Gut Microbiota for Precision Psychiatry in Bipolar Disorder

Subjects: Neurosciences

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Bipolar disorder (BD) is a highly disabling condition with a chronic and relapsing nature. Despite the substantial socioeconomic burden associated with BD, there are still significant research gaps in risk stratification, diagnostic accuracy, and treatment selection, all key components of precision psychiatry. One possible strategy to increase the validity of precision psychiatry approaches in BD is to increase the knowledge of disorder-associated gut microbiota perturbations.

Keywords: bipolar disorder ; brain-gut axis ; Gut Microbiota

1. Introduction

Bipolar disorder (BD) is a complex and clinically heterogeneous disorder associated with a significant morbidity and disability burden. Globally, it has been estimated that BD may account for 9.9 million disability-adjusted life years (DALY), corresponding to 0.4% of total DALYs and 1.3% of years lost due to a disability (YLD) [1]. BD is in itself a well-recognized risk factor for suicide [2][3], and its association with an excess mortality associated with cancer and cardiovascular disorders is increasingly evident [3][4][5]. Affected individuals have, on average, a life expectancy 20 years shorter than the general population [6]. Despite the high costs in terms of individual suffering and socioeconomic impact [7][8], there are still numerous unmet needs in risk stratification, diagnostic accuracy, and treatment selection, all key components of precision psychiatry [9][10]. Precision psychiatry postulates that diagnosis and treatment selection could be made based on knowledge of the phenotypic and biological characteristics of any given individual affected by a mental disorder. A broad range of different interventions has been proven effective in improving BD symptoms [11], with pharmacotherapy representing an important component. The landmark study Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) provided invaluable data regarding illness course, treatments and assessment models for this heterogeneous disorder [12]. Bipolar depression has a prominent role in the course of illness and in causing disability as it may occur at twice the rate observed for hypomania, manic or mixed episodes [12]. BD severity is closely linked to its chronicity, with 60% to 80% of relapses occurring in the two years following an antecedent episode, either depressive or manic [13]. The relative paucity of efficacious treatment modalities available for bipolar depression further complicates its management [14]. Diagnosing BD may be difficult, even for mental health specialists. Patients often receive an alternative diagnosis, frequently unipolar depression, substance abuse disorder or schizophrenia spectrum disorder depending on the most significant symptoms present at the time of the evaluation [15]. According to recent estimates [15], the average diagnostic delay ranges from 15 to 20 years for BD. Even when BD is appropriately identified, the choice for a particular pharmacological agent is typically based on a trial-and-error approach, as is often the case for mental health disorders in general [16]. Arguably, this factor may lead to further prolongation of the time required to achieve an adequate symptomatic amelioration. Taken together, these factors further underscore the need to develop more accurate risk stratification models, as well as reliable algorithms for treatment selection and optimization of currently available treatments to increase effectiveness and decrease safety risks [17]. This is indeed the core mission of precision psychiatry [18][19]. Psychiatry is personalized in that it relies deeply on descriptive psychopathology and phenomenology, but it remains imprecise since the integration of biological data with detailed clinical information to increase the accuracy of prediction is still in its infancy. However, it is conceivable that the brain-gut-microbial axis may represent a novel avenue for the personalization of treatment in mental health disorders [20]. Evidence deriving from preclinical data increasingly suggests that gut microbiota perturbations might contribute to pathophysiological mechanisms for mental disorders. A fecal microbiota transplant from affected human individuals to germ-free mice was associated with the development of the pathological phenotype observed in the mice model for various psychiatric and neurological conditions [21][22][23]. Remarkably, the transplant from healthy human donors did not result in the same changes [21], and may instead thereafter attenuate some of the induced anomalies through such paradigm [22].

2. Gut Microbiota for Precision Psychiatry in Bipolar Disorder

Precision psychiatry is a promising but still unachieved healthcare model. This delay has been mainly determined by the lack of definitive data on risk stratification and prediction in mental disorders, and BD is not an exception in this regard. It is plausible that the analysis of brain-gut microbiota influence on BD disease trajectories might increase the levels of precision needed to make this construct clinically applicable. Indeed, how the host genetic factors may interact with the gut microbiota may represent an additional layer of complexity to be considered, either in predicting treatment efficacy or the tolerability profile of existing treatments. A recent example derives from rheumatoid arthritis research [24], where the authors report on a significant association for rheumatoid arthritis polygenic risk score, *Prevotella* spp. and the presence of preclinical rheumatoid arthritis phases. Remarkably, the host genotype was associated with an increased probability of microbiota perturbations that might predate the onset of the disease. A paper [25] reported on the possible association of gut microbiota perturbations with the inflammatory status, tryptophan/kynurenine levels, oxidative stress, and metabolic syndrome using a cross-sectional design. The authors described the association between a relative group difference in genus Faecalibacterium, at the phylum of Actinobacteria and at the family level for Coriobacteriaceae among BD patients as compared with healthy controls. The findings regarding Faecalibacterium were partly in line with a previous report [26] and deserve further replication. Tryptophan levels, inflammation status and anthropometric indices (e.g., body mass index) were instead associated with increases in the relative abundance in the family of Lactobacillaceae, among the others. These data offer interesting prospects regarding the possible role played by gut microbiota in the complex interplay between lifestyle, metabolism, and mood levels in BD. A largely untapped area of research is the potential bidirectional relationship between oral microbiota derangements and mental health. A cross-sectional study [27] described the association of variations of oral microbiota composition with depressive and anxiety symptoms among adolescents. The study participants have been recruited from the participants of a prior study investigating the efficacy of a mindfulness-based intervention in preventing the onset of depression in at-risk individuals. Intriguingly, the relative abundance of Spirochaetes and its member family Spirocheataceae was associated with anxiety and depression symptoms, whilst several families and species were associated solely with depressive symptoms. Considering the study design, it was impossible to establish any causal link for the observed associations. However, if replicated in prospective studies, these results would represent a significant turning point in the research for a viable biomarker as oral microbiota could be even more easily probed as compared with intestinal microbiota. A recent meta-analysis [28] reported on the results of 59 case-control studies, finding that microbiota perturbations could be associated with a pro-inflammatory state transdiagnostically. The work by Paribello et al. confirms this impression, highlighting the presence of only two studies using gut microbiota analysis for precision approaches. This should lead to an increase in research in this area. Indeed, several lines of evidence suggest a possible bidirectional role for microbiota alterations as a possible environmental factor contributing to BD relapses. Bengesser et al. [29] reported on a cross-sectional study investigating the possible association between microbial alpha diversity and aryl hydrocarbon receptor nuclear translocator-like gene (ARNTL) methylation profiled in BD. Bacterial diversity correlated significantly with ARNTL methylation status and the mood phase of BD, further underscoring the need to explore the possible intricate relationship between the microbiota and how it might affect the host. An intensified synergy between preclinical and clinical research might be helpful in developing more useful cross-species approaches which are instrumental to improving the chances of closing the ever-increasing gap between basic research and clinical applications for neuroscience [30]. For example, a recent study [31] on combined human and clinical models investigated the impact of gut microbiota in regulating the tetratricopeptide repeat and ankyrin repeat containing 1 gene (TRANK1) expression, a gene that has been associated with an increased risk of BD and encoding for a protein secreted mainly by immunocytes. Interestingly, the authors reported that while TRANK1 mRNA expression appears higher in bipolar depression, fecal transplantation from these individuals to mice also resulted in greater expression of TRANK1 mRNA. Despite requiring validation and replication and notwithstanding the significance of these findings, the approach itself may be important in this sense. More recently, it has been increasingly evident how epigenetic changes of bacteria may be significant in determining their virulence. Hopefully, it will be possible in the future to better estimate the eventual impact of microbiota epigenetic changes on host health status [32] and how these modifications may interact with the individual predisposition to develop an illness (or in-treatment response) rather than the microbiota composition itself.

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