# Translating big data to better treatment in bipolar disorder - a manifesto for coordinated action

Manchia, Mirko; Vieta, Eduard; Smeland, Olav B.; Altimus, Cara; Bechdolf, Andreas; Bellivier, Frank; Bergink, Veerle; Fagiolini, Andrea; Geddes, John R.; Hajek, Tomas; Henry, Chantal; Kupka, Ralph; Lagerberg, Trine V.; Licht, Rasmus W.; Martinez-Cengotitabengoa, Monica; Morken, Gunnar; Nielsen, René E.; Pinto, Ana Gonzalez; Reif, Andreas; Rietschel, Marcella; Ritter, Phillip; Schulze, Thomas G.; Scott, Jan; Severus, Emanuel; Yildiz, Aysegul; Kessing, Lars Vedel; Bauer, Michael; Goodwin, Guy M.; Andreassen, Ole A.; for the European College of Neuropsychopharmacology (ECNP) Bipolar Disorders Network

*Published in:*
European Neuropsychopharmacology

*DOI (link to publication from Publisher):*
10.1016/j.euroneuro.2020.05.006

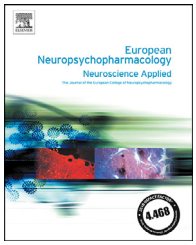


*Publication date:*
2020

*Document Version*
Publisher's PDF, also known as Version of record

European Neuropsychopharmacology (2020) 36, 121–136

www.elsevier.com/locate/euroneuro



# Translating big data to better treatment in bipolar disorder - a manifesto for coordinated action

Mirko Manchia[a,b,c], Eduard Vieta[d], Olav B. Smeland[e], Cara Altimus[f], Andreas Bechdolf[g,h,i], Frank Bellivier[j,k], Veerle Bergink[l,m], Andrea Fagiolini[n], John R. Geddes[o], Tomas Hajek[p,q], Chantal Henry[r], Ralph Kupka[s], Trine V. Lagerberg[e], Rasmus W. Licht[t,u], Monica Martinez-Cengotitabengoa[v], Gunnar Morken[w,x], René E. Nielsen[t,u], Ana Gonzalez Pinto[v], Andreas Reif[y], Marcella Rietschel[z], Phillip Ritter[aa], Thomas G. Schulze[ab,ac,ad,ae], Jan Scott[k,x,af], Emanuel Severus[aa], Aysegul Yildiz[ag], Lars Vedel Kessing[ah], Michael Bauer[aa], Guy M. Goodwin[o], Ole A. Andreassen[e,1,*], for the European College of Neuropsychopharmacology (ECNP) Bipolar Disorders Network

[a] *Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy*
[b] *Unit of Clinical Psychiatry, University Hospital Agency of Cagliari, Cagliari, Italy*
[c] *Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada*
[d] *Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain*
[e] *NORMENT, Institute of Clinical Medicine, University of Oslo and Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway*
[f] *Milken Institute, New York, US*
[g] *Vivantes Klinikum im Friedrichshain, Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, Charité-Universitätsmedizin, Berlin, Germany*
[h] *Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany*

* Corresponding author at: CoE NORMENT, Building 49, Oslo University Hospital, Ullevål, Kirkeveien 166, PO Box 4956 Nydalen, 0424 Oslo, Norway.
*E-mail addresses:* o.a.andreassen@medisin.uio.no, ole.andreassen@medisin.uio.no (O.A. Andreassen).
[1] http://www.med.uio.no/norment/.

https://doi.org/10.1016/j.euroneuro.2020.05.006

[i] *ORYGEN, The National Centre of Excellence in Youth Mental Health, Melbourne, Victoria, Australia*
[j] *Université de Paris and INSERM UMRS 1144, Paris, France*
[k] *AP-HP, Groupe Hospitalo-Universitaire AP-HP Nord, Hopital Fernand Widal, DMU Neurosciences, Département de Psychiatrie et de Médecine Addictologique, Paris, France*
[l] *Department of Psychiatry – Erasmus Medical Center, Rotterdam, the Netherlands*
[m] *Department of Psychiatry, Department of Obstetrics, Icahn School of Medicine at Mount Sinai, New York, USA*
[n] *Department of Molecular Medicine, University of Siena, Siena, Italy*
[o] *Department of Psychiatry and Oxford Health NHS Foundation Trust, University of Oxford, Oxford, United Kingdom*
[p] *Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada*
[q] *National Institute of Mental Health, Klecany, Czech Republic*
[r] *Department of Psychiatry, Service Hospitalo-Universitaire, GHU Paris Psychiatrie & Neurosciences, F-75014 Paris, France*
[s] *Amsterdam UMC, Vrije Universiteit, Department of Psychiatry, Amsterdam, Netherlands*
[t] *Department of Clinical Medicine, Aalborg University, Aalborg, Denmark*
[u] *Psychiatry - Aalborg University Hospital, Aalborg, Denmark*
[v] *Hospital Universitario de Alava. BIOARABA, UPV/EHU. CIBERSAM. Vitoria, Spain*
[w] *Østmarka Department of Psychiatry, St Olav University Hospital, Trondheim, Norway*
[x] *Department of Mental Health, Faculty of Medicine and Healthsciences, Norwegian University of Science and Technology, Trondheim, Norway*
[y] *Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, Germany and German Society for Bipolar Disorders (DGBS), Frankfurt am Main, Germany*
[z] *Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany*
[aa] *Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany*
[ab] *Institute of Psychiatric Phenomics and Genomics, University Hospital, Ludwig-Maximilian University of Munich, Munich, Germany*
[ac] *Department of Psychiatry and Psychotherapy, Ludwig-Maximilian University of Munich, Munich, Germany*
[ad] *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, Maryland, USA*
[ae] *Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA*
[af] *Academic Psychiatry, Institute of Neuroscience, Newcastle University, UK*
[ag] *Dokuz Eylül University Department of Psychiatry, Izmir, Turkey*
[ah] *Psychiatric Center Copenhagen and University of Copenhagen, Faculty of Health and Medical Sciences, Denmark*

Received 25 February 2020; received in revised form 15 May 2020; accepted 24 May 2020

**KEYWORDS**
Machine learning;
Open science;
Philanthropy;
Precision medicine;
Risk prediction

**Abstract**
Bipolar disorder (BD) is a major healthcare and socio-economic challenge. Despite its substantial burden on society, the research activity in BD is much smaller than its economic impact appears to demand. There is a consensus that the accurate identification of the underlying pathophysiology for BD is fundamental to realize major health benefits through better treatment and preventive regimens. However, to achieve these goals requires coordinated action and innovative approaches to boost the discovery of the neurobiological underpinnings of BD, and rapid translation of research findings into development and testing of better and more specific treatments. To this end, we here propose that only a large-scale coordinated action can be successful in integrating international big-data approaches with real-world clinical interventions. This could be achieved through the creation of a Global Bipolar Disorder Foundation, which could bring government, industry and philanthropy together in common cause. A global initiative for BD research would come at a highly opportune time given the seminal advances promised for our understanding of the genetic and brain basis of the disease and the obvious areas of unmet clinical need. Such an endeavour would embrace the principles of open science and see the strong involvement of user groups and integration of dissemination and public in-

volvement with the research programs. We believe the time is right for a step change in our approach to understanding, treating and even preventing BD effectively.


## 1. Introduction

Bipolar disorder (BD) has been classically depicted as the presence of alternating episodes of mood disturbances of opposite polarity (hypomania/mania versus depression) interspersed with periods of well-being (also defined as free intervals) (Grande et al., 2016). It is more than that. This description of episodic BD fails to include those presentations where clinical course has a chronic irregular pattern, including rapid cycling (Koukopoulos et al., 2013) and enduring subthreshold symptoms (Bonnín et al., 2019) that exert a higher toll in terms of long-term disability (Arvilommi et al., 2015). Indeed, only a longitudinal perspective can fully account for the suffering endured by patients and their relatives, and the substantial socio-economic burden of BD: a recent prospective study of individuals with a BD diagnosed in youth, showed the significantly worse psychosocial functioning when mood symptoms were persistent (i.e. a chronic course) (Hower et al., 2019; Scott et al., 2014). These features translate into the high socio-economic costs and decreased quality of life associated with BD (Cloutier et al., 2018; Gustavsson et al., 2011). In Europe, mood disorders, including BD, are the most costly mental health conditions with an estimate of more than €120 billion due to high direct healthcare costs and even higher indirect costs (Gustavsson et al., 2011). Contributing factors to this figure are the high prevalence in the general population (around 4% considering the whole BD spectrum) (Grande et al., 2016), the early age of onset of the disorder (Bauer et al., 2015), the premature mortality (Plana-Ripoll et al., 2019), the number of disability-adjusted life years (DALYs) (Ferrari et al., 2016), and the high rates of substance abuse (Zorrilla et al., 2015) and psychiatric (Krishnan, 2005) and medical comorbidities (Sinha et al., 2018) associated with BD. In summary, BD represents a major healthcare and socio-economic challenge. We believe the time is right for a step change in our approach to understanding, treating and even preventing BD effectively.

There is a consensus that the accurate identification of the underlying pathophysiology for BD is fundamental to realize major health benefits through better acute and preventive treatments (Bauer et al., 2018). BD is perhaps best conceived to be an umbrella term for a variety of underlying pathologies which might be reflected by different biomarkers and which might call for different treatments in the sense of precision medicine. Risk prediction in BD, which could inform prevention and stratification strategies, is similarly lacking (Vieta et al., 2018). Novel approaches are needed to provide solutions to these problems. Many have questioned the traditional way mental health research has been conducted, often based on "silos" with little interaction and even conflict between disciplines (Holmes et al., 2018). There is the need for a truly *multidisciplinary* approach that brings together basic science research (computer science, mathematics/statistics, genetics), with different health professions (medicine, psychology), social sciences, and patient/advocate perspectives (Scott et al., 2018). There is a clear demand for greater *patient involvement*. Patients will need to help shape the scientific and ethical challenges that will directly concern them and the lives of their families (Maassen et al., 2018a). Thus, by integrating excellent multidisciplinary scientists and patient experts, this new research approach will produce synergies and deliver major added value, with impact beyond the standard grant funding periods.

In this paper, the Bipolar Disorders Network of the European College of Neuropsychopharmacology (ECNP) suggests a series of priorities, a manifesto, for the development of future research initiatives in the area of BD. These recommendations will highlight approaches to boost the discovery of the neurobiological underpinnings of BD and suggest an integrated approach to transition of these findings into discovery of new more specific treatments. We have selectively reviewed the evidence of the neurobiological underpinnings of BD, selected what we argue are the most significant remaining challenges, including the limited transition of research findings into better diagnostics and treatment of BD. We describe how big data and related research approaches can improve BD discoveries, focusing on the translation to clinically relevant information, and the potential role in precision medicine. The final part outlines a roadmap for the creation of a Global Bipolar Disorder Foundation, which could coordinate international big data approaches and integrate with real-world clinical interventions. This will be a fundamental step as big data can be instrumental in advancing BD research. The key research questions that could be addressed by the "big data" approach are: 1) Stratifying treatment response: who will respond to mood stabilized given baseline clinical genetic and brain imaging phenotype? 2) Predicting outcome: who will have life-time episode and who will develop rapid cycling? 3) Developing new treatment: How can better insight into disease biology and treatment effect determinants help drug development/drug repurposing in BD. Indeed, the goal is to obtain unique synergy by providing relevant clinical data for new analytical approaches and integrate big data results in a clinical trial network for development of personalized treatment regimens. This has been made possible by recent technical developments allowing high throughput, large scale genetic and brain imaging data collection, as well as novel clinical information communication technology (ICT) tools for efficient, user based clinical assessments.

## 2. Role of the patient community perspective

A recent survey of over 6,000 individuals living with depression and BD from the Depression and Bipolar Support

Alliance and the Milken Institute (Altimus, 2019) showed that patients want improved treatments. However, the way that patients define successful outcomes may not align with the traditional goals of researchers and research agency programs. The survey identified the ability to have an independent and self-determined life as the top priority. Only 20% of respondents identified the reduction of traditional symptoms of BD as a measure of wellness. How we measure outcomes must respect patient expectations and views of what really matters. To do so, we need better integration of individuals with BD in the planning of research programs. This will assist researchers in incorporating consumer perspectives (patients and advocates) patient related outcome measures (PROMS) (Calvert et al., 2018) and personal recovery targets (Jonas et al., 2012) in the repertoire of response/outcome measures. Patients also placed a high priority on understanding why they developed BD as well as objective diagnostic measures.

Medical research and treatment call for practical solutions of ethical problems. Genetic and behavioural profiling may play an important part in improving the understanding of BD, just as it has in other diseases. However, psychiatric disorders are still stigmatizing: this demands particular sensitivity in research design and implementation that must be informed by the perspectives of people living with the disorder.

There is also inconsistency between the expectations of clinicians and researchers and the preferences of patients and their relatives in assessing the quality of care for BD patients in mental health services (Maassen et al., 2018b; Skelly et al., 2013). Specifically, the implementation of best practice guidelines does not necessarily improve quality of care from the patient perspective (Skelly et al., 2013). Other surveys have highlighted the importance of gathering individuals' experiences on various aspects of BD, including treatment (Davenport et al., 2018; Maassen et al., 2017). Indeed, Davenport et al. (2018) show that even psychological interventions in BD often fail to recognize the individual as having agency in their recovery. Generally, emphasis needs to be paid to overall functional outcome, morbidity and quality of life rather than just symptom-based outcomes proximal to treatment delivery.

Overall, these findings suggest that patient preference is crucial to target and refine interventions at a clinical level, and to make policy related to organization of healthcare services and research funding. Indeed, seminal research in BD has come from initiatives, such as those of the registries, that have seen the merging of clinical care and research involvement of users (Chengappa et al., 2003; Hajek et al., 2005; Kupfer et al., 2002). Dissemination of research findings as well as of clinical guidelines, should be available for patients, as recently exemplified for individuals with BD treated with lithium (Tondo et al., 2019).

## 3. Causal factors – the 'polygenic architecture' and interplay with environment

BD is a complex genetic disorder with a heritability estimated at 60–95% (Kieseppä et al., 2004; Lichtenstein et al., 2009; McGuffin et al., 2003). The genetic architecture of BD is determined by the effects of multiple genes (i.e. 'polygenic') in combination with environmental factors (Sullivan et al., 2017). To date, only a small fraction of the heritability and the polygenic architecture of BD has been determined (Sklar et al., 2011; Stahl et al., 2019). This is largely attributable to inadequately powered sample sizes of genetic studies (Sullivan et al., 2017). Another concern is that since the samples are mainly restricted to the European population, the generalizability of the genetic findings across populations may be questionable.

The large fraction of heritability accounted for by common genetic variants with small effects (Sklar et al., 2011; Stahl et al., 2019) poses considerable challenges to analytical methods and sample size. Despite the assembly of very large GWAS samples, the proportion of identified phenotypic variance is only close to 8% in BD (Stahl et al., 2019). Although larger sample sizes will increase GWAS statistical power, small genetic effects are difficult to detect with traditional statistical methods due to the burden of multiple testing. Moreover, the power of GWAS is largely dependent on the level of polygenicity of the phenotype; high polygenicity leads to lower genetic effects per locus at a fixed heritability, making loci harder to detect (Holland et al., 2016). Heterogeneity also dramatically reduces the power to detect significant associations (Manchia et al., 2013b). *Novel biostatistical tools* may help discover more of the genetic architecture underlying highly polygenic disorders like BD (Smeland et al., 2019). For example, accumulating evidence indicates that some genetic loci are more likely to harbour causal effects than others; as examples the coding and regulatory regions (Schork et al., 2013) and loci associated with two phenotypes (pleiotropy) (Schork et al., 2013). This knowledge can be exploited with biostatistical tools incorporating auxiliary genetic information which substantially increase statistical power (Andreassen et al., 2013a, 2013b; Schork et al., 2013; Wang et al., 2016).

An international large-scale genetic consortium (Psychiatric Genetics Consortium; PGC https://www.med.unc.edu/pgc/) is successfully collaborating to implement these approaches for the discovery of the genetic causes of psychiatric disorders (Sullivan, 2009; Sullivan et al., 2017). The Bipolar Disorder Working group (https://www.med.unc.edu/pgc/pgc-workgroups/bipolar-disorder/) includes nearly 300 scientists across the world, and thanks to international large-scale genotyping efforts, current sample sizes are close to 40,000 cases and 220,000 controls. Preliminary results presented at the World Congress of Psychiatric Genetics (WCPG) in 2019 demonstrated more than 60 genetic loci to be associated with BD (Mullins et al. *in preparation*). However, detailed clinical information and longitudinal data are largely missing. Longitudinal cohorts are particularly suited to aid the discovery of *novel* genetic and environmental factors that, in interplay, might contribute to BD (Grande et al., 2016; Vieta et al., 2018). This is exemplified by the role of substance use, such as cannabis, that represents a risk factor for BD (Grande et al., 2016), and that might further interplay with polygenic burden (Aas et al., 2018). The interplay between genetic predisposition and environmental factors can be discovered by the multidisciplinary integration of large samples with relevant data and analytical tools, as suggested in the Nordic countries (Njølstad et al., 2019). As the environmental factors are potentially modifiable,

the implementation of preventive strategies could become a real possibility. Finally, the causal role of protective genetic and environmental factors (resilience factors) remains largely unknown, although physical activity, sleep habits and certain diets (Campbell and Campbell, 2019; Koga et al., 2019; Pancheri et al., 2019) are correlated with reduced risk.

## 4. Impact of heterogeneity and the need to improve phenotyping: big data and information communication technology

BD occurs with episodes of different severity and duration, with varying predominance of polarity (more mania than depression, or, more commonly, more depression than mania) and different degrees of chronicity of residual symptoms (usually depressive) (Grande et al., 2016; Vieta et al., 2018). Moving along such a mood disorder spectrum from unipolar disorder – not the topic of this review – to BD type II with predominantly depressive polarity to BD type I disorder with predominantly manic polarity goes along with changing polygenic risk scores (Coleman et al., 2019). Therefore, precise clinical phenotyping is essential and to capture the relevant properties may require dense measurement. The most obvious approach is to measure what we see and what patients tell us; this allows us to define operational criteria for identifying key features (or symptoms). The use of operational definitions of mental states was adopted by analogy with the physical sciences use of operational definitions (for example, of mass or energy). It dates from 1980 and the publication of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III as the basis for diagnosis and classification in psychiatry. It represented a radical move away from trying to classify mental illness with reference to the meaning or psychological origin of the patients' symptoms. Rather, DSM classification created broad categories based on signs and symptoms. In BD the lifetime occurrence of mania resulted in different types, based on the intensity of manic symptoms: BD type I requires an episode of mania, BD type II requires an episode of hypomania and there is also a group of conditions where manic symptoms are definitely present but do not meet the criteria for an episode of mania or hypomania. These categories capture some of the heterogeneity of the illness course (Kapczinski et al., 2014) and the validity of the BD diagnosis, in terms of reliability and longitudinal stability, has in part been supported by the success of the molecular genetic project (Stahl et al., 2019). However, many of the genes associated with BD are also associated with other psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019), just as its comorbidity (with e.g. anxiety, impulse control disorders, and addictions) would have predicted. This indicates that the psychiatric diagnostic categories defined by DSM and ICD-11 (Stein et al., 2020) criteria do not capture distinct genetic aetiologies, in contrast to neurological disorders that are defined by both symptoms and, recently, pathobiological criteria (Brainstorm Consortium, 2018). The time is right to accept the challenge of transforming the traditional diagnostic map of BD into something that reflects our emerging understanding of its aetiology.

A key limiting factor in the study of the phenotype of BD is the absence of very large, longitudinally well-characterised patient cohorts. Given the lack of reliable disease biomarkers (Carvalho et al., 2016), BD can only be diagnosed by physicians/psychologists through subjective physician-patient interactions without recourse to objective laboratory, imaging, or pathological testing. As described, important advances in our understanding of the pathophysiology of BD have come from international consortia and collaborative efforts pooling and merging large databases and samples of genetic and neuroimaging data. However, two important limitations have hampered these efforts: one is the poor granularity of the clinical phenotype, and the other is the cross-sectional nature of the data. Although efforts are being made to understand genetics, neuroimaging, and biomarkers as reflecting dynamic processes, longitudinal clinical studies are still in their infancy (Kessing et al., 2017).

Hence, although the scientific community has been able successfully to pool thousands of DNA and brain imaging samples (Nunes et al., 2018; Stahl et al., 2019), most of those biological samples go along with quite inadequate phenotypic data (often only age, sex and diagnosis). Discussing the limitations of our official diagnostic systems (DSM-5, ICD-11) is beyond the scope of this article, but it is quite obvious that much more detail in describing and understanding the mechanisms underlying symptoms and signs of the disorder will be essential. Initiatives such as the Research Domain Criteria (RDoC) (Insel et al., 2010), promote a dimensional rather than a categorical approach to neuropsychiatric research and may explain basic mechanisms underlying simple behaviours. The strong pleiotropy that affects BD and most mental disorders (Andlauer et al., 2019; Lee et al., 2019) and the difficulties of harmonizing biomarker information from multiple and heterogeneous sources such as different MRI scanners and laboratories is very similar to the difficulties of collecting phenotypic data from different sites in a reliable way. Indeed, psychopathology is culturally sensitive and harmonizing this kind of data is not an easy task, but this is perhaps the greatest unmet need if we really want to understand human behaviour and its anomalies. This may especially help our understanding of juvenile as compared with adult-pattern presentations of BD.

In addition, large scale phenotyping may include blood biomarkers, which can now be obtained for low cost. There are several promising types of blood-based biomarkers including as oxidative, neurotrophic, and inflammation markers which may be involved in BD (Fries et al., 2020; Rosenblat and McIntyre, 2016). Furthermore, recent high-throughput assessments of neurophysiological markers have also been developed, such as easy to use EEG equipment and other tools for assessment of brain function (Maggioni et al., 2017). By building large training samples, these factors can be added to the models, and validated in independent test cohorts.

One of the greatest barriers to improving clinical information has been, perhaps surprisingly, the cost; it is way less expensive to perform brain scans or sophisticated blood tests to large samples of people than to do thorough, fine-grained assessments by well-trained, experts in psychopathology (most large studies, such as epidemiology

surveys, use students or volunteers to assess potential patients). As the RDoC initiative bears fruit (Ahmed et al., 2018), the phenotype may be seen in a less arbitrary light than traditional phenomenology. However, the detailed collection of clinical data may still be the only way to reconcile psychopathology with biomarkers, phenotype and genotype (Hidalgo-Mazzei et al., 2016). This could be of relevance also for randomized clinical trials in BD. The enormous costs related to the large sample sizes needed to reach adequate statistical power have a negative impact on their feasibility. Conversely, dense coverage of the longitudinal phenotypic variation in BD patients trialled for a specific intervention (e.g. ICT), could increase the signal to noise ratio, reducing the need for large sample size and facilitating the realization of these fundamental studies. Furthermore, randomized clinical trials are primarily designed to decrease confounding and, in some instances, restricted sampling or other design elements can lead to a loss of external validity. As such, pragmatic trials and observational studies are needed to determine the comparative effectiveness of putative personalised treatments in real-world settings, to define their impact on outcomes that patients identify as important to them and to clarify potential mediators of any benefits that these interventions may bring in day to day practice.

Fortunately, BD is very well suited for large scale screening by patients themselves using digital technology and ICT tools (Faurholt-Jepsen et al., 2019; 2018; Hidalgo-Mazzei et al., 2018). Furthermore, exploiting secure questionnaires and secure storage (Bauer et al., 2017) allows health services to monitor personal perception of core psychiatric disease symptomatology. Combining ICT tools with genotyping technology provides a unique opportunity to leverage existing biobanks and healthcare registries to substantially increase patient cohort sample sizes for BD. These resources will be highly useful for large scale recruitment and discovery of novel modifiable risk factors, identifying interactions between genes and environmental triggers in BD, and to facilitate clinical trials. Furthermore, ICT might also play a role in developing methodologies for prevention and public health studies, with a large potential for innovation and new treatment alternatives. It will be crucial to the success of such a global collaborative enterprise for BD research to ensure adequate reliability of measures across participating centres and consistent assessment procedures (Chase et al., 2015; Manchia et al., 2013a).

## 5. Large-scale brain imaging phenotyping

In contrast to most major somatic and neurological conditions, whose incidence and prevalence increase with advancing age, the first manifestations of BD appear in adolescence and in young adulthood (Duffy et al., 2018). Indeed, on average BD patients have their illness onset at 18 years of age (Bauer et al., 2015). Thus, BD onset coincides with profound neurodevelopmental changes and transitions to new life-roles during adolescence. However, the mechanisms underlying risk and resilience in the adolescent brain are largely unknown, seriously impeding the development of useful tools for early detection, individual prediction and prevention.

Individual risk factors, together with critical time-periods of susceptibility to environmental stressors during brain development, influence the onset of BD. One important research goal is to identify the "windows of opportunity" where preventive strategies might be effective. This could be investigated by the analysis of brain alterations in BD patients during illness onset or peak risk for diagnostic conversion (e.g. from major depressive disorder to BD). International brain imaging efforts combining existing large-scale brain imaging genetics databases ($n>50,000$) with novel neuroimaging approaches may provide new insights into the mechanisms underlying BD risk and resilience. In this context, the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Bipolar Disorder Working Group was formed to improve the statistical power, replication, and generalizability of neuroimaging findings in BD research, bringing together over 150 researchers from 20 countries. By pooling data and resources, they have conducted the largest neuroimaging studies of BD to date. The use of standardized and publicly available processing and analysis techniques (http://enigma.ini.usc.edu/protocols/), has advanced large-scale meta- and mega-analyses of multimodal brain MRI, clinical, and genetic data. Recent findings from ENIGMA showed that BD was associated with lower cortical thickness in bilateral frontal, temporal and parietal brain regions, areas known to underlie the circuitry of emotion and reward processing (Hibar et al., 2018). Furthermore, lithium use was associated with a widespread pattern of thicker cortex, whereas anticonvulsant treatment was associated with lower cortical thickness (Hibar et al., 2018). The ENIGMA Bipolar Disorder Working Group also examined case-control differences in subcortical volumes and found that BD was associated with lower hippocampus, thalamus, and amygdala volumes, as well as larger lateral ventricular volumes, with small to moderate effect sizes (Hibar et al., 2016). In a recent follow-up study using machine learning methods, these regional brain measures (cortical thickness, cortical surface area, and subcortical volume) were effective in differentiating individuals with BD from healthy controls at above chance accuracy in a large and heterogeneous sample ($N = 3020$) (Nunes et al., 2018). Future multi-site brain-imaging machine learning studies are moving beyond the use of engineered brain features (i.e. volume, thickness, etc.) or site-level results, and towards sharing of raw, individual subject data, where unsupervised machine learning techniques may offer potential to better stratify the heterogeneity in this complex disorder.

## 6. Transforming big data discoveries to clinically relevant information

Over the last decades, there have been numerous attempts to stratify BD patients according to specific clinical characteristics, such as, early age of onset (Etain et al., 2010; Manchia et al., 2017, 2008), mood-incongruent psychosis (Goes et al., 2007; Hamshere et al., 2009), and response to lithium treatment (Hou et al., 2016). Besides the dichotomy of BD type I and II, and the possible exception of lithium-responsive BD (Nunes et al., 2019), the delineation of subgroups has had negligible impact on clinical decision making or knowledge of the neurobiology of BD. Therefore, there

is an urgent need for operational, rational approaches that take into account the impact of heterogeneity (Nunes et al., 2020). This can be achieved with implementation of promising analytical methods, such as machine learning (and statistical learning) algorithms. These approaches applied to big data are becoming increasingly relevant in psychiatric research (Iniesta et al., 2016), allowing identification of relevant predictors of specific outcomes, enabling risk stratification and facilitating individualized approaches in BD (Scott et al., 2019). Indeed, machine learning methods have helped identifying predictors of treatment response (Nunes et al., 2019) and risk of episode recurrences in pregnancy and post-partum (Di Florio et al., 2018). In addition, recent evidence shows that machine learning applied to grey matter and diffusion tensor neuroimaging data might be useful in differentiating major depressive disorder from BD (Vai et al., 2020). Furthermore, the application of these algorithms to proton magnetic resonance spectroscopy ($^{1}$H-MRS) data has predicted diagnostic conversion to BD in high-risk offspring (Zhang et al., 2020). Finally, when these analytical approaches were applied to daily self-assessments collected via a smartphone-based system they predicted future mood scores, especially in short terms with low error (Busk et al., 2020). Although these results point to clinical relevance, at the moment they generally fall short of the accuracy threshold needed for practical implementation and much larger training datasets are required to achieve their highest potential. Machine learning methods face important challenges related to reproducibility of models and the desirability for prediction based on mechanistic understanding rather than post hoc associations (Beam et al., 2020). To this end, future research directions should not only move toward increasing sample sizes, but also facilitating open science (sharing codes and results) as we will discuss below.

## 7. Stratifying treatment – individualized response (precision medicine)

Combining big data and individual level phenotyping is extremely valuable in order to characterize the unique, additive and interactive effects of common and rare genetic variants on the developing brain. This approach might enable the characterization of the common and unique spatiotemporal brain characteristics across BD. By means of novel data mining approaches based on machine learning and pattern recognition, it is possible to use existing clinical imaging databases as training sets to identify clinically predictive brain patterns related to specific diagnostic categories, and then apply these models to clinical test samples characterized for treatment response or from RCTs. Indeed, using machine learning algorithms applied to purely clinical data, a recent study has been able to identify an accurate predictive model of response to lithium treatment in 1,266 BD patients with a particularly low false-positive rate (specificity 0.91) (Nunes et al., 2019). This work underlines how clinical data can inform out-of-sample lithium response prediction to a clinically relevant degree (Nunes et al., 2019). Similar approaches might be applied to brain imaging also in combination with genetic and clinical data. Variability of brain structure related to common genetic variants and polygenic scores can be applied to clinical data. This can include datasets collected in pharmacological trials, or other types of treatment, in interventional studies and prospective cohorts.

This novel brain based individual level phenotyping - "fingerprinting" - has great potential for stratification, defining prognosis and predicting treatment outcome. It represents a unique example of the power offered in combining large-scale normative data with rich clinical cohorts (Kaufmann et al., 2017). Jointly, this large-scale brain imaging approach might provide a novel glimpse into disease mechanisms and offer novel opportunities for brain-based stratification in future RCTs and clinical decision making. This big data approach applied to BD makes use of advanced biostatistical tools to estimate normative models of brain development based on huge datasets to form individual predictions in well-characterized clinical and prospective cohorts. This unique combination of hypothesis-generating data mining and carefully characterized samples might allow the identification of phenotypes cutting across clinical characteristics, enabling a new clinical nosology. Individual brain maps might be used against normative metrics in development to estimate the probability of clinical traits and outcomes. The vision is of an objective brain-based dissection and prediction of complex traits. In addition, combining big data with a personalized phenotype approach has the potential to investigate the sex specific characteristics of BD. In fact, BD has a specific exacerbation/onset immediately after delivery and women might be at increased risk during menopause as well (Bergink et al., 2016).

## 8. Smaller studies focussing on shorter term effects and clinical trials

With the exception of lithium, there has been no medicine developed with BD as its specific indication. Instead, innovation has been limited to medicines already approved for another indication (epilepsy or schizophrenia) like carbamazepine, valproate, lamotrigine and the dopamine antagonists/partial agonists. Clearly, we have lacked a convincing account of BD's pathophysiology. It has also been a problem that an effective treatment has traditionally been trialled in the manic phase, the depressive phase and in relapse prevention. Such studies are immensely expensive and, in the case of relapse prevention, very time consuming. Moreover, the development of long-term treatments – the greatest unmet need - may need to be de-coupled from the requirement for short term efficacy. Effective anti-epileptic agents are not necessarily effective in status epilepticus, to state one obvious analogy. Recent research on mood stability in BD suggests that experimental medicine studies in this disorder may be feasible, in which putative treatments are studied over relatively short but intensively monitored intervals in small groups of patients. More precise measurement may allow the treatment effects of different drugs to be compared in a more accurate way. Such an approach has potential to assist companies wishing to evaluate new compounds at the proof of concept stage. To give a single example, there is convergent evidence implicating calcium biochemistry in the neurobiology of BD (Harrison et al., 2019). Experimental studies are now entirely feasible to examine novel drugs that modify calcium channels in the brain and

an early confirmation of proof of concept would be essential before the necessary investment for clinical development.

However, it could also help in the re-purposing of existing drugs (Kessing et al., 2019). One of the most interesting recent findings has been the observation that commonly used drugs to treat physical disorders have an important effect on psychiatric admissions. Intriguingly, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), L-Type Calcium channel antagonists and biguanides are associated with reduced admissions and reports of self-harm in BD (and schizophrenia) (Hayes et al., 2019). It will be fruitful to coordinate single site/deep phenotyping studies with the big data approach in an iterative manner. This can provide large synergies, and help understand specific core pathology for BD, such as, for example, the switch process.

## 9. Moving forward - global bipolar disorder foundation

Our conclusions are simple. An increase in funding for BD would come at a highly opportune time given the seminal advances promised for our understanding of the genetic and brain basis of the disease and the obvious areas of unmet clinical need. It is conceivable that in the next two-three years, big data approach in BD research can provide new insights that can be translated into clinical care. One example is the application of polygenic risk scores for improved diagnosis (e.g. distinguishing between unipolar and bipolar depressive episodes). Another critical area for translation is applying deep learning algorithms to the huge amount of data collected via smartphones to improve forecasting of new episodes (time of event) (Busk et al., 2020; Faurholt-Jepsen et al., 2019). In any instance, to spend money wisely, requires a strategy for the goal of improved understanding and treatment of BD based on the need for very large samples. The time may be right to attract philanthropic donations specifically for this end.

### 9.1. The case for increased investment in BD now

BD has long attracted less support for research than its economic impact appears to demand. The contrast with schizophrenia was noted almost 20 years ago (Clement et al., 2003), and a systematic study of funding in the UK suggested little has changed since (MQ: Transforming Mental Health, 2018). There is an extraordinary difference in money spent on research on psychiatric disorders compared with cancer, cardiovascular disease and dementia. There is every reason to think that we are at a scientific crossroads now where a step change in research activity could yield the real returns on investment for BD that are apparent for medical research in general (Buxton et al., 2008).

### 9.2. A foundation for bipolar disorder

Harnessing the brightest and the best across the globe will require funding, but it will also benefit from greater coordination and a sense of strategy. Previous similar attempts in the area of mood disorders include the Stanley Foundation bipolar treatment outcome network (Altshuler et al., 2010), or the Mood Network of the patient-centred outcomes research institute (PCORI) (Selby et al., 2012). These initiatives failed to obtain the critical mass, necessary global involvement and scientific coordination that is needed to form a "game-changing" effort in BD research. However, we are not committed to a particular way of achieving these ends. We should look for inspiration in the private sector to the Michael J. Fox Foundation for Parkinson's research (https://www.michaeljfox.org). Parkinson's disease offers some analogies with BD. The Fox Foundation has massively raised awareness, provided leadership, increased communication and has become a critical funding vehicle for research. Cancer Research UK has been similarly successful in a quite different disease area and has offered world-class scientific direction in applying science to pathology. Finally, a public-private partnership like UK Biobank (www.ukbiobank.ac.uk) offers a further successful example of a generic platform that can serve a variety of different chronic disease areas and is intended for use world-wide. Unfortunately, it was not originally designed for diseases with onset in adolescence and early adulthood, like BD and the majority of psychiatric disorders.

We must create an appropriate mechanism for BD research which shamelessly copies what has worked well for other diseases. For example, a Global Foundation for Bipolar Disorder could provide a focus to bring government, industry and philanthropy together in common cause. Alternatively, there may already be more generic platforms to which BD questions can be appended, as has happened for dementia and UK Biobank, and from which a collaborative project can develop. The best scientists need to be motivated to join an international effort to beat BD. The human spirit will provide the genius to do the rest. However, an insistence on strategic direction and goal will be essential, which the foundation could provide.

### 9.3. Building an infrastructure and database

Thus, we recommend a task force to integrate international big data approach with real-world clinical interventions and longitudinal cohorts. By coordinated action, it is possible to obtain unique synergy by providing relevant clinical data to the big data analytical approaches and integrate big data results in a clinical trial network for the development of personalized treatment regimens. This is recently made possible due to technology development allowing high throughput, large scale genetic and brain imaging data collection, neurophysiological data as well as novel clinical ICT tools for efficient, user-based clinical assessments.

### 9.4. User involvement and dissemination

A critical factor for success is a strong involvement of user groups in the foundation and integration of dissemination and public involvement with the research programs. Frontline research discoveries in BD will, in addition to scientific breakthroughs, help reduce stigma and increase awareness,

which can impact the lives of people currently affected by the disorder.

### 9.5. Open science

There is rising concern about failures of replicability and associated waste of resources that seem to result from the traditional way in which science has been conducted. The Foundation can help establish a common database similar to the UK Biobank and a culture of open science in the BD research community. Open science generates transparent and accessible knowledge that is shared and developed through collaborative networks. Modern BD research in genetics and imaging is showing the way this works. Open science would be a defining feature of work funded through the Bipolar Disorder Foundation. Lack of data sharing is one of the main obstacles, which hinders the full realization of the potential of many research fields, which generate massive amounts of data per participants, such as brain imaging or genetics. Confidentiality and privacy issues are often cited as obstacles to such sharing, especially for legacy datasets. These problems must be taken seriously into account and the development of adequate ethical-legal framework, which would facilitate safe data sharing, should be a key and critical component of such international endeavors. The benefit to the society in terms of development of new diagnostic or prognostic tools for some of the most disabling and costly conditions will be potentially massive.

### 9.6. A roadmap to the global bipolar disorder foundation

The creation of a Global Foundation will depend on funding, coordination and the support of global network of experts in BD, as well as user groups and their families. A Global Foundation aims to promote the much-needed cross-fertilisation of expertise across leading world research institutions that is necessary to address the complexity of BD, overcome current limitations of knowledge and advance research in this field. We outline how 'big data' approaches can be an overreaching topic securing global, multidisciplinary and translational research support. It will be of importance of ensuring the participation of the main public and private stakeholders (NIH, EU, philanthropists), policymakers, as well as patients and family organizations. A Global Foundation will play ideally a pivotal role in disseminating the outputs produced through workshops, seminars and symposia organised at conferences. One specific task will be to support young clinicians and researchers with an interest in diverse areas of BD research."

## 10. Conclusion

We have argued that BD is an extremely significant challenge for the healthcare and the socio-economic system at a global level. We believe the time is right for a step change in our approach to understanding, preventing and treating it effectively. This can be achieved toward an innovative model integrating novel big data approaches with clinical studies.

## Role of funding sources

Supported by unrestricted grants from the ECNP network program, Research Council of Norway (#223273), and European Union's Horizon 2020 research and innovation programme (#847776).

## Contributors

The concept and content of the paper were outlined and discussed on the ECNP Bipolar Disorder Network meeting in Copenhagen 2019. MM, OBS, EV, GG, OAA drafted the manuscript. All authors revised and approved the final version

## Conflict of Interest

OAA has received speaker honorarium from Lundbeck, and is a consultant to HealthLytix. LVK declares having received consultancy fees from Lundbeck in the past three years. AB declares having received travelling fees and funding for IITs from Otsuka and Janssen. REN has received research grants from H. Lundbeck and Otsuka Pharmaceuticals for clinical trials, received speaking fees from Bristol-Myers Squibb, Astra Zeneca, Janssen & Cilag, Lundbeck, Servier, Otsuka Pharmaceuticals, Teva A/S, and Eli Lilly and has acted as advisor to Astra Zeneca, Eli Lilly, Lundbeck, Otsuka Pharmaceuticals, Takeda, and Medivir. AGP has received grants and served as consultant, advisor or CME speaker for the following entities: Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Sanofi-Aventis, Alter, Angelini, Exeltis, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), the Basque Governement, the Stanley Medical Research Institute. RWL has received research grant from Glaxo Smith Kline, honoraria for lecturing from Pfizer, Glaxo Smith Kline, Eli Lilly, Astra-Zeneca, Bristol-Myers Squibb, Janssen Cilag, Lundbeck, Otsuka, Servier and honoraria from advisory board activity from Glaxo Smith Kline, Eli Lilly, Astra-Zeneca, Bristol-Myers Squibb, Janssen Cilag, Sunovion and Sage. AR as served on advisory boards of Janssen, SAGE, Shire/Takeda and Medice; has received speaker's honoraria from Janssen, Medice, Shire/Takeda, Servier, and Neuraxpharm; and has received research grants from Medice. GG is a NIHR Emeritus Senior Investigator, holds shares in P1vital and P1Vital products and has served as consultant, advisor or CME speaker in the last 3 years for Allergan, Angelini, Compass pathways, MSD, Janssen, Lundbeck (/Otsuka or /Takeda), Medscape, Minerva, P1Vital, Pfizer, Sage, Servier, Shire, Sun Pharma. All other authors declare no conflict of interest.

## Acknowledgements

We thank Chris Chang for input on the description of the ENIGMA project. The views expressed are those of the au-

thor(s) and not necessarily those of the NHS, the NIHR or the Department of Health in the UK. Ole A. Andreassen is together with Paolo Fusar-Poli co-chairing the Prevention of Severe Mental Disorders (PSMD) cluster, which is supported by the European Brain Research Area project. EBRA has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825348.

## References

Aas, M., Melle, I., Bettella, F., Djurovic, S., Le Hellard, S., Bjella, T., Ringen, P.A., Lagerberg, T.V., Smeland, O.B., Agartz, I., 2018. Psychotic patients who used cannabis frequently before illness onset have higher genetic predisposition to schizophrenia than those who did not. Psychol. Med. 48, 43–49.

Ahmed, A.T., Frye, M.A., Rush, A.J., Biernacka, J.M., Craighead, W.E., McDonald, W.M., Bobo, W.V., Riva-Posse, P., Tye, S.J., Mayberg, H.S., 2018. Mapping depression rating scale phenotypes onto research domain criteria (RDoC) to inform biological research in mood disorders. J. Affect. Disord. 238, 1–7.

Altimus, C., 2019. Supporting Wellness: A Survey of Lived Experience. Milken Institute.

Altshuler, L.L., Kupka, R.W., Hellemann, G., Frye, M.A., Sugar, C.A., McElroy, S.L., Nolen, W.A., Grunze, H., Leverich, G.S., Keck, P.E., Zermeno, M., Post, R.M., Suppes, T., 2010. Gender and depressive symptoms in 711 patients with bipolar disorder evaluated prospectively in the stanley foundation bipolar treatment outcome network. Am. J. Psychiatry 167, 708–715.

Andlauer, T.F.M., Guzman-Parra, J., Streit, F., Strohmaier, J., Gonzalez, M.J., Flores, S.G., Fabeiro, F.J.C., del Rio Noriega, F., Perez, F.P., Gonzalez, J.H., 2019. Bipolar multiplex families have an increased burden of common risk variants for psychiatric disorders. Mol. Psychiatry 1–13.

Andreassen, O.A., Djurovic, S., Thompson, W.K., Schork, A.J., Kendler, K.S., O'Donovan, M.C., Rujescu, D., Werge, T., van de Bunt, M., Morris, A.P., 2013a. Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. Am. J. Hum. Genet. 92, 197–209.

Andreassen, O.A., Thompson, W.K., Schork, A.J., Ripke, S., Mattingsdal, M., Kelsoe, J.R., Kendler, K.S., O'Donovan, M.C., Rujescu, D., Werge, T., 2013b. Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional false discovery rate. PLoS Genet. 9, e1003455.

Arvilommi, P., Suominen, K., Mantere, O., Valtonen, H., Leppämäki, S., Isometsä, E., 2015. Predictors of long-term work disability among patients with type I and II bipolar disorder: a prospective 18-month follow-up study. Bipolar Disord. 17, 821–835.

Bauer, M., Andreassen, O.A., Geddes, J.R., Kessing, L.V., Lewitzka, U., Schulze, T.G., Vieta, E., 2018. Areas of uncertainties and unmet needs in bipolar disorders: clinical and research perspectives. Lancet Psychiatry 5, 930–939.

Bauer, M., Glenn, T., Alda, M., Andreassen, O.A., Angelopoulos, E., Ardau, R., Baethge, C., Bauer, R., Bellivier, F., Belmaker, R.H., Berk, M., Bjella, T.D., Bossini, L., Bersudsky, Y., Cheung, E.Y.W., Conell, J., Del Zompo, M., Dodd, S., Etain, B., Fagiolini, A., Frye, M.A., Fountoulakis, K.N., Garneau-Fournier, J., Gonzalez-Pinto, A., Harima, H., Hassel, S., Henry, C., Iacovides, A., Isometsä, E.T., Kapczinski, F., Kliwicki, S., König, B., Krogh, R., Kunz, M., Lafer, B., Larsen, E.R., Lewitzka, U., Lopez-Jaramillo, C., MacQueen, G., Manchia, M., Marsh, W., Martinez-Cengotitabengoa, M., Melle, I., Monteith, S., Morken, G., Munoz, R., Nery, F.G., O'Donovan, C., Osher, Y., Pfennig, A., Quiroz, D., Ramesar, R., Rasgon, N., Reif, A., Ritter, P., Rybakowski, J.K., Sagduyu, K., Scippa, A.M., Severus, E., Simhandl, C., Stein, D.J., Strejilevich, S., Hatim Sulaiman, A., Suominen, K., Tagata, H., Tatebayashi, Y., Torrent, C., Vieta, E., Viswanath, B., Wanchoo, M.J., Zetin, M., Whybrow, P.C., 2015. Influence of birth cohort on age of onset cluster analysis in bipolar I disorder. Eur. Psychiatry 30.

Bauer, M., Glenn, T., Monteith, S., Bauer, R., Whybrow, P.C., Geddes, J., 2017. Ethical perspectives on recommending digital technology for patients with mental illness. Int. J. Bipolar Disord. 5, 1–14.

Beam, A.L., Manrai, A.K., Ghassemi, M., 2020. Challenges to the reproducibility of machine learning models in health care. JAMA 323 (4), 305–306.

Bergink, V., Rasgon, N., Wisner, K.L., 2016. Postpartum psychosis: madness, mania, and melancholia in motherhood. Am. J. Psychiatry 173, 1179–1188.

Bonnín, C.M., Jiménez, E., Solé, B., Torrent, C., Radua, J., Reinares, M., Grande, I., Ruíz, V., Sánchez-Moreno, J., Martínez-Arán, A., 2019. Lifetime psychotic symptoms, subthreshold depression and cognitive impairment as barriers to functional recovery in patients with bipolar disorder. J. Clin. Med. 8, 1046.

Brainstorm Consortium, V., Anttila, V., Bulik-Sullivan, B., Finucane, H.K., Walters, R.K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G.J., Gormley, P., Malik, R., Patsopoulos, N.A., Ripke, S., Wei, Z., Yu, D., Lee, P.H., Turley, P., Grenier-Boley, B., Chouraki, V., Kamatani, Y., Berr, C., Letenneur, L., Hannequin, D., Amouyel, P., Boland, A., Deleuze, J.-.F., Duron, E., Vardarajan, B.N., Reitz, C., Goate, A.M., Huentelman, M.J., Kamboh, M.I., Larson, E.B., Rogaeva, E., St George-Hyslop, P., Hakonarson, H., Kukull, W.A., Farrer, L.A., Barnes, L.L., Beach, T.G., Demirci, F.Y., Head, E., Hulette, C.M., Jicha, G.A., Kauwe, J.S.K., Kaye, J.A., Leverenz, J.B., Levey, A.I., Lieberman, A.P., Pankratz, V.S., Poon, W.W., Quinn, J.F., Saykin, A.J., Schneider, L.S., Smith, A.G., Sonnen, J.A., Stern, R.A., Van Deerlin, V.M., Van Eldik, L.J., Harold, D., Russo, G., Rubinsztein, D.C., Bayer, A., Tsolaki, M., Proitsi, P., Fox, N.C., Hampel, H., Owen, M.J., Mead, S., Passmore, P., Morgan, K., Nöthen, M.M., Rossor, M., Lupton, M.K., Hoffmann, P., Kornhuber, J., Lawlor, B., McQuillin, A., Al-Chalabi, A., Bis, J.C., Ruiz, A., Boada, M., Seshadri, S., Beiser, A., Rice, K., van der Lee, S.J., De Jager, P.L., Geschwind, D.H., Riemenschneider, M., Riedel-Heller, S., Rotter, J.I., Ransmayr, G., Hyman, B.T., Cruchaga, C., Alegret, M., Winsvold, B., Palta, P., Farh, K.-.H., Cuenca-Leon, E., Furlotte, N., Kurth, T., Ligthart, L., Terwindt, G.M., Freilinger, T., Ran, C., Gordon, S.D., Borck, G., Adams, H.H.H., Lehtimäki, T., Wedenoja, J., Buring, J.E., Schürks, M., Hrafnsdottir, M., Hottenga, J.-.J., Penninx, B., Artto, V., Kaunisto, M., Vepsäläinen, S., Martin, N.G., Montgomery, G.W., Kurki, M.I., Hämäläinen, E., Huang, H., Huang, J., Sandor, C., Webber, C., Muller-Myhsok, B., Schreiber, S., Salomaa, V., Loehrer, E., Göbel, H., Macaya, A., Pozo-Rosich, P., Hansen, T., Werge, T., Kaprio, J., Metspalu, A., Kubisch, C., Ferrari, M.D., Belin, A.C., van den Maagdenberg, A.M.J.M., Zwart, J.-.A., Boomsma, D., Eriksson, N., Olesen, J., Chasman, D.I., Nyholt, D.R., Avbersek, A., Baum, L., Berkovic, S., Bradfield, J., Buono, R.J., Catarino, C.B., Cossette, P., De Jonghe, P., Depondt, C., Dlugos, D., Ferraro, T.N., French, J., Hjalgrim, H., Jamnadas-Khoda, J., Kälviäinen, R., Kunz, W.S., Lerche, H., Leu, C., Lindhout, D., Lo, W., Lowenstein, D., McCormack, M., Møller, R.S., Molloy, A., Ng, P.-.W., Oliver, K., Privitera, M., Radtke, R., Ruppert, A.-.K., Sander, T., Schachter, S., Schankin, C., Scheffer, I., Schoch, S., Sisodiya, S.M., Smith, P., Sperling, M., Striano, P., Surges, R., Thomas, G.N., Visscher, F., Whelan, C.D.,

Zara, F., Heinzen, E.L., Marson, A., Becker, F., Stroink, H., Zimprich, F., Gasser, T., Gibbs, R., Heutink, P., Martinez, M., Morris, H.R., Sharma, M., Ryten, M., Mok, K.Y., Pulit, S., Bevan, S., Holliday, E., Attia, J., Battey, T., Boncoraglio, G., Thijs, V., Chen, W.-.M., Mitchell, B., Rothwell, P., Sharma, P., Sudlow, C., Vicente, A., Markus, H., Kourkoulis, C., Pera, J., Raffeld, M., Silliman, S., Boraska Perica, V., Thornton, L.M., Huckins, L.M., William Rayner, N., Lewis, C.M., Gratacos, M., Rybakowski, F., Keski-Rahkonen, A., Raevuori, A., Hudson, J.I., Reichborn-Kjennerud, T., Monteleone, P., Karwautz, A., Mannik, K., Baker, J.H., O'Toole, J.K., Trace, S.E., Davis, O.S.P., Helder, S.G., Ehrlich, S., Herpertz-Dahlmann, B., Danner, U.N., van Elburg, A.A., Clementi, M., Forzan, M., Docampo, E., Lissowska, J., Hauser, J., Tortorella, A., Maj, M., Gonidakis, F., Tziouvas, K., Papezova, H., Yilmaz, Z., Wagner, G., Cohen-Woods, S., Herms, S., Julià, A., Rabionet, R., Dick, D.M., Ripatti, S., Andreassen, O.A., Espeseth, T., Lundervold, A.J., Steen, V.M., Pinto, D., Scherer, S.W., Aschauer, H., Schosser, A., Alfredsson, L., Padyukov, L., Halmi, K.A., Mitchell, J., Strober, M., Bergen, A.W., Kaye, W., Szatkiewicz, J.P., Cormand, B., Ramos-Quiroga, J.A., Sánchez-Mora, C., Ribasés, M., Casas, M., Hervas, A., Arranz, M.J., Haavik, J., Zayats, T., Johansson, S., Williams, N., Dempfle, A., Rothenberger, A., Kuntsi, J., Oades, R.D., Banaschewski, T., Franke, B., Buitelaar, J.K., Arias Vasquez, A., Doyle, A.E., Reif, A., Lesch, K.-.P., Freitag, C., Rivero, O., Palmason, H., Romanos, M., Langley, K., Rietschel, M., Witt, S.H., Dalsgaard, S., Børglum, A.D., Waldman, I., Wilmot, B., Molly, N., Bau, C.H.D., Crosbie, J., Schachar, R., Loo, S.K., McGough, J.J., Grevet, E.H., Medland, S.E., Robinson, E., Weiss, L.A., Bacchelli, E., Bailey, A., Bal, V., Battaglia, A., Betancur, C., Bolton, P., Cantor, R., Celestino-Soper, P., Dawson, G., De Rubeis, S., Duque, F., Green, A., Klauck, S.M., Leboyer, M., Levitt, P., Maestrini, E., Mane, S., De-Luca, D.M.-., Parr, J., Regan, R., Reichenberg, A., Sandin, S., Vorstman, J., Wassink, T., Wijsman, E., Cook, E., Santangelo, S., Delorme, R., Rogé, B., Magalhaes, T., Arking, D., Schulze, T.G., Thompson, R.C., Strohmaier, J., Matthews, K., Melle, I., Morris, D., Blackwood, D., McIntosh, A., Bergen, S.E., Schalling, M., Jamain, S., Maaser, A., Fischer, S.B., Reinbold, C.S., Fullerton, J.M., Guzman-Parra, J., Mayoral, F., Schofield, P.R., Cichon, S., Mühleisen, T.W., Degenhardt, F., Schumacher, J., Bauer, M., Mitchell, P.B., Gershon, E.S., Rice, J., Potash, J.B., Zandi, P.P., Craddock, N., Ferrier, I.N., Alda, M., Rouleau, G.A., Turecki, G., Ophoff, R., Pato, C., Anjorin, A., Stahl, E., Leber, M., Czerski, P.M., Cruceanu, C., Jones, I.R., Posthuma, D., Andlauer, T.F.M., Forstner, A.J., Streit, F., Baune, B.T., Air, T., Sinnamon, G., Wray, N.R., MacIntyre, D.J., Porteous, D., Homuth, G., Rivera, M., Grove, J., Middeldorp, C.M., Hickie, I., Pergadia, M., Mehta, D., Smit, J.H., Jansen, R., de Geus, E., Dunn, E., Li, Q.S., Nauck, M., Schoevers, R.A., Beekman, A.T., Knowles, J.A., Viktorin, A., Arnold, P., Barr, C.L., Bedoya-Berrio, G., Bienvenu, O.J., Brentani, H., Burton, C., Camarena, B., Cappi, C., Cath, D., Cavallini, M., Cusi, D., Darrow, S., Denys, D., Derks, E.M., Dietrich, A., Fernandez, T., Figee, M., Freimer, N., Gerber, G., Grados, M., Greenberg, E., Hanna, G.L., Hartmann, A., Hirschtritt, M.E., Hoekstra, P.J., Huang, A., Huyser, C., Illmann, C., Jenike, M., Kuperman, S., Leventhal, B., Lochner, C., Lyon, G.J., Macciardi, F., Madruga-Garrido, M., Malaty, I.A., Maras, A., McGrath, L., Miguel, E.C., Mir, P., Nestadt, G., Nicolini, H., Okun, M.S., Pakstis, A., Paschou, P., Piacentini, J., Pittenger, C., Plessen, K., Ramensky, V., Ramos, E.M., Reus, V., Richter, M.A., Riddle, M.A., Robertson, M.M., Roessner, V., Rosário, M., Samuels, J.F., Sandor, P., Stein, D.J., Tsetsos, F., Van Nieuwerburgh, F., Weatherall, S., Wendland, J.R., Wolanczyk, T., Worbe, Y., Zai, G., Goes, F.S., McLaughlin, N., Nestadt, P.S., Grabe, H.-.J., Depienne, C., Konkashbaev, A., Lanzagorta, N., Valencia-Duarte, A., Bramon, E., Buccola, N., Cahn, W., Cairns, M., Chong, S.A., Cohen, D., Crespo-Facorro, B., Crowley, J., Davidson, M., DeLisi, L., Dinan, T., Donohoe, G., Drapeau, E., Duan, J., Haan, L., Hougaard, D., Karachanak-Yankova, S., Khrunin, A., Klovins, J., Kučinskas, V., Lee Chee Keong, J., Limborska, S., Loughland, C., Lönnqvist, J., Maher, B., Mattheisen, M., McDonald, C., Murphy, K.C., Nenadic, I., van Os, J., Pantelis, C., Pato, M., Petryshen, T., Quested, D., Roussos, P., Sanders, A.R., Schall, U., Schwab, S.G., Sim, K., So, H.-.C., Stögmann, E., Subramaniam, M., Toncheva, D., Waddington, J., Walters, J., Weiser, M., Cheng, W., Cloninger, R., Curtis, D., Gejman, P.V., Henskens, F., Mattingsdal, M., Oh, S.-.Y., Scott, R., Webb, B., Breen, G., Churchhouse, C., Bulik, C.M., Daly, M., Dichgans, M., Faraone, S.V., Guerreiro, R., Holmans, P., Kendler, K.S., Koeleman, B., Mathews, C.A., Price, A., Scharf, J., Sklar, P., Williams, J., Wood, N.W., Cotsapas, C., Palotie, A., Smoller, J.W., Sullivan, P., Rosand, J., Corvin, A., Neale, B.M., Schott, J.M., Anney, R., Elia, J., Grigoroiu-Serbanescu, M., Edenberg, H.J., Murray, R., 2018. In: Analysis of Shared Heritability in Common Disorders of the Brain, 360. Science, p. eaap8757.

Busk, J., Faurholt-Jepsen, M., Frost, M., Bardram, J.E., Vedel Kessing, L., Winther, O., 2020. Forecasting mood in bipolar disorder from smartphone self-assessments: hierarchical bayesian approach. JMIR mHealth uHealth 8, e15028.

Buxton, M., Hanney, S., Morris, S., Sundmacher, L., Mestre-Ferrandiz, J., Garau, M., Sussex, J., Grant, J., Ismail, S., Nason, E., 2008. Medical Research: What's it Worth? Estimating the Economic Benefits from Medical Research in the UK. UK Evaluation Forum (Academy of Medical Sciences, MRC, Wellcome Trust, London.

Calvert, M., Kyte, D., Mercieca-Bebber, R., Slade, A., Chan, A.-.W., King, M.T., Hunn, A., Bottomley, A., Regnault, A., Ells, C., 2018. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension. JAMA 319, 483–494.

Campbell, I.H., Campbell, H., 2019. Ketosis and bipolar disorder: controlled analytic study of online reports. BJPsych Open 5 (4), e58.

Carvalho, A.F., Köhler, C.A., Fernandes, B.S., Quevedo, J., Miskowiak, K.W., Brunoni, A.R., Machado-Vieira, R., Maes, M., Vieta, E., Berk, M., 2016. Bias in emerging biomarkers for bipolar disorder. Psychol. Med. 46, 2287–2297.

Chase, H.W., Fournier, J.C., Greenberg, T., Almeida, J.R., Stiffler, R., Zevallos, C.R., Aslam, H., Cooper, C., Deckersbach, T., Weyandt, S., Adams, P., Toups, M., Carmody, T., Oquendo, M.A., Peltier, S., Fava, M., McGrath, P.J., Weissman, M., Parsey, R., McInnis, M.G., Kurian, B., Trivedi, M.H., Phillips, M.L., 2015. Accounting for Dynamic Fluctuations across Time when Examining fMRI Test-Retest Reliability: analysis of a Reward Paradigm in the EMBARC Study. PLoS ONE 10, e0126326.

Chengappa, K.N., Kupfer, D.J., Frank, E., Houck, P.R., Grochocinski, V.J., Cluss, P.A., Stapf, D.A., 2003. Relationship of birth cohort and early age at onset of illness in a bipolar disorder case registry. Am J Psychiatry 160, 1636–1642.

Clement, S., Singh, S.P., Burns, T., 2003. Status of bipolar disorder research: bibliometric study. Br. J. Psychiatry 182, 148–152.

Cloutier, M., Greene, M., Guerin, A., Touya, M., Wu, E., 2018. The economic burden of bipolar I disorder in the United States in 2015. J. Affect. Disord. 226, 45–51.

Coleman, J.R.I., Gaspar, H.A., Bryois, J., Byrne, E.M., Forstner, A.J., Holmans, P.A., de Leeuw, C.A., Mattheisen, M., McQuillin, A., Pavlides, J.M.W., 2019. The genetics of the mood disorder spectrum: Genome-wide Association analyses of more than 185,000 cases and 439,000 controls. Biol. Psychiatry.

Won, V., Feng, H., C.A., Y., Rosenthal, J., Zhu, Z., Tucker-Drob, E.M., Nivard, M.G., Grotzinger, A.D., Posthuma, D., Wang, M.M.-J., Yu, D., Stahl, E.A., Walters, R.K., Anney, R.J.L., Duncan, L.E., Ge, T., Adolfsson, R., Banaschewski, T., Be-

langero, S., Cook, E.H., Coppola, G., Derks, E.M., Hoekstra, P.J., Kaprio, J., Keski-Rahkonen, A., Kirov, G., Kranzler, H.R., Luykx, J.J., Rohde, L.A., Zai, C.C., Agerbo, E., Arranz, M.J., Asherson, P., Bækvad-Hansen, M., Baldursson, G., Bellgrove, M., Belliveau, R.A., Buitelaar, J., Burton, C.L., Bybjerg-Grauholm, J., Casas, M., Cerrato, F., Chambert, K., Churchhouse, C., Cormand, B., Crosbie, J., Dalsgaard, S., Demontis, D., Doyle, A.E., Dumont, A., Elia, J., Grove, J., Gudmundsson, O.O., Haavik, J., Hakonarson, H., Hansen, C.S., Hartman, C.A., Hawi, Z., Hervás, A., Hougaard, D.M., Howrigan, D.P., Huang, H., Kuntsi, J., Langley, K., Lesch, K.-P., Leung, P.W.L., Loo, S.K., Martin, J., Martin, A.R., McGough, J.J., Medland, S.E., Moran, J.L., Mors, O., Mortensen, P.B., Oades, R.D., Palmer, D.S., Pedersen, C.B., Pedersen, M.G., Peters, T., Poterba, T., Poulsen, J.B., Ramos-Quiroga, J.A., Reif, A., Ribasés, M., Rothenberger, A., Rovira, P., Sánchez-Mora, C., Satterstrom, F.K., Schachar, R., Artigas, M.S., Steinberg, S., Stefansson, H., Turley, P., Walters, G.B., Werge, T., Zayats, T., Arking, D.E., Bettella, F., Buxbaum, J.D., Christensen, J.H., Collins, R.L., Coon, H., De Rubeis, S., Delorme, R., Grice, D.E., Hansen, T.F., Holmans, P.A., Hope, S., Hultman, C.M., Klei, L., Ladd-Acosta, C., Magnusson, P., Nærland, T., Nyegaard, M., Pinto, D., Qvist, P., Rehnström, K., Reichenberg, A., Reichert, J., Roeder, K., Rouleau, G.A., Saemundsen, E., Sanders, S.J., Sandin, S., St Pourcain, B., Stefansson, K., Sutcliffe, J.S., Talkowski, M.E., Weiss, L.A., Willsey, A.J., Agartz, I., Akil, H., Albani, D., Alda, M., Als, T.D., Anjorin, A., Backlund, L., Bass, N., Bauer, M., Baune, B.T., Bellivier, F., Bergen, S.E., Berrettini, W.H., Biernacka, J.M., Blackwood, D.H.R., Bøen, E., Budde, M., Bunney, W., Burmeister, M., Byerley, W., Byrne, E.M., Cichon, S., Clarke, T.-K., Coleman, J.R.I., Craddock, N., Curtis, D., Czerski, P.M., Dale, A.M., Dalkner, N., Dannlowski, U., Degenhardt, F., Di Florio, A., Elvsåshagen, T., Etain, B., Fischer, S.B., Forstner, A.J., Forty, L., Frank, J., Frye, M., Fullerton, J.M., Gade, K., Gaspar, H.A., Gershon, E.S., Gill, M., Goes, F.S., Gordon, S.D., Gordon-Smith, K., Green, M.J., Greenwood, T.A., Grigoroiu-Serbanescu, M., Guzman-Parra, J., Hauser, J., Hautzinger, M., Heilbronner, U., Herms, S., Hoffmann, P., Holland, D., Jamain, S., Jones, I., Jones, L.A., Kandaswamy, R., Kelsoe, J.R., Kennedy, J.L., Joachim, O.K., Kittel-Schneider, S., Kogevinas, M., Koller, A.C., Lavebratt, C., Lewis, C.M., Li, Q.S., Lissowska, J., Loohuis, L.M.O., Lucae, S., Maaser, A., Malt, U.F., Martin, N.G., Martinsson, L., McElroy, S.L., McMahon, F.J., McQuillin, A., Melle, I., Metspalu, A., Millischer, V., Mitchell, P.B., Montgomery, G.W., Morken, G., Morris, D.W., Müller-Myhsok, B., Mullins, N., Myers, R.M., Nievergelt, C.M., Nordentoft, M., Adolfsson, A.N., Nöthen, M.M., Ophoff, R.A., Owen, M.J., Paciga, S.A., Pato, C.N., Pato, M.T., Perlis, R.H., Perry, A., Potash, J.B., Reinbold, C.S., Rietschel, M., Rivera, M., Roberson, M., Schalling, M., Schofield, P.R., Schulze, T.G., Scott, L.J., Serretti, A., Sigurdsson, E., Smeland, O.B., Stordal, E., Streit, F., Strohmaier, J., Thorgeirsson, T.E., Treutlein, J., Turecki, G., Vaaler, A.E., Vieta, E., Vincent, J.B., Wang, Y., Witt, S.H., Zandi, P., Adan, R.A.H., Alfredsson, L., Ando, T., Aschauer, H., Baker, J.H., Bencko, V., Bergen, A.W., Birgegård, A., Perica, V.B., Brandt, H., Burghardt, R., Carlberg, L., Cassina, M., Clementi, M., Courtet, P., Crawford, S., Crow, S., Crowley, J.J., Danner, U.N., Davis, O.S.P., Degortes, D., DeSocio, J.E., Dick, D.M., Dina, C., Docampo, E., Egberts, K., Ehrlich, S., Espeseth, T., Fernández-Aranda, F., Fichter, M.M., Foretova, L., Forzan, M., Gambaro, G., Giegling, I., Gonidakis, F., Gorwood, P., Mayora, M.G., Guo, Y., Halmi, K.A., Hatzikotoulas, K., Hebebrand, J., Helder, S.G., Herpertz-Dahlmann, B., Herzog, W., Hinney, A., Imgart, H., Jiménez-Murcia, S., Johnson, C., Jordan, J., Julià, A., Kaminská, D., Karhunen, L., Karwautz, A., Kas, M.J.H., Kaye, W.H., Kennedy, M.A., Kim, Y.-R., Klareskog, L., Klump, K.L., Knudsen, G.P.S., Landén, M., Le Hellard, S., Levitan, R.D., Li, D., Lichtenstein, P., Maj, M., Marsal, S., McDevitt, S., Mitchell, J., Monteleone, P., Monteleone, A.M., Munn-Chernoff, M.A., Nacmias, B., Navratilova, M., O'Toole, J.K., Padyukov, L., Pantel, J., Papezova, H., Rabionet, R., Raevuori, A., Ramoz, N., Reichborn-Kjennerud, T., Ricca, V., Roberts, M., Rujescu, D., Rybakowski, F., Scherag, A., Schmidt, U., Seitz, J., Slachtova, L., Slof-Op't Landt, M.C.T., Slopien, A., Sorbi, S., Southam, L., Strober, M., Tortorella, A., Tozzi, F., Treasure, J., Tziouvas, K., van Elburg, A.A., Wade, T.D., Wagner, G., Walton, E., Watson, H.J., Wichmann, H.-E., Woodside, D.B., Zeggini, E., Zerwas, S., Zipfel, S., Adams, M.J., Andlauer, T.F.M., Berger, K., Binder, E.B., Boomsma, D.I., Castelao, E., Colodro-Conde, L., Direk, N., Docherty, A.R., Domenici, E., Domschke, K., Dunn, E.C., Foo, J.C., de. Geus, E.J.C., Grabe, H.J., Hamilton, S.P., Horn, C., Hottenga, J.-J., Howard, D., Ising, M., Kloiber, S., Levinson, D.F., Lewis, G., Magnusson, P.K.E., Mbarek, H., Middeldorp, C.M., Mostafavi, S., Nyholt, D.R., Penninx, B.W., Peterson, R.E., Pistis, G., Porteous, D.J., Preisig, M., Quiroz, J.A., Schaefer, C., Schulte, E.C., Shi, J., Smith, D.J., Thomson, P.A., Tiemeier, H., Uher, R., van der Auwera, S., Weissman, M.M., Alexander, M., Begemann, M., Bramon, E., Buccola, N.G., Cairns, M.J., Campion, D., Carr, V.J., Cloninger, C.R., Cohen, D., Collier, D.A., Corvin, A., DeLisi, L.E., Donohoe, G., Dudbridge, F., Duan, J., Freedman, R., Gejman, P.V., Golimbet, V., Godard, S., Ehrenreich, H., Hartmann, A.M., Henskens, F.A., Ikeda, M., Iwata, N., Jablensky, A.V., Joa, I., Jönsson, E.G., Kelly, B.J., Knight, J., Konte, B., Laurent-Levinson, C., Lee, J., Lencz, T., Lerer, B., Loughland, C.M., Malhotra, A.K., Mallet, J., McDonald, C., Mitjans, M., Mowry, B.J., Murphy, K.C., Murray, R.M., O'Neill, F.A., Oh, S.-Y., Palotie, A., Pantelis, C., Pulver, A.E., Petryshen, T.L., Quested, D.J., Riley, B., Sanders, A.R., Schall, U., Schwab, S.G., Scott, R.J., Sham, P.C., Silverman, J.M., Sim, K., Steixner, A.A., Tooney, P.A., van Os, J., Vawter, M.P., Walsh, D., Weiser, M., Wildenauer, D.B., Williams, N.M., Wormley, B.K., Zhang, F., Androutsos, C., Arnold, P.D., Barr, C.L., Barta, C., Bey, K., Bienvenu, O.J., Black, D.W., Brown, L.W., Budman, C., Cath, D., Cheon, K.-A., Ciullo, V., Coffey, B.J., Cusi, D., Davis, L.K., Denys, D., Depienne, C., Dietrich, A., Eapen, V., Falkai, P., Fernandez, T.V., Garcia-Delgar, B., Geller, D.A., Gilbert, D.L., Grados, M.A., Greenberg, E., Grünblatt, E., Hagstrøm, J., Hanna, G.L., Hartmann, A., Hedderly, T., Heiman, G.A., Heyman, I., Hong, H.J., Huang, A., Huyser, C., Ibanez-Gomez, L., Khramtsova, E.A., Kim, Y.K., Kim, Y.-S., King, R.A., Koh, Y.-J., Konstantinidis, A., Kook, S., Kuperman, S., Leventhal, B.L., Lochner, C., Ludolph, A.G., Madruga-Garrido, M., Malaty, I., Maras, A., McCracken, J.T., Meijer, I.A., Mir, P., Morer, A., Müller-Vahl, K.R., Münchau, A., Murphy, T.L., Naarden, A., Nagy, P., Nestadt, G., Nestadt, P.S., Nicolini, H., Nurmi, E.L., Okun, M.S., Paschou, P., Fabrizio, Piras, Federica, Piras, Pittenger, C., Plessen, K.J., Richter, M.A., Rizzo, R., Robertson, M., Roessner, V., Ruhrmann, S., Samuels, J.F., Sandor, P., Schlögelhofer, M., Shin, E.-Y., Singer, H., Song, D.-H., Song, J., Spalletta, G., Stein, D.J., Stewart, S.E., Storch, E.A., Stranger, B., Stuhrmann, M., Tarnok, Z., Tischfield, J.A., Tübing, J., Visscher, F., Vulink, N., Wagner, M., Walitza, S., Wanderer, S., Woods, M., Worbe, Y., Zai, G., Zinner, S.H., Sullivan, P.F., Franke, B., Daly, M.J., Bulik, C.M., Lewis, C.M., McIntosh, A.M., O'Donovan, M.C., Zheutlin, A., Andreassen, O.A., Børglum, A.D., Breen, G., Edenberg, H.J., Fanous, A.H., Faraone, S.V., Gelernter, J., Mathews, C.A., Mattheisen, M., Mitchell, K.S., Neale, M.C., Nurnberger, J.I., Ripke, S., Santangelo, S.L., Scharf, J.M., Stein, M.B., Thornton, L.M., Walters, J.T.R., Wray, N.R., Geschwind, D.H., Neale, B.M., Kendler, K.S., Smoller, J.W.Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019. Genomic relationships, novel

loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell 179, 1469–1482 e11.
Davenport, K., Hardy, G., Tai, S., Mansell, W., 2018. Individual experiences of psychological-based interventions for bipolar disorder: a systematic review and thematic synthesis. Psychol. Psychother. Theory, Res. Pract. 92 (4), 499–522.
Di Florio, A., Gordon-Smith, K., Forty, L., Kosorok, M.R., Fraser, C., Perry, A., Bethell, A., Craddock, N., Jones, L., Jones, I., 2018. Stratification of the risk of bipolar disorder recurrences in pregnancy and postpartum. Br. J. Psychiatry 213, 542–547.
Duffy, A., Goodday, S., Keown-Stoneman, C., Grof, P., 2018. The emergent course of bipolar disorder: observations over two decades from the Canadian high-risk offspring cohort. Am. J. Psychiatry APPI-AJP.
Etain, B., Dumaine, A., Mathieu, F., Chevalier, F., Henry, C., Kahn, J.-.P., Deshommes, J., Bellivier, F., Leboyer, M., Jamain, S., 2010. A SNAP25 promoter variant is associated with early-onset bipolar disorder and a high expression level in brain. Mol. Psychiatry 15, 748–755.
Faurholt-Jepsen, M., Bauer, M., Kessing, L.V., 2018. Smartphone-based objective monitoring in bipolar disorder: status and considerations. Int. J. Bipolar Disord. 6, 1–7.
Faurholt-Jepsen, M., Torri, E., Cobo, J., Yazdanyar, D., Palao, D., Cardoner, N., Andreatta, O., Mayora, O., Kessing, L.V., 2019. Smartphone-based self-monitoring in bipolar disorder: evaluation of usability and feasibility of two systems. Int. J. Bipolar Disord. 7, 1.
Faurholt-Jepsen, M., Frost, M., Busk, J., Christensen, E.M., Bardram, J.E., Vinberg, M., Kessing, L.V., 2019. Is smartphone-based mood instability associated with stress, quality of life, and functioning in bipolar disorder? Bipolar Disord. 21 (7), 611–620.
Ferrari, A.J., Stockings, E., Khoo, J.-.P., Erskine, H.E., Degenhardt, L., Vos, T., Whiteford, H.A., 2016. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. Bipolar Disord 18, 440–450.
Fries, G.R., Zamzow, M.J., Andrews, T., Pink, O., Scaini, G., Quevedo, J., 2020. Accelerated aging in bipolar disorder: a comprehensive review of molecular findings and their clinical implications. Neurosci. Biobehav. Rev. 112, 107–116.
Goes, F.S., Zandi, P.P., Miao, K., McMahon, F.J., Steele, J., Willour, V.L., MacKinnon, D.F., Mondimore, F.M., Schweizer, B., Nurnberger, J.I., Rice, J.P., Scheftner, W., Coryell, W., Berrettini, W.H., Kelsoe, J.R., Byerley, W., Murphy, D.L., Gershon, E.S., DePaulo, J.R., McInnis, M.G., Potash, J.B.Bipolar Disorder Phenome Group, 2007. Mood-incongruent psychotic features in bipolar disorder: familial aggregation and suggestive linkage to 2p11-q14 and 13q21-33. Am. J. Psychiatry 164, 236–247.
Grande, I., Berk, M., Birmaher, B., Vieta, E., 2016. Bipolar disorder. Lancet 387, 1561–1572.
Gustavsson, A., Svensson, Jacobi, M., Allgulander, F., Alonso, C., Beghi, J., Dodel, E., Ekman, R., Faravelli, M., Fratiglioni, C., Gannon, L., Jones, B., Jennum, D.H., Jordanova, P., Jönsson, A., Karampampa, L., Knapp, K., Kobelt, M., Kurth, G., Lieb, T., Linde, R., Ljungcrantz, M., Maercker, C., Melin, A., Moscarelli, B., Musayev, M., Norwood, A., Preisig, F., Pugliatti, M., Rehm, M., Salvador-Carulla, J., Schlehofer, L., Simon, B., Steinhausen, R., Stovner, H.-.C., Vallat, L.J., Van den Bergh, J.-.M., den Bergh, P., Van, P., van Os, Vos, J., Xu, P., Wittchen, W., Jönsson, H.-.U., Olesen, B., CDBE2010Study Group, J., 2011. Cost of disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 21, 718–779.
Hajek, T., Slaney, C., Garnham, J., Ruzickova, M., Passmore, M., Alda, M., 2005. Clinical correlates of current level of functioning in primary care-treated bipolar patients. Bipolar Disord. 7, 286–291.
Hamshere, M.L., Schulze, T.G., Schumacher, J., Corvin, A., Owen, M.J., Jamra, R.A., Propping, P., Maier, W., Orozco y Diaz, G., Mayoral, F., Rivas, F., Jones, I., Jones, L., Kirov, G., Gill, M., Holmans, P.A., Nöthen, M.M., Cichon, S., Rietschel, M., Craddock, N., 2009. Mood-incongruent psychosis in bipolar disorder: conditional linkage analysis shows genome-wide suggestive linkage at 1q32.3, 7p13 and 20q13.31. Bipolar Disord. 11, 610–620.
Harrison, P.J., Geddes, J.R., Tunbridge, E.M., 2019. The emerging neurobiology of bipolar disorder. Focus (Madison) 17, 284–293.
Hayes, J.F., Lundin, A., Wicks, S., Lewis, G., Wong, I.C.K., Osborn, D.P.J., Dalman, C., 2019. Association of hydroxylmethyl glutaryl coenzyme A reductase inhibitors, L-Type calcium channel antagonists, and biguanides with rates of psychiatric hospitalization and self-harm in individuals with serious mental illness. JAMA Psychiatry 76, 382–390.
Hibar, D.P., Westlye, L.T., Doan, N.T., Jahanshad, N., Cheung, J.W., Ching, C.R.K., Versace, A., Bilderbeck, A.C., Uhlmann, A., Mwangi, B., Krämer, B., Overs, B., Hartberg, C.B., Abé, C., Dima, D., Grotegerd, D., Sprooten, E., Bøen, E., Jimenez, E., Howells, F.M., Delvecchio, G., Temmingh, H., Starke, J., Almeida, J.R.C., Goikolea, J.M., Houenou, J., Beard, L.M., Rauer, L., Abramovic, L., Bonnin, M., Ponteduro, M.F., Keil, M., Rive, M.M., Yao, N., Yalin, N., Najt, P., Rosa, P.G., Redlich, R., Trost, S., Hagenaars, S., Fears, S.C., Alonso-Lana, S., van Erp, T.G.M., Nickson, T., Chaim-Avancini, T.M., Meier, T.B., Elvsåshagen, T., Haukvik, U.K., Lee, W.H., Schene, A.H., Lloyd, A.J., Young, A.H., Nugent, A., Dale, A.M., Pfennig, A., McIntosh, A.M., Lafer, B., Baune, B.T., Ekman, C.J., Zarate, C.A., Bearden, C.E., Henry, C., Simhandl, C., McDonald, C., Bourne, C., Stein, D.J., Wolf, D.H., Cannon, D.M., Glahn, D.C., Veltman, D.J., Pomarol-Clotet, E., Vieta, E., Canales-Rodriguez, E.J., Nery, F.G., Duran, F.L.S., Busatto, G.F., Roberts, G., Pearlson, G.D., Goodwin, G.M., Kugel, H., Whalley, H.C., Ruhe, H.G., Soares, J.C., Fullerton, J.M., Rybakowski, J.K., Savitz, J., Chaim, K.T., Fatjó-Vilas, M., Soeiro-de-Souza, M.G., Boks, M.P., Zanetti, M.V., Otaduy, M.C.G., Schaufelberger, M.S., Alda, M., Ingvar, M., Phillips, M.L., Kempton, M.J., Bauer, M., Landén, M., Lawrence, N.S., van Haren, N.E.M., Horn, N.R., Freimer, N.B., Gruber, O., Schofield, P.R., Mitchell, P.B., Kahn, R.S., Lenroot, R., Machado-Vieira, R., Ophoff, R.A., Sarró, S., Frangou, S., Satterthwaite, T.D., Hajek, T., Dannlowski, U., Malt, U.F., Arolt, V., Gattaz, W.F., Drevets, W.C., Caseras, X., Agartz, I., Thompson, P.M., Andreassen, O.A., 2018. Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. Mol. Psychiatry 23, 932–942.
Hibar, D.P., Westlye, L.T., van Erp, T.G.M., Rasmussen, J., Leonardo, C.D., Faskowitz, J., Haukvik, U.K., Hartberg, C.B., Doan, N.T., Agartz, I., 2016. Subcortical volumetric abnormalities in bipolar disorder. Mol. Psychiatry 21, 1710.
Hidalgo-Mazzei, D., Young, A.H., Vieta, E., Colom, F., 2018. Behavioural biomarkers and mobile mental health: a new paradigm. Int. J. Bipolar Disord. 6, 9.
Hidalgo-Mazzei, D., Murru, A., Reinares, M., Vieta, E., Colom, F., 2016. Big Data in mental health: a challenging fragmented future. World Psychiatry 15, 186–187.
Holland, D., Wang, Y., Thompson, W.K., Schork, A., Chen, C.-.H., Lo, M.-.T., Witoelar, A., Werge, T., O'donovan, M., Andreassen, O.A., 2016. Estimating effect sizes and expected replication probabilities from GWAS summary statistics. Front. Genet. 7, 15.
Holmes, E.A., Ghaderi, A., Harmer, C.J., Ramchandani, P.G., Cuijpers, P., Morrison, A.P., Roiser, J.P., Bockting, C.L.H., O'Connor, R.C., Shafran, R., 2018. The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science. The Lancet Psychiatry 5, 237–286.
Hou, L., Heilbronner, U., Degenhardt, F., Adli, M., Akiyama, K.,

Akula, N., Ardau, R., Arias, B., Backlund, L., Banzato, C.E.M., Benabarre, A., Bengesser, S., Bhattacharjee, A.K., Biernacka, J.M., Birner, A., Brichant-Petitjean, C., Bui, E.T., Cervantes, P., Chen, G.-.B., Chen, H.-.C., Chillotti, C., Cichon, S., Clark, S.R., Colom, F., Cousins, D.A., Cruceanu, C., Czerski, P.M., Dantas, C.R., Dayer, A., Étain, B., Falkai, P., Forstner, A.J., Frisén, L., Fullerton, J.M., Gard, S., Garnham, J.S., Goes, F.S., Grof, P., Gruber, O., Hashimoto, R., Hauser, J., Herms, S., Hoffmann, P., Hofmann, A., Jamain, S., Jiménez, E., Kahn, J.-.P., Kassem, L., Kittel-Schneider, S., Kliwicki, S., König, B., Kusumi, I., Lackner, N., Laje, G., Landén, M., Lavebratt, C., Leboyer, M., Leckband, S.G., Jaramillo, C.A.L., Macqueen, G., Manchia, M., Martinsson, L., Mattheisen, M., McCarthy, M.J., McElroy, S.L., Mitjans, M., Mondimore, F.M., Monteleone, P., Nievergelt, C.M., Nöthen, M.M., Ösby, U., Ozaki, N., Perlis, R.H., Pfennig, A., Reich-Erkelenz, D., Rouleau, G.A., Schofield, P.R., Schubert, K.O., Schweizer, B.W., Seemüller, F., Severino, G., Shekhtman, T., Shilling, P.D., Shimoda, K., Simhandl, C., Slaney, C.M., Smoller, J.W., Squassina, A., Stamm, T., Stopkova, P., Tighe, S.K., Tortorella, A., Turecki, G., Volkert, J., Witt, S., Wright, A., Young, L.T., Zandi, P.P., Potash, J.B., Depaulo, J.R., Bauer, M., Reininghaus, E.Z., Novák, T., Aubry, J.-.M., Maj, M., Baune, B.T., Mitchell, P.B., Vieta, E., Frye, M.A., Rybakowski, J.K., Kuo, P.-.H., Kato, T., Grigoroiu-Serbanescu, M., Reif, A., Del Zompo, M., Bellivier, F., Schalling, M., Wray, N.R., Kelsoe, J.R., Alda, M., Rietschel, M., McMahon, F.J., Schulze, T.G., 2016. Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. Lancet 387 (10023), 1085–1093.

Hower, H., Lee, E.J., Jones, R.N., Birmaher, B., Strober, M., Goldstein, B.I., Merranko, J., Keller, M.B., Goldstein, T.R., Weinstock, L.M., Dickstein, D.P., Hunt, J.I., Diler, R.S., Ryan, N.D., Gill, M.K., Axelson, D., Yen, S., 2019. Predictors of longitudinal psychosocial functioning in bipolar youth transitioning to adults. J. Affect. Disord. 246, 578–585.

Iniesta, R., Stahl, D., McGuffin, P., 2016. Machine learning, statistical learning and the future of biological research in psychiatry. Psychol. Med. 46, 2455–2465.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. 167(7):748–51.

Jonas, D.E., Mansfield, A.J., Curtis, P., Gilmore, J.H., Watson, L.C., Brode, S., Tyutyulkova, S., Crotty, K., Viswanathan, M., Tant, E., 2012. Identifying priorities for patient-centered outcomes research for serious mental illness. Psychiatr. Serv. 63, 1125–1130.

Kapczinski, F., Magalhães, P.V.S., Balanzá-Martinez, V., Dias, V.V., Frangou, S., Gama, C.S., Gonzalez-Pinto, A., Grande, I., Ha, K., Kauer-Sant'Anna, M., 2014. Staging systems in bipolar disorder: an International Society for Bipolar Disorders Task Force Report. Acta Psychiatr. Scand. 130, 354–363.

Kaufmann, T., Alnæs, D., Doan, N.T., Brandt, C.L., Andreassen, O.A., Westlye, L.T., 2017. Delayed stabilization and individualization in connectome development are related to psychiatric disorders. Nat. Neurosci. 20, 513–515.

Kessing, L.V., Munkholm, K., Faurholt-Jepsen, M., Miskowiak, K.W., Nielsen, L.B., Frikke-Schmidt, R., Ekstrøm, C., Winther, O., Pedersen, B.K., Poulsen, H.E., 2017. The Bipolar Illness Onset study: research protocol for the BIO cohort study. BMJ Open 7, e015462.

Kessing, L.V., Rytgaard, H.C., Gerds, T.A., Berk, M., Ekstrøm, C.T., Andersen, P.K., 2019. New drug candidates for bipolar disorder—a nation-wide population-based study. Bipolar Disord 21, 410–418.

Kieseppä, T., Partonen, T., Haukka, J., Kaprio, J., Lönnqvist, J., 2004. High concordance of bipolar I disorder in a nationwide sample of twins. Am. J. Psychiatry 161, 1814–1821.

Koga, N., Ogura, J., Yoshida, F., Hattori, K., Hori, H., Aizawa, E., Ishida, I., Kunugi, H., 2019. Altered polyunsaturated fatty acid levels in relation to proinflammatory cytokines, fatty acid desaturase genotype, and diet in bipolar disorder. Transl. Psychiatry 9, 1–9.

Koukopoulos, A., Reginaldi, D., Tondo, L., Visioli, C., Baldessarini, R.J., 2013. Course sequences in bipolar disorder: depressions preceding or following manias or hypomanias. J. Affect. Disord. 151, 105–110.

Krishnan, K.R.R., 2005. Psychiatric and medical comorbidities of bipolar disorder. Psychosom. Med. 67, 1–8.

Kupfer, D.J., Frank, E., Grochocinski, V.J., Cluss, P.A., Houck, P.R., Stapf, D.A., 2002. Demographic and clinical characteristics of individuals in a bipolar disorder case registry. J. Clin. Psychiatry 63, 120–125.

Lee, P.H., Anttila, V., Won, H., Feng, Y.-C.A., Rosenthal, J., Zhu, Z., Tucker-Drob, E.M., Nivard, M.G., Grotzinger, A.D., Posthuma, D., 2019. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell 179, 1469–1482.

Lichtenstein, P., Yip, B.H., Bjork, C., Pawitan, Y., Cannon, T.D., Sullivan, P.F., Hultman, C.M., 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 373, 234–239.

Maassen, E.F., Regeer, B.J., Bunders, J.F.G., Regeer, E.J., Kupka, R.W., 2018a. A research agenda for bipolar disorder developed from a patients' perspective. J. Affect. Disord. 239, 11–17.

Maassen, E.F., Regeer, B.J., Regeer, E.J., Bunders, J.F.G., Kupka, R.W., 2018b. The challenges of living with bipolar disorder: a qualitative study of the implications for health care and research. Int. J. Bipolar Disord. 6, 1–10.

Maassen, E.F., Schrevel, S.J.C., Dedding, C.W.M., Broerse, J.E.W., Regeer, B.J., 2017. Comparing patients' perspectives of "good care" in Dutch outpatient psychiatric services with academic perspectives of patient-centred care. J. Ment. Heal. 26, 84–94.

Maggioni, E., Bianchi, A.M., Altamura, A.C., Soares, J.C., Brambilla, P., 2017. The putative role of neuronal network synchronization as a potential biomarker for bipolar disorder: a review of EEG studies. J. Affect. Disord. 212, 167–170.

Manchia, M., Adli, M., Akula, N., Ardau, R., Aubry, J.-.M., Backlund, L., Banzato, C.E.M., Baune, B.T., Bellivier, F., Bengesser, S., Biernacka, J.M., Brichant-Petitjean, C., Bui, E., Calkin, C.V., Cheng, A.T.A., Chillotti, C., Cichon, S., Clark, S., Czerski, P.M., Dantas, C., Del Zompo, M., DePaulo, J.R., Detera-Wadleigh, S.D., Etain, B., Falkai, P., Frisén, L., Frye, M.A., Fullerton, J., Gard, S., Garnham, J., Goes, F.S., Grof, P., Gruber, O., Hashimoto, R., Hauser, J., Heilbronner, U., Hoban, R., Hou, L., Jamain, S., Kahn, J.-.P., Kassem, L., Kato, T., Kelsoe, J.R., Kittel-Schneider, S., Kliwicki, S., Kuo, P.-.H., Kusumi, I., Laje, G., Lavebratt, C., Leboyer, M., Leckband, S.G., López Jaramillo, C.A., Maj, M., Malafosse, A., Martinsson, L., Masui, T., Mitchell, P.B., Mondimore, F., Monteleone, P., Nallet, A., Neuner, M., Novák, T., O'Donovan, C., Ösby, U., Ozaki, N., Perlis, R.H., Pfennig, A., Potash, J.B., Reich-Erkelenz, D., Reif, A., Reininghaus, E., Richardson, S., Rouleau, G.A., Rybakowski, J.K., Schalling, M., Schofield, P.R., Schubert, O.K., Schweizer, B., Seemüller, F., Grigoroiu-Serbanescu, M., Severino, G., Seymour, L.R., Slaney, C., Smoller, J.W., Squassina, A., Stamm, T., Steele, J., Stopkova, P., Tighe, S.K., Tortorella, A., Turecki, G., Wray, N.R., Wright, A., Zandi, P.P., Zilles, D., Bauer, M., Rietschel, M., McMahon, F.J., Schulze, T.G., Alda, M., 2013a. Assessment of response to lithium maintenance treatment in bipolar disorder: a consortium on lithium genetics (ConLiGen) report. PLoS ONE 8.

Manchia, M., Cullis, J., Turecki, G., Rouleau, G.A., Uher, R., Alda, M., 2013b. The impact of phenotypic and genetic hetero-

geneity on results of genome wide association studies of complex diseases. PLoS ONE 8.

Manchia, M., Lampus, S., Chillotti, C., Sardu, C., Ardau, R., Severino, G., Del Zompo, M., 2008. Age at onset in Sardinian bipolar I patients: evidence for three subgroups. Bipolar Disord. 10 (3), 443–446.

Manchia, M., Maina, G., Carpiniello, B., Pinna, F., Steardo, L., D'Ambrosio, V., Salvi, V., Alda, M., Tortorella, A., Albert, U., 2017. Clinical correlates of age at onset distribution in bipolar disorder: a comparison between diagnostic subgroups. Int. J. Bipolar Disord. 5.

McGuffin, P., Rijsdijk, F., Andrew, M., Sham, P., Katz, R., Cardno, A., 2003. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch. Gen. Psychiatry 60, 497–502.

MQ: Transforming Mental Health, 2018. UK Mental Health Research Funding 2014–2017 London, UK.

Njølstad, P.R., Andreassen, O.A., Brunak, S., Børglum, A.D., Dillner, J., Esko, T., Franks, P.W., Freimer, N., Groop, L., Heimer, H., Hougaard, D.M., Hovig, E., Hveem, K., Jalanko, A., Kaprio, J., Knudsen, G.P., Melbye, M., Metspalu, A., Mortensen, P.B., Palmgren, J., Palotie, A., Reed, W., Stefánsson, H., Stitziel, N.O., Sullivan, P.F., Thorsteinsdóttir, U., Vaudel, M., Vuorio, E., Werge, T., Stoltenberg, C., Stefánsson, K., 2019. Roadmap for a precision-medicine initiative in the Nordic region. Nat. Genet. 51, 924–930.

Nunes, A., Ardau, R., Berghöfer, A., Bocchetta, A., Chillotti, C., Deiana, V., Garnham, J., Grof, E., Hajek, T., Manchia, M., 2019. Prediction of lithium response using clinical data. Acta Psychiatr. Scand. 141 (2), 131–141.

Nunes, A., Schnack, Ching, H.G., Agartz, C.R.K., Akudjedu, I., Alda, T.N., Alnæs, M., Alonso-Lana, D., Bauer, S., Baune, J., Bøen, B.T., Bonnin, E., del, C., Busatto, M., Canales-Rodríguez, G.F., Cannon, E.J., Caseras, D.M., Chaim-Avancini, X., Dannlowski, T.M., Díaz-Zuluaga, U., Dietsche, A.M., Doan, B., Duchesnay, N.T., Elvsåshagen, E., Emden, T., Eyler, D., Fatjó-Vilas, L.T., Favre, M., Foley, P., Fullerton, S.F., Glahn, J.M., Goikolea, D.C., Grotegerd, J.M., Hahn, D., Henry, T., Hibar, C., Houenou, D.P., Howells, J., Jahanshad, F.M., Kaufmann, N., Kenney, T., Kircher, J., Krug, T.T.J., Lagerberg, A., Lenroot, T.V., López-Jaramillo, R.K., Machado-Vieira, C., Malt, R., McDonald, U.F., Mitchell, C., Mwangi, P.B., Nabulsi, B., Opel, L., Overs, N., Pineda-Zapata, B.J., Pomarol-Clotet, J.A., Redlich, E., Roberts, R., Rosa, G., Salvador, P.G., Satterthwaite, R., Soares, T.D., Stein, J.C., Temmingh, D.J., Trappenberg, H.S., Uhlmann, T., van Haren, A., Vieta, N.E.M., Westlye, E., Wolf, L.T., Yüksel, D.H., Zanetti, D., Andreassen, M.V., Thompson, O.A., Hajek, P.M., ENIGMA Bipolar Disorders Working Group, T., 2018. Using structural MRI to identify bipolar disorders – 13 site machine learning study in 3020 individuals from the ENIGMA Bipolar Disorders Working Group. Mol. Psychiatry. https://doi.org/10.1038/s41380-018-0228-9.

Nunes, A., Trappenberg, T., Alda, M., 2020. We need an operational framework for heterogeneity in psychiatric research. J. Psychiatry Neurosci. 45, 3–6. https://doi.org/10.1503/jpn.190198.

Pancheri, C., Verdolini, N., Pacchiarotti, I., Samalin, L., Delle Chiaie, R., Biondi, M., Carvalho, A.F., Valdes, M., Ritter, P., Vieta, E., 2019. A systematic review on sleep alterations anticipating the onset of bipolar disorder. Eur. Psychiatry 58, 45–53.

Plana-Ripoll, O., Pedersen, C.B., Agerbo, E., Holtz, Y., Erlangsen, A., Canudas-Romo, V., Andersen, P.K., Charlson, F.J., Christensen, M.K., Erskine, H.E., Ferrari, A.J., Iburg, K.M., Momen, N., Mortensen, P.B., Nordentoft, M., Santomauro, D.F., Scott, J.G., Whiteford, H.A., Weye, N., McGrath, J.J., Laursen, T.M., 2019. A comprehensive analysis of mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study. Lancet 394, 1827–1835.

Rosenblat, J.D., McIntyre, R.S., 2016. Bipolar disorder and inflammation. Psychiatr. Clin. North Am. 39, 125–137.

Schork, A.J., Thompson, W.K., Pham, P., Torkamani, A., Roddey, J.C., Sullivan, P.F., Kelsoe, J.R., O'Donovan, M.C., Furberg, H., Schork, N.J., 2013. All SNPs are not created equal: genome-wide association studies reveal a consistent pattern of enrichment among functionally annotated SNPs. PLoS Genet. 9, e1003449.

Scott, J., Etain, B., Bellivier, F., 2018. Can an integrated science approach to precision medicine research improve lithium treatment in bipolar disorders? Front. Psychiatry 9, 360.

Scott, J., Hidalgo-Mazzei, D., Strawbridge, R., Young, A., Resche-Rigon, M., Etain, B., Andreassen, O.A., Bauer, M., Bennabi, D., Blamire, A.M., Boumezbeur, F., Brambilla, P., Cattane, N., Cattaneo, A., Chupin, M., Coello, K., Cointepas, Y., Colom, F., Cousins, D.A., Dubertret, C., Duchesnay, E., Ferro, A., Garcia-Estela, A., Goikolea, J., Grigis, A., Haffen, E., Høegh, M.C., Jakobsen, P., Kalman, J.L., Kessing, L.V., Klohn-Saghatolislam, F., Lagerberg, T.V., Landén, M., Lewitzka, U., Lutticke, A., Mazer, N., Mazzelli, M., Mora, C., Muller, T., Mur-Mila, E., Oedegaard, K.J., Oltedal, L., Pålsson, E., Papadopoulos Orfanos, D., Papiol, S., Perez-Sola, V., Reif, A., Ritter, P., Rossi, R., Schulze, T., Senner, F., Smith, F.E., Squarcina, L., Steen, N.E., Thelwall, P.E., Varo, C., Vieta, E., Vinberg, M., Wessa, M., Westlye, L.T., Bellivier, F., 2019. Prospective cohort study of early biosignatures of response to lithium in bipolar-I-disorders: overview of the H2020-funded R-LiNK initiative. Int. J. Bipolar Disord. 7, 20.

Scott, J., Scott, E.M., Hermens, D.F., Naismith, S.L., Guastella, A.J., White, D., Whitwell, B., Lagopoulos, J., Hickie, I.B., 2014. Functional impairment in adolescents and young adults with emerging mood disorders. Br. J. Psychiatry 205, 362–368.

Selby, J.V., Beal, A.C., Frank, L., 2012. The Patient-Centered Outcomes Research Institute (PCORI) national priorities for research and initial research agenda. JAMA 307, 18–19.

Sinha, A., Shariq, A., Said, K., Sharma, A., Jeffrey Newport, D., Salloum, I.M., 2018. Medical Comorbidities in Bipolar Disorder. Curr. Psychiatry Rep. 20, 36.

Skelly, N., Schnittger, R.I., Butterly, L., Frorath, C., Morgan, C., McLoughlin, D.M., Fearon, P., 2013. Quality of care in psychosis and bipolar disorder from the service user perspective. Qual. Health Res. 23, 1672–1685.

Sklar, P., Ripke, S., Scott, L.J., Andreassen, O.A., Cichon, S., Craddock, N., Edenberg, H.J., Nurnberger Jr, J.I., Rietschel, M., Blackwood, D., 2011. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat. Genet. 43, 977.

Smeland, O.B., Frei, O., Fan, C.-.C., Shadrin, A., Dale, A.M., Andreassen, O.A., 2019. The emerging pattern of shared polygenic architecture of psychiatric disorders, conceptual and methodological challenges. Psychiatr. Genet. 29, 152–159.

Stahl, E.A., Breen, G., Forstner, A.J., McQuillin, A., Ripke, S., Trubetskoy, V., Mattheisen, M., Wang, Y., Coleman, J.R.I., Gaspar, H.A., 2019. Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat. Genet. 51, 793.

Stein, D.J., Szatmari, P., Gaebel, W., Berk, M., Vieta, E., Maj, M., de Vries, Y.A., Roest, A.M., de Jonge, P., Maercker, A., Brewin, C.R., Pike, K.M., Grilo, C.M., Fineberg, N.A., Briken, P., Cohen-Kettenis, P.T., Reed, G.M., 2020. Mental, behavioral and neurodevelopmental disorders in the ICD-11: an international perspective on key changes and controversies. BMC Med. 18, 21.

Sullivan, P., 2009. A framework for interpreting genome-wide association studies of psychiatric disorders. Mol. Psychiatry. 14 (1), 10–17.

Sullivan, P.F., Agrawal, A., Bulik, C.M., Andreassen, O.A., Børglum, A.D., Breen, G., Cichon, S., Edenberg, H.J.,

Faraone, S.V., Gelernter, J., 2017. Psychiatric genomics: an update and an agenda. Am. J. Psychiatry 175, 15–27.
Tondo, L., Alda, M., Bauer, M., Bergink, V., Grof, P., Hajek, T., Lewitka, U., Licht, R.W., Manchia, M., Müller-Oerlinghausen, B., Nielsen, R.E., Selo, M., Simhandl, C., Baldessarini, R.J.International Group for Studies of Lithium (IGSLi), 2019. Clinical use of lithium salts: guide for users and prescribers. Int. J. Bipolar Disord. 7, 16.
Vai, B., Parenti, L., Bollettini, I., Cara, C., Verga, C., Melloni, E., Mazza, E., Poletti, S., Colombo, C., Benedetti, F., 2020. Predicting differential diagnosis between bipolar and unipolar depression with multiple kernel learning on multimodal structural neuroimaging. Eur. Neuropsychopharmacol. 1–11.
Vieta, E., Berk, M., Schulze, T.G., Carvalho, A.F., Suppes, T., Calabrese, J.R., Gao, K., Miskowiak, K.W., Grande, I., 2018. Bipolar disorders. Nat. Rev. Dis. Prim. 4, 18008.
Wang, Y., Thompson, W.K., Schork, A.J., Holland, D., Chen, C.-.H., Bettella, F., Desikan, R.S., Li, W., Witoelar, A., Zuber, V., 2016. Leveraging genomic annotations and pleiotropic enrichment for improved replication rates in schizophrenia GWAS. PLoS Genet. 12, e1005803.
Zhang, W., Nery, F.G., Tallman, M.J., Patino, L.R., Adler, C.M., Strawn, J.R., Fleck, D.E., Barzman, D.H., Sweeney, J.A., Strakowski, S.M., 2020. Individual prediction of symptomatic converters in youth offspring of bipolar parents using proton magnetic resonance spectroscopy. Eur. Child Adolesc. Psychiatry 1–10.
Zorrilla, I., Aguado, J., Haro, J.M., Barbeito, S., Lopez Zurbano, S., Ortiz, A., Lopez, P., Gonzalez-Pinto, A., 2015. Cannabis and bipolar disorder: does quitting cannabis use during manic/mixed episode improve clinical/functional outcomes? Acta Psychiatr. Scand. 131, 100–110.