagnostic, clinical, cognitive, and functional features in the format of Table 2. Each site provided results from a Shapiro-Wilk statistical test for normality (for relevant variables), where a $p < 0.05$ indicated non-normal distribution.

Participating sites were not required to have all of the variables described in Table 2. Only "level one" measures were required. For those sites with cognitive data, we included a composite of general cognitive ability (g) (see below for derivation of g) and a premorbid estimate of IQ (typically a reading-based task).

The listing of the variables available at each site were reviewed by the first and second authors (KEB; CEM) and recommendations were made as to which variables should be included in the regression model at each site. This decision was based upon considerations of statistical power (e.g., the sample size at each site) and the validity of the data collected for each variable. After a consensus was achieved, sites were instructed to conduct a logistic regression with functional outcome as the dependent variable (dichotomized as higher versus lower global functioning) using the entry method while model-level and predictor-level results were collated. Example analysis scripts and instructions were provided to each participating site for consistency and checked upon completion. These are provided in the supplemental materials.

Analyses:

In preparation for collating results, each site coded dichotomous variables as 0 or 1 (yes) to allow for uniform interpretation of results and to label variables in English. Any site that had cognitive data from at least 3 different cognitive domains was instructed to derive a general cognitive ability index "g" using an unrotated principal components analysis (PCA) with up to two representative measures per cognitive domain. Estimates of g can be reliably derived with only 3 measures provided that they assay different domains and the measure is stable across different datasets regardless of the measures included in analyses[34]. Sites were instructed to select one or more tests within a purported 'domain' as most representative of that domain, allowing for more than one test per domain (e.g. 'attention') if available, provided they did not violate the 10:1 ratio rule (10 participants per one variable). Next, they were asked to select the "best" or most representative item-level variable from each test to be included in the analysis (only one per test). These variables were standardized on a z-score scale using the mean and standard deviation from their own BD sample (within-sample normalization). Finally, an unrotated PCA was conducted to include factors with eigenvalues > 1.0 and component 1 was defined as g. Individual scores for each g factor for each patient were analyzed by logistic regression.

The results of each site's logistic regression were then compared descriptively side-by-side, i.e., the results were not *directly* combined as each site had different predictors/definitions of outcome. The goal herein was to find consistencies across samples and to identify where differences exist by individual site. Thus, meta-analyses were not conducted, rather a multiple cohort replication and expansion approach was used.

Results

In total, analyses included 5,882 individuals with a diagnosis of BD. Each site was different with regard to sample characteristics and measures included. These individual cohort descriptives are presented by site in Supplemental Table 1.

The prevalence of *a priori* defined "lower" functioning across sites ranged from 41–75% (Figure 1). Although different measures were used at nearly every site, each of which had had different ascertainment criteria and target populations ranging from population-based through to tertiary referral centers, these estimates are consistent with prior literature reporting high rates of lower functioning or impairment in BD.

Regression results by site are presented in detail in Supplemental Table 2. The differences in the regression results at each site likely reflect differences in the sample characteristics, sample size, and the measures used at each site.

Table 3 illustrates the frequency at which each of the measures contributed at a statistically-significant or trend level to the regression models predicting outcome (e.g., how many sites reported any given factor as significant in their regression model). There are several findings that are consistent across sites, and some that are relatively site-specific. The most commonly reported finding was that depressive symptoms (even subthreshold symptoms) were the strongest predictor of lower community functioning (10/12 sites reported). Severel additional factors that were noted as significant or trend level predictors of lower function across at least 25% of the sites reporting on that factor included: 1) Lower levels of education; 2) Greater number of prior manic episodes; 3) Greater number of prior depressive episodes; 4) Comorbid substance use; 5) Comorbid anxiety disorders; and 6) Greater of total number of psychotropic medications. We include a detailed discussion below on any factor that was found to be significant or trend-level significant (p   0.10) in at least 25% of the sites reporting on that measure.

Discussion

The current study set out to measure the influence of key demographic, clinical, and cognitive factors on community function in multiple international cohorts of well-characterized populations with BD (n=5,882) and to collate and compare results. The study design was intentionally inclusive, allowing sites to contribute results regardless of the specific measures used to assess mood, disability, and other illness features. As such, and for other practical reasons, we did not combine *data* across cohorts, but used a distributed data analyses framework. This approach has inherent limitations, but served as an opportunity to pool resources from multiple international groups, *as a necessary first step in building the*

field-wide capacity for a scalable global initiative and to define the current state of the field, recognizing that more cohorts are available that were not included in this project.

First, our results are consistent with prior reports of high rates of functional impairment in individuals diagnosed with BD. This is consistent with a multitude of single-site studies as well as a recent meta-analysis of 13 studies that reported prevalence rates of functional impairment in several domains using the FAST (global, 58.6%; occupational, 65.6%; cognitive, 49.2%; autonomy, 42.6%; interpersonal relationships, 42.1%; leisure, 29.2%; and financial issues, 28.8%)[27]. The range of functional impairment that we report here is broad; being dependent upon site-specific sample characteristics as well as the granularity of the measure used to assess function. Still, these data capture the pressing need to assess everyday functioning in BD and to consider interventions that aggressively target those illness features that contribute to disability in hopes of promoting full recovery.

Second, across the majority of our cohorts, our results were consistent with prior reports showing the critical role that depressive symptoms play in functional status. Of the 12 cohorts where depression was examined (one site, Mayo Clinic, did not include current mood symptoms in the regression due to a loss of sample size), 10 report that the severity of depression symptoms present at the time of assessment significantly contributed to low functional status. Consistent with prior work[1,27] this points to the consistent and deleterious effects of depressive symptoms on how people with BD function in their daily lives, and further emphasizes the need for treatment beyond the acute phase of the illness to include the low-grade persistent affective symptoms that are common even in "remitted" individuals.

Third, additional factors that were significant predictors of lower function across at least 25% of the sites reporting on that feature included: 1) Lower levels of education; 2) Greater number of prior manic episodes; 3) Greater number of prior depressive episodes; 4) Comorbid substance use; 5) Comorbid anxiety disorders; and 6) Greater of total number of psychotropic medications. Each of these premorbid and illness-related factors has been previously reported as contributing to poor outcomes[1,27].

With regard to medication, several sites were able to evaluate the effects of the use of a specific medication classese in their cohort (including lithium, anticonvulsants, antidepressants, antipsychotics, and benzodiazepines); however, we did not examine polypharmacy, which is highly prevalent in BD. Further, we did not explicitly ask for timing and length of treatment with each medication class. One site reported that lithium use was associated with better community functioning, consistent with a recent report of benefits to cognition[35]; while other medication classes showed negative effects (anticonvulsants and antipsychotics) on broad community functioning. These effects may be related to the medications themselves or the patient characteristics that are associated with the use of certain medications but are concordant with historical and emergent data on the primacy of lithium for bipolar disorder[36]. Of note, we cannot rule out the possibility that those taking anticonvulsants and antipsychotics were initial lithium non-responders (i.e., these individuals would have a poor outcome regardless)—more granular, time-course data is necessary to tease apart the subtleties in medication usage and outcomes.

Measures of cognitive function were of great interest to us, as many studies have reported a relationship between cognitive impairment and psychosocial impairment in BD[9,37]; however, only 6 of the sites had cognitive data available for inclusion in the prediction models. Somewhat surprisingly, only 1 site found cognitive impairment was a significant predictor of lower function. This may be due to cohort characteristic differences by site, differences in the cognitive tasks included at each site, relatively small sample sizes of some cohorts or different functional outcome measures. Indeed, since the cognitive batteries did not overlap completely, we opted to calculate a general cognitive ability (g) index using factor analyses to capture a single measure of global cognition that has been shown to be stable and valid regardless of the tasks included in the factor analysis[34]. As a result, we sacrificed potentially relevant granularity in our measurement, as we were unable to look at deficits in specific cognitive domains (e.g., attention, memory, executive function) as potential predictors of functioning. Often used as a proxy of intellectual capacity, educational attainment was found to be a significant predictor of lower functioning in 25% of the sites who collected that information, notwithstanding that education is also a proxy of other variables such as socio-economic advantage or disadvantage.

There are several limitations to this study. Whilst we were able to convene a large team of collaborators, we did not directly combine data; therefore, the limitations that apply to single-site data (e.g. limited sample sizes) still apply here. Moreover, there are a number of additional factors that contribute to community functioning in BD beyond what we were able to capture, including financial and social support, among others. We acknowledge that the planned analyses across cohorts using the identicial analytic methods inherently reduced the granularity that could be achieved if any single site attempted to address the same question independently (e.g., by dichotomizing the functional measure). This indeed was part of the exercise and illustrates the need for a unified protocol to be adopted for future prospective studies.

Our findings are consistent with a convergent body of literature on functional impairment in BD. However, the primary purpose of this study was to demonstrate the value of large-scale collaborative networks in order to provide a snapshot of the BD global research landscape, and to highlight the current barriers to move beyond typical within-cohort analytic frameworks in order to advance progress in BD research and care. While we provide data and results from parallel analyses across cohorts, this manuscript is, in many ways, a perspective piece that serves as a call to arms. Specifically, the information gathered emphasizes several necessary next steps: 1) We need large samples, that reach beyond single sites and encompass the full spectrum of diversity within this heterogeneous condition, taking geographic, cultural and societal aspects into account. It is critical to include participants from non-European ancestries, to address the global impact of BD, which were not included in these analyses. Existing consortia have been fruitful and highly successful (e.g., Psychiatric Genomics Consortium, ENIGMA) but are inherently limited for fine-grained analysis, typically only including relatively superficial clinical phenotype data, allowing for limited to no follow-up over time. 2) We need comprehensive and integrated phenotyping with standardized measures which allow for data sharing and harmonization across studies. Many individual investigators are successful at collecting well-characterized cohorts but sample size is inherently limited at any single site and merging of data across

sites is difficult because measures are not uniform, preventing more optimal meta- or mega-analyses. 3) Long-term, repeated assessment of clinical, cognitive, and functional measures alongside key biomarkers (e.g., genetic, immune, imaging, digital) is necessary if we are to unravel the complexity of this illness. There are several longitudinal studies that are ongoing around the world, but the duration and frequency of follow-up is both limited and variable, usually due to funding constraints, and protocols are not uniform across sites. 4) A centralized coordinating center to direct the complex infrastructure of a global research effort (e.g., compliance/human subjects oversight, data use and sharing agreements, and database management). We propose the imminent and urgent need for a carefully designed, well-resourced, prospective global longitudinal study of BD that will allow the necessary methods to be applied in order to make game-changing discoveries and substantive improvements to the lives of individuals living with BD.

Data sharing: Deidentified data that underlie the results reported in this Article will be made available upon reasonable request to the PI at the relevant organizing institution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Disclosures:

References

1. Sanchez-Moreno J, Martinez-Aran A, Tabares-Seisdedos R, Torrent C, Vieta E, Ayuso-Mateos JL. Functioning and disability in bipolar disorder: an extensive review. Psychother Psychosom. 2009;78(5):285–297. [PubMed: 19602917]

2. Altshuler LL, Post MR, Black OD, et al. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. The Journal of clinical psychiatry. 2006;67(10):1551–1560. [PubMed: 17107246]

3. Nabavi B, Mitchell AJ, Nutt D. A Lifetime Prevalence of Comorbidity Between Bipolar Affective Disorder and Anxiety Disorders: A Meta-analysis of 52 Interview-based Studies of Psychiatric Population. EBioMedicine. 2015;2(10):1405–1419. [PubMed: 26629535]

4. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: A Swedish national cohort study. JAMA Psychiatry. 2013;70(9):931–939. [PubMed: 23863861]

5. Carney CP, Jones LE. Medical comorbidity in women and men with bipolar disorders: A population-based controlled study. Psychosomatic Medicine. 2006;68(5):684–691. [PubMed: 17012521]

6. Fornaro M, Solmi M, Veronese N, et al. The burden of mood-disorder/cerebrovascular disease comorbidity: essential neurobiology, psychopharmacology, and physical activity interventions. In. Vol 29: Taylor and Francis Ltd; 2017:425–435.

7. Cerullo MA, Strakowski SM. The prevalence and significance of substance use disorders in bipolar type I and II disorder. In. Vol 2: BioMed Central; 2007:29–29.

8. Ng TH, Chung KF, Ho FYY, Yeung WF, Yung KP, Lam TH. Sleep-wake disturbance in interepisode bipolar disorder and high-risk individuals: A systematic review and meta-analysis. In. Vol 20: W.B. Saunders Ltd; 2015:46–58.

9. Depp CA, Mausbach BT, Harmell AL, et al. Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. Bipolar disorders. 2012;14(3):217–226. [PubMed: 22548895]

10. Burdick KE, Russo M, Frangou S, et al. Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. Psychol Med. 2014;44(14):3083–3096. [PubMed: 25065409]

11. Martino DJ, Strejilevich SA, Scápola M, et al. Heterogeneity in cognitive functioning among patients with bipolar disorder. Journal of Affective Disorders. 2008;109(1–2):149–156. [PubMed: 18234352]

12. Green MJ, Girshkin L, Kremerskothen K, Watkeys O, Quidé Y. A Systematic Review of Studies Reporting Data-Driven Cognitive Subtypes across the Psychosis Spectrum. In. Vol 30: Springer; 2020:446–460.

13. Solé B, Bonnin CM, Jiménez E, et al. Heterogeneity of functional outcomes in patients with bipolar disorder: a cluster-analytic approach. Acta Psychiatr Scand. 2018;137(6):516–527. [PubMed: 29508379]

14. Momen NC, Plana-Ripoll O, Agerbo E, et al. Association between Mental Disorders and Subsequent Medical Conditions. New England Journal of Medicine. 2020;382(18):1721–1731. [PubMed: 32348643]

15. Wahlbeck K, Westman J, Nordentoft M, Gissler M, Laursen TM. Outcomes of Nordic mental health systems: Life expectancy of patients with mental disorders. British Journal of Psychiatry. 2011;199(6):453–458.

16. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry. 2003;60(3):261–269. [PubMed: 12622659]

17. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002;59(6):530–537. [PubMed: 12044195]

18. Altshuler LL, Kupka RW, Hellemann G, et al. Gender and depressive symptoms in 711 patients with bipolar disorder evaluated prospectively in the Stanley Foundation bipolar treatment outcome network. Am J Psychiatry. 2010;167(6):708–715. [PubMed: 20231325]

19. Gignac A, McGirr A, Lam R, Yatham L. Recovery and recurrence following a first episode of mania: a systematic review and meta-analysis of prospectively characterized cohorts. The Journal of clinical psychiatry. 2015;76(9):1241–1248. [PubMed: 25845021]

20. Kessing LV, Andersen PK. Evidence for clinical progression of unipolar and bipolar disorders. Acta psychiatrica Scandinavica. 2017;135(1):51–64. [PubMed: 27858964]

21. Kapczinski F, Magalhães PVS, Balanzá-Martinez V, et al. Staging systems in bipolar disorder: an International Society for Bipolar Disorders Task Force Report. Acta Psychiatrica Scandinavica. 2014;130(5):354–363. [PubMed: 24961757]

22. Vieta E, Berk M, Schulze TG, et al. Bipolar disorders. Nature reviews Disease primers. 2018;4.

23. Demmo C, Lagerberg T, Kvitland L, et al. Neurocognitive functioning, clinical course and functional outcome in first-treatment bipolar I disorder patients with and without clinical relapse: A 1-year follow-up study. Bipolar disorders. 2018;20(3):228–237. [PubMed: 29121444]

24. Post RM. A shocking deficit in bipolar disorder treatment research funding. Bipolar disorders. 2020;22(8):864–865. [PubMed: 32989875]

25. Vieta E, Angst J. Bipolar disorder cohort studies: Crucial, but underfunded. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2021;47:31–33. [PubMed: 33895615]

26. Mullins N, Forstner AJ, O'Connell KS, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nature Genetics. 2021;53(6):817–829. [PubMed: 34002096]

27. Léda-Rêgo G, Bezerra-Filho S, Miranda-Scippa Â. Functioning in euthymic patients with bipolar disorder: A systematic review and meta-analysis using the Functioning Assessment Short Test. Bipolar Disorders. 2020;22(6):569–581. [PubMed: 32243046]

28. Miskowiak KW, Rush AJ, Gerds TA, Vinberg M, Kessing LV. Targeting Treatments to Improve Cognitive Function in Mood Disorder: Suggestions From Trials Using Erythropoietin. The Journal of clinical psychiatry. 2016;77(12):e1639–e1646. [PubMed: 27835716]

29. Henry C, Godin O, Courtet P, et al. Outcomes for bipolar patients assessed in the French expert center network: A 2-year follow-up observational study (FondaMental Advanced Centers of Expertise for Bipolar Disorder [FACE-BD]). Bipolar Disorders. 2017;19(8):651–660. [PubMed: 28944553]

30. Sajatovic M, Eyler LT, Rej S, et al. The Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD) project: Understanding older-age bipolar disorder by combining multiple datasets. Bipolar Disorders. 2019;21(7):642–649. [PubMed: 31081573]

31. Üstün TB, Chatterji S, Kostanjsek N, et al. Developing the world health organization disability assessment schedule 2.0. Bulletin of the World Health Organization. 2010;88(11):815–823. [PubMed: 21076562]

32. Mundt JC, Marks IM, Shear MK, Greist JH. The Work and Social Adjustment Scale: A simple measure of impairment in functioning. British Journal of Psychiatry. 2002;180(MAY):461–464.

33. Rosa AR, Sánchez-Moreno J, Martínez-Aran A, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clinical Practice and Epidemiology in Mental Health. 2007;3.

34. Lyall DM, Cullen B, Allerhand M, et al. Cognitive Test Scores in UK Biobank: Data Reduction in 480,416 Participants and Longitudinal Stability in 20,346 Participants. PLOS ONE. 2016;11(4):e0154222–e0154222. [PubMed: 27110937]

35. Burdick KE, Millett CE, Russo M, et al. The association between lithium use and neurocognitive performance in patients with bipolar disorder. Neuropsychopharmacology 2020 45:10. 2020;45(10):1743–1749. [PubMed: 32349118]

36. Del Matto L, Muscas M, Murru A, et al. Lithium and suicide prevention in mood disorders and in the general population: A systematic review. Neuroscience and biobehavioral reviews. 2020;116:142–153. [PubMed: 32561344]

37. Burdick KE, Millett CE. Cognitive heterogeneity is a key predictor of differential functional outcome in patients with bipolar disorder. European Neuropsychopharmacology. 2021;53:4–6. [PubMed: 34256309]

38. Jaeger J, Berns SM, Czobor P. The Multidimensional scale of independent functioning: A new instrument for measuring functional disability in psychiatric populations. In. Vol 29: DHHS Public Health Service; 2003:153–167.

39. Spitzer R, Gibbon MJ, Williams J, Endicott J. Global Assessment of Functioning (GAF) Scale. undefined. 1996.

40. Leon AC, Solomon DA, Mueller TI, Turvey CL, Endicott J, Keller MB. The Range of Impaired Functioning Tool (LIFE-RIFT): A brief measure of functional impairment. Psychological Medicine. 1999;29(4):869–878. [PubMed: 10473314]

41. Nurnberger JI, Blehar MC, Kaufmann CA, et al. Diagnostic interview for genetic studies: Rationale, unique features, and training. In. Vol 51: American Medical Association; 1994.
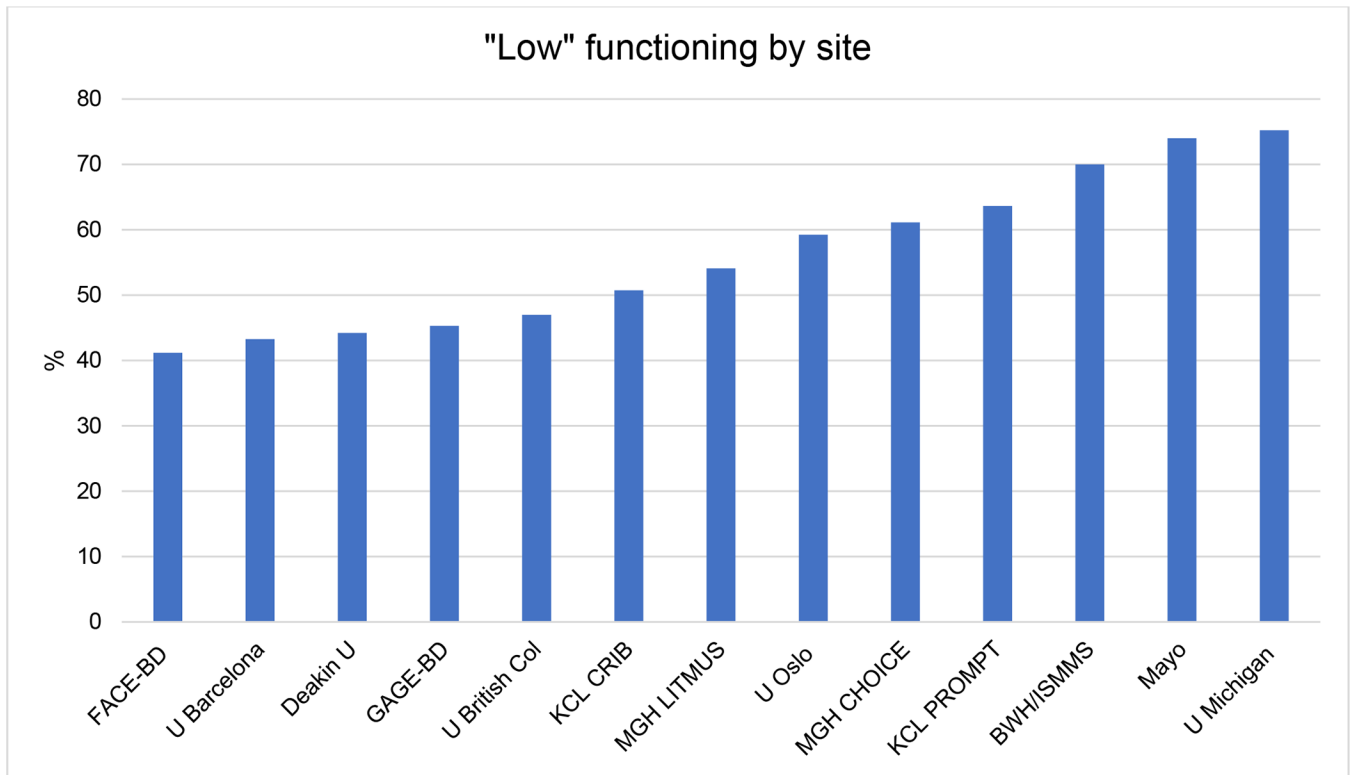
Figure 1.
The rate of low functioning at each site.

Table 1.

Defining "lower" functioning at each site

Cohort	Country	Lower function defined
FACE-BD (Fondation FondaMental)	France	FAST 21
University of Michigan	USA	Best Estimate Illness Impact 2
King's College London PROMPT	England	WSAS 20
King's College London CRIB	England	FAST 21
University of British Colombia	Canada	MSIF 4
University of Barcelona	Spain	FAST 21
Deakin University	Australia	GAF 60
Mass General Hospital LITMUS	USA	LIFTRIFT 14
Mass General Hospital CHOICE	USA	LIFTRIFT 14
Mayo Clinic	USA	Not working full time
Oslo University Hospital	Norway	GAF <60
GAGE-BD (consortium)	USA	GAF 60
Brigham and Women's Hospital/Icahn School of Medicine at Mount Sinai	USA	WHODAS >5

Functional Assessment Short Test (FAST)[33]; Work and Social Adjustment Scale (WSAS)[32]; Multidimensional Scale of Independent Functioning (MSIF)[38]; Global Assessment of Function (GAF)[39]; Longitudinal Interval Follow Up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT)[40]; WHO Disability Adjustment Schedule (WHODAS)[31]; Best Estiamte of Illness Impact from Diagnostic Interview for Genetic Studies (DIGS)41.

FAST is a 24 item assessment of 6 domains of function (autonomy, occupational functioning, cognitive functioning, financial, interpersonal, and leisure time); MSIF assesses occupational, education and residential domains of function; WSAS is a brief, 5-item questionnaire that assesses one's ability to work, home management, social and private leisure activities and close relationships; WHODAS assesses 6 domains of function (cognition, mobility, self-care, getting along, life activities, and participation); LIFE-RIFT assesses 4 domains of function (work, interpersonal, satisfaction, and recreation); GAF is a continuous scale of function based on the DSM-IV, rated from 0–100, with higher scores indicating higher functional capacity; Best Estimate of Illness Impact is derived from a diagnostic interview that classifies the impact of the patient's illness on their life.

Table 2.

An informational table completed by each site

	Mean (SD)	Range	Distribution[**] Shapiro-Wilk (p)	Descriptor
LEVEL ONE MEASURES	---	---	---	---
Age	In years			e.g., first episode
Sex	%Female			
Race	%White			
Education level	In years			Primary/secondary
LEVEL TWO MEASURES	---	---	---	---
BD subtype	%BDI/BDII/NOS			
Psychosis Hx	%yes/no			Lifetime presence
Current depressive sx	HDRS/MDRS score			mild/mod/severe
Current manic sx	YMRS/other score			mild/mod/severe
Age at onset dep	In years			
Age at onset mania	In years			
# Prior manias				
#Prior depressions				
# total episodes				Full mania/depression
#Hospitalizations				
#Suicide attempts				
Comorbid substance dx	%yes/no			Lifetime presence
Comorbid anxiety dx	%yes/no			Lifetime presence
LEVEL THREE MEASURES	---	---	---	---
Global cognition				Calculated g using PCA
Premorbid IQ				e.g., proxy WRAT/NART
Medications				
Lithium	% Yes			
Anticonvulsants	% Yes			
Antipsychotics	% Yes			
Antidepressants	% Yes			
Benzodiazepines	% Yes			
Total number of psychotropic meds	Mean (SD)			
---	---	---	---	---
OUTCOME MEASURES				
Global functioning				Provide name of scale
Global functioning impaired				Provide name of scale
Social functioning				Provide name of scale
Occupational fx				Provide name of scale
Independent living				Provide name of scale

	Mean (SD)	Range	Distribution[**] Shapiro-Wilk (p)	Descriptor
Employed	Yes/no			

[**] Shapiro-Wilk test for normality should be reported for each measure

Table 3.

Summary of results from logistic regression analyses

Characteristic	Proportion of sites reporting significance	Direction of results
Age	1/13 (8%)	Older age → more impairment
Sex	2/13 (16%)	Female → more impairment
Race	0/8 (0%)	---
Education level	3/12 (25%)	Lower education → more impairment
BD subtype	3/12 (25%)	BD I and SZA/BD → more impairment
Psychosis history	3/11 (27%)	Mixed direction: 2 sites Psychosis hx → more impairment; 1 site Psychosis hx → less impairment
Current depressive symptoms	10/12 (83%)	More severe depression → more impairment
Current manic symptoms	2/11 (18%)	More severe mania → more impairment
Age at onset depression	0/6 (0%)	---
Age at onset mania	0/6 (0%)	---
# Prior manias	2/7 (29%)	More prior episodes → more impairment
#Prior depressions	2/8 (25%)	More prior episodes → more impairment
# Total episodes	0/2 (0%)	---
Comorbid substance diagnosis	2/8 (25%)	Comorbid substance use d/o → more impairment
Comorbid anxiety diagnosis	3/6 (50%)	Comorbid anxiety d/o → more impairment
Global cognition (g)	1/6 (17%)	Lower g → more impairment
Premorbid intelligence quotient	0/5 (0%)	---
Lithium	1/6 (17%)	Lithium use → less impairment
Anticonvulsants	2/6 (33%)	Anticonvulsant use → more impairment
Antipsychotics	3/7 (43%)	Antipsychotic use → more impairment
Antidepressants	0/7 (0%)	---
Benzodiazepines	0/6 (0%)	---
Total number of psychotropic meds	2/7 (29%)	More psychotropic meds → more impairment