The **I**nternational **Con**sortium **I**nvestigating **N**eurocognition in **B**ipolar **D**isorder (*ICONIC-BD*)

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Bipolar Disorder (BD) is the 4th leading cause of disability worldwide among young people ages 10-24 years. Although the diagnosis is largely defined by the mood episodes associated with the illness, cognitive deficits are among the most persistent and disabling symptoms of illness and have a profound impact on clinical course and functional outcome. Specifically, trait-like impairment is common in the domains of attention, verbal learning, and executive function; these deficits contribute to functional disability and are targets for emerging treatments and preventions. Although considerable progress has been made over the past two decades, our understanding of the underlying causes of the cognitive deficits in BD remains surprisingly limited. As such, there are no approved treatments for this disabling symptom specific to BD[1].

Clinicians who treat patients with BD can attest to the vast range of functioning seen within BD, with some individuals achieving high-level occupational and social status while others are broadly disabled for most of their lives[2]. Research has shown that at the group level, cognitive deficits are present in euthymic BD patients, and are qualitatively similar to those seen in schizophrenia (SZ), albeit consistently less severe; however, group-level comparisons inherently fail to take into account heterogeneity in cognitive profiles *within* the disorder. In stark contrast to the very high rates of cognitive deficits in SZ, data suggest that approximately 30-50% of BD patients present as "neuropsychologically normal" (not different from age-matched non-psychiatric controls) during periods of euthymia[3]. We cannot yet answer the critical question of why some patients with BD develop significant cognitive deficits while others appear relatively resilient to cognitive decline and maintain high levels of social and occupational functioning. *Large-scale studies are needed to better identify both risk and resilience factors for cognitive impairment in BD.*

What diagnostic and clinical factors account for cognitive and functional heterogeneity in BD? Several clinical factors have been associated with cognitive impairment in BD**,** including *bipolar subtype (BD I versus BD II)*; however, considerable discrepancy is notable across studies, and recent meta-analyses suggest that between-group differences are very subtle[4]. Previously-reported subgroup differences may be - at least in part - due to the greater frequency of *psychosis* in BD I vs BD II, but individual studies have thus far been underpowered to test these types of fine-grained hypotheses. Beyond diagnostic heterogeneity, the course of the illness varies considerably among BD patients and is thought to contribute to cognitive and functional outcomes. Meta-analytic (cross-sectional) data suggest that a longer duration of illness, higher number of prior mood episodes, and history of psychosis are associated with more pronounced cognitive impairment indicative of a neuroprogressive course; however, each individual study has been small and thereby unable to address specific questions such as whether the polarity of prior episodes, duration of illness, or medication effects are relevant to cognitive outcome. Interestingly, very few studies have adequately addressed one of the most basic questions in BD – how does current symptom severity affect the nature and extent of cognitive impairment and is this a bidirectional effect? Many other illness-related factors are likely to contribute to cognitive and functional outcomes in BD (e.g. sleep, obesity, comorbid medical and psychiatric conditions, among others); however, these are relatively understudied and sample sizes are modest.

In an effort to advance the field through collaboration and open data-sharing, we have initiated the first international consortium focused on this highly significant topic: The International Consortium Investigating Cognition in Bipolar Disorder (*ICONIC-BD*). This effort brings together a large, international team of experts in BD with existing data on cognition in individuals with BD to form a unique consortium with the ability to unambiguously address some of these important questions through large-scale mega-analyses.

The idea for this project stemmed from the *International Society for Bipolar Disorder (ISBD) Targeting Cognition Task Force* meeting held in Mexico City in March 2018. All task force members were initially invited to contribute data to the consortium. Each investigator who had data to contribute enthusiastically agreed to do so – indicating a strong collaborative network.

We have assembled a strong team of investigators from across the world to form ICONIC-BD; however, to optimize the impact that this consortium will have, global outreach is necessary. We hope to identify other investigators via PubMed searches and word of mouth who have existing cognitive data in BD patients and invite them to join us. This will be open to any investigator with data to contribute who is interested in participating.

The coordinating site for ICONIC-BD is the Brigham and Women's Hospital (BWH); Harvard Medical School in Boston, Massachusetts – USA, led by Katherine Burdick. She is joined by co-leaders Kamilla Miskowiak (University of Copenhagen); Eduard Vieta (University of Barcelona); and Lakshmi Yatham (University of British Columbia) forming a 4-member executive committee who will oversee the effort. To date, we have already enlisted participation from a total of 15 sites who have provided meta-data for inclusion in this initiative (Table 1). Estimated sample sizes (as of 12/2018) are >3000 BD individuals and >2000 healthy controls.

After evaluating the nature of the existing data, we have begun the development of a single platform (e.g. define variables of interest from each measure, provide uniform labels) into which each site will place their data for transfer to BWH and upon which the master database will be built. As different neurocognitive batteries were used across sites, data harmonization will be critical to optimize the utility of the merged dataset. Quality control methods will be implemented to handle missing values to optimize available information while maintaining data integrity; data will be examined for normality and transformed as necessary; and all test scores will be converted to standard scales based upon the healthy control normative sample (e.g. z-scores with mean of zero and standard deviation of one).

Preliminary analyses will be conducted to define primary outcome measures at three levels. *Global outcomes* will be calculated using principal components analyses (PCA) to derive a general cognitive ability '*g*' score. This will be done in a standard manner where *g* is defined as the first factor from an unrotated PCA, which will be conducted separately as each site using the maximum number of tests available (but at least 3 tests) to calculate *g*. The global measure *g* has distinct advantages in consortium analyses, as it allows all cases (with at least 3 cognitive measures) to be included in analyses, regardless of the different batteries used at each site. This is based on data that show that when large samples have been tested on different cognitive test batteries, the derived general cognitive factors (*g*) correlate very highly with one another (approaching r =1.0); that is, *g* factors derived from different groups of tests rank people almost identically[5]. An additional advantage of this measure is that it captures a large percentage of the variance on other cognitive domains/tests and, as such, it is predictive of many important functional outcomes. The relative disadvantage is that *g* may not capture some of the more nuanced aspects of neurocognitive functioning that are impaired in BD or the cognitive heterogeneity that exists. As such, the second level of analyses will focus on *domain-level outcomes,* which will be defined based upon results from the PCA as well as calculating mean z-scores across similar pre-determined tasks. Finally, *test-level outcomes* will be selected based upon the most representative (and available) variables for each individual task.

Data from other measures that are related to cognitive outcome in BD will also need to be summarized and merged into the database. This will include demographic information and several illness-related scales. Data from standardized mood ratings are available from each site; however, not all sites use the same scales [e.g. Montgomery Asberg (MADRS) vs Hamilton (HamD) depression rating scales]. As such, severity of mood symptoms at the time of assessment will be converted to a common metric to be used in analyses. Illness history captured by different diagnostic interviews (i.e. MINI vs SCID) will also be standardized to capture important diagnostic features (e.g. BD subtype; psychosis subtype; # prior episodes; comorbidities) on the same scale. Measures of everyday functioning, including interpersonal, occupational and independent living status will be incorporated to provide a benchmark of how cognitive capacity translates to some of the most important aspects of a patient's life. Again, as different groups use unique tests to assess these constructs, we will devise metrics to allow for inclusion of data from multiple different scales.

Data analyses will begin by asking the simple questions first, including but not limited to: a) As a group, how do BD patients compare with healthy controls on cognitive outcomes (case vs control)? b) How does current mood symptom severity influence cognition in BD? c) Do BD I patients differ from BD II patients on cognitive measures? d) Do BD patients with a history of psychosis fare worse than those without such a history? e) How does duration of illness influence cognitive performance, and is this relative to episode load? f) What role do comorbidities (substance use disorders, anxiety disorders) play in cognitive outcome? g) How can we best address the confounder of medication effects on cognitive performance? The list of possible questions to be addressed is extensive and ICONIC-BD will provide a rich data set with unmatched statistical power to begin to answer many of them.

While clinical outcome measures related to social, personal, and vocational functioning form the core of the collaboration, it is imperative to consider the course of cognitive capacity as the individual with BD ages. Since cognitive decline with age is an inevitable component of humanity, are individuals with BD affected sooner? How can the consequences of such decline be mitigated in the bipolar population? To study and answer such questions it is necessary to study a large population over time, in many cultures and locations.

While these questions may seem straightforward, they have not yet been unambiguously answered in any single dataset. Moreover, with the power of collaboration, we will be able to conduct more sophisticated analyses to answer questions that can better address the multi-factorial nature of cognition in BD. Analyses of mediators and moderators of cognitive outcome can address interactions among these key illness features. Classification methods (e.g. clustering, latent profiles) can be used to empirically parse cognitive heterogeneity, establishing potentially meaningful new 'subtypes' in the largest study to date. Addressing these complex questions is key to understanding what causes cognitive impairment in a large subset of patients with BD. This is the first (and a critical) step in determining how best to treat and ultimately prevent this disabling symptom, which would have direct and immediate effects on quality of life for many patients with BD.

Beyond the initial set-up of this data base, ICONIC-BD will also serve as a platform for additional collaborative projects (e.g. subcommittees for those sites that have DNA, or those with neuroimaging data, or those interested in establishing a network for treatment trials targeting cognition). We hope that this dataset and interconnected worldwide network will also lead to additional funding for this very important and understudied area of research.

The overarching goal of this initiative is the creation of the world's largest, publicly-available database on cognition in BD. This will promote work that could not be done by any single investigator/lab. The massive success of other similar consortia in psychiatry [Psychiatric Genomics Consortium (PGC); Enhancing NeuroImaging Genetics through Meta-analysis (ENIGMA); Cognitive Genomics Consortium (COGENT), among others] provides strong support for scientific advances through the kind of collaboration and data sharing that is planned in ICONIC-BD. Moreover, collaborative initiatives such as ICONIC-BD may foster agreement across research groups, not only in analyzing the available data, but in generating new data using common instruments and methodologies moving forward.

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Conflicts of Interest

KEB has served on advisory boards for Neuralstem and Dainippon Sumitomo Pharma.

CB has received grant support from Pfizer, Lundbeck and Takeda, and acts as a consultant for Boehringer Ingelheim, Lundbeck and Pfizer.

PH has received consulting fees or travel reimbursements from Allergan, Alkermes, Akili, Biogen, Boehringer Ingelheim, Forum Pharma, Genentech (Roche Pharma), Intra-Cellular Therapies, Jazz Pharma, Lundbeck Pharma, Minerva Pharma, Otsuka America (Otsuka Digital Health), Sanofi Pharma, Sunovion Pharma, Takeda Pharma, and Teva, within the last three years. He receives royalties from the Brief Assessment of Cognition in Schizophrenia and the MATRICS Consensus Battery. He is chief scientific officer of i-Function, Inc. He has a research grant from Takeda and from the Stanley Medical Research Foundation.

SL has received consulting fees from EPI-Q, Cogstate LTD, and Gift of Hope, all unrelated to this work.

MM has consulted with and receives research support from Janssen Pharmaceuticals in the last three years. He has consulted with Otsuka Pharmaceuticals. He is a co-owner of *priori ai, LLC.*

KM has received consultancy fees from Lundbeck, Janssen and Allergan in the past three years.

RP has received support for travel to scientific meetings from Lundbeck and Servier. He uses scientific software for research provided free of charge by SBT-pro.

TVR has received grant funding from the National Health and Medical Research Council, Club Melbourne, the Henry Freeman Trust, Jack Brockhoff Foundation, University of Melbourne, Barbara Dicker Brain Sciences Foundation, Rebecca L Cooper Foundation and the Society of Mental Health Research.

TS has received honoraria for advisory board, consultations, and/or speaker's role from Dainippon Sumitomo Pharmaceutical, Otsuka Pharmaceutical,
Mochida Pharmaceutical, Takeda Pharmaceutical, and NeuroCog Trials Co. Ltd.

IT has received research funding from the Canadian Institutes of Health Research (CIHR) and has served as consultant to Dainippon Sumitomo and Lundbeck Canada.

EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, SAGE, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Spanish Ministry of Science, Universities and Innovation (CIBERSAM), the Seventh European Framework Programme and Horizon 2020, the Brain and Behaviour Foundation (NARSAD) and the Stanley Medical Research Institute.

LY has been a member of advisory boards, received research grants, or been a speaker for Allergan, Alkermes, Astrazeneca, Bristol Myers Squibb, Canadian Institutes of Health Research, Canadian Foundation for Innovation, Dainippon Sumitomo Pharma, GSK, Janssen, Lilly, NARSAD, Otsuka, Pfizer, Servier, Stanely Foundation, Sunovion and Teva.

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AC, BL, KEL, CL and AM have no conflicts associated with this work.

TABLE 1. INITIAL SITES FOR ICONIC-BD

Site	Investigator name(s)	Location
Brigham and Women's Hospital/Harvard	*Katherine Burdick*	*USA*
Copenhagen University Hospital	*Kamilla Miskowiak, Lars Kessing*	*Denmark*
University of Otago	*Richard Porter*	*New Zealand*
University of Melbourne	*Tamsyn Van Rheenen*	*Australia*
King's College London	*Allan Young*	*UK*
National Center for Neurology and Psychiatry	*Tomiki Sumiyoshi*	*Japan*
University of Barcelona	*Eduard Vieta, Anabel Martinez-Aran*	*Spain*
University of British Columbia	*Yatham Lakshmi, Ivan Torres*	*Canada*
University of Sao Paulo	*Beny Lafer*	*Brazil*
Newcastle University	*Peter Gallagher*	*UK*
McLean Hospital	*Kathryn Eve Lewandowski*	*USA*
University of Michigan	*Melvin McInnis*	*USA*
Queens University	*Christopher Bowie, Philip Harvey, Ann Pulver*	*Canada*
Vanderbilt University	*Neil Woodward, Stephan Heckers*	*USA*
University of California at San Diego	*Lisa Eyler*	*USA*

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