A Comparative Analysis of Traditional Pharmacotherapy and Neurotechnology-Based Interventions

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Abstract. Bipolar disorder (BD) is a psychiatric disorder associated with periodic cyclical episodes of symptoms of mania and depression. The current therapeutic options to treat BD include the use of pharmacotherapy, psychotherapy, neurostimulation and brain connectivity. Since the discovery of lithium's antimanic properties in 1949, treatment of BD has focused on medication, and this remains the most common approach to date. However, despite more than 60 years of dedicated efforts, both lithium and other antipsychotic drugs have demonstrated limited efficacy and have often failed to alleviate residual symptoms and side-effects. Owing to certain limitations of pharmacotherapy, there is an urging clinical need to target underlying neurobiology of BD and improve the patient outcomes. The advancement in neurosciences and use of increasingly more sensitive brain imaging tools have provided an opportunity to develop a cutting-edge treatment strategy such as neuromodulation and neurofeedback. Due to their ability to modulate the neural circuits implicated in BD, and encourage neuroplasticity, these novel neurotechnology based treatment approaches may potentially yield superior results in the treatment of BD, leading to greater patient outcomes and reduction in relapse. However, further research is needed to formally establish its clinical benefits and address feasibility issues to facilitate its translation in the clinic. Neurotechnology-based approaches may well offer a new paradigm in BD treatment by combining medication, cognitive therapies and potentially crucial novel approaches that have the power to improve societal wellbeing and improve the quality of life of a highly underserved patient group.

Keywords: BD, Neurotechnology, Neuromodulation, Neurofeedback, Neuroplasticity

1. Introduction

Reviewing the evolution of psychiatric treatments reveals that pharmacotherapy and psychotherapy, which are the traditional approaches, have been foundational in treating mood disorders. However, bipolar disorder (BD) emerges and remains as a significant challenge, characterized by its complex and varied symptoms, especially unstable mood swings between mania and depressive episodes. Bipolar disorder is a severe and complex mental illness that affects approximately 1-3% of the global population [1]. Characterized by alternating episodes of mania and depression, BD exerts a negatively profound impact on people, families, and society, increasing the risk of suicide and leading to substantial functional impairment and diminished quality of life [2]. Despite advancements in pharmacotherapy over recent years, treatment outcomes remain suboptimal for a large proportion of patient's population, with high rates of non-response, relapse, and residual symptoms [3]. Conventional medications and psychotherapeutic interventions face challenges in aiming at the rooting cause and treating the patients effectively as they may yield limited improvements in brain function and cause irreversible side effects. In the realm of long-term treatments, traditional methodologies, antipsychotic drugs are primarily used for managing mania, lithium is most strongly supported for long-term relapse prevention, and anticonvulsants show comparatively weaker improvements [4].

The field of neurotechnology presents novel possibilities for overcoming these limitations and enhancing the management of BD. The staging model provides a framework for precisely targeting each patient's unique conditions. Neurotechnology-based interventions, such as neuromodulation and neurofeedback, aim to modulate the neural circuits underlying BD and harness the brain's capacity for neuroplasticity [5]. By targeting the root causes of the disorder, these innovative approaches hold the potential to enhance treatment efficacy, reduce the risk of relapse, and foster functional recovery.

This paper aims to provide a comprehensive overview of BD, critically analyze the limitations of conventional medication, and explore the potential of neurotechnology-based interventions. It aims to provide a throughout view of the current treatment landscape, highlighting the strengths and limitations of conventional method and comparing them to innovative neuro-technological interventions. By directly targeting the parts of central nervous system of BD and utilizing neuroplasticity, neurotechnology-based interventions present a promising alternative. By evaluating the capacity of these cutting-edge tools to bridge the gaps in current treatment methodologies, this essay seeks to guide future directions in the management of BD—a future that embraces the full spectrum of available therapeutic modalities.

2. Understanding the Pathophysiology of Bipolar Disorder

Because it is a multifactorial neuropsychiatric disorder, with genetic, environmental, and developmental factors, BD has higher heritability than other psychiatric disorders, given the high risk of morbidity and mortality, and cognitive impairment. Presently, our understanding of BD pathophysiology indicates that disruption of neural circuits for affective/emotional control, memory and behavior – particularly prefrontal circuitry, anterior cingulate cortical (ACC), hippocampi and amygdala circuits – underlies the core affective and cognitive/psychotic symptoms in BD [6]. Focusing on the effect of early developmental factors, brain organization and connectivity is disrupted between ventral prefrontal networks and limbic brain regions with the amygdala being particularly affected [7]. Neuroimaging has shown structural and functional abnormalities in the brain, including lower grey matter volume, changes in white matter organization, decreased myelination or loss of prefrontal neurons, and aberrant patterns of neural activations, in the context of specific connectivity [8]. At the cellular level, neuroplasticity – the brain's ability to react, adapt and reorganize its architecture, and move resources from one part of the brain to another in the wake of environmental demands and experiences – is hypofunctional, and resilience is compromised [9]. The most compelling finding based on DTI studies in BD is white matter hyperintensity, abnormal in subcortical white matter, which results in disrupted connectivity for emotional processing by affect brain regions that underlie limbic disorganization to regulate emotion.

Moreover, reduced neurotrophic support has been highlighted in BD, including reduced levels of brain-derived neurotrophic factor (brain-derived neurotrophic factor (BDNF)), an essential mediator of neuronal survival, differentiation, and synaptic plasticity [10]. Altered glutamatergic and GABAergic neurotransmission, key mediators of synaptic plasticity and neural circuit function, are also implicated in BD. Since glutamate is the major excitatory neurotransmitter in the brain, polymorphisms of the genes that encode the NR1 and NR2A subunits of NMDA glutamate receptors have been associated with BD [11]. Impaired neuroplasticity in BD implies important therapeutic implications at the cellular level. As the disease progresses, the ability of the brain to adapt to stress or actually a new environment becomes increasingly impaired. In addition, as the brain circuits become less flexible and less sensitive, this might explain the cognitive deficits and emotional dysregulation – the core features of BD.

3. Traditional Pharmacotherapy for Bipolar Disorder: Limitations and Challenges

3.1. Overview

Historically, pharmacotherapy has represented the cornerstone treatment target of bipolar disorder (BD) and has become the most frequently prescribed aspect of BD care [12]. There is controversy surrounding treatment for BD, including the role and risks of antidepressants, and whether BD is a severe mental disorder – that is, a condition with progressive course associated with increasing severity and frequency of episodes, resulting in cognitive impairment and functional decline [12]. Cognitive impairment is a core feature of BD, and affects domains including attention, memory, and

executive functioning [13]. Additionally, there is growing evidence that cognitive impairment can persist even during euthymic states. The variety of indices indicate that cognitive impairment occurs in mania, depression and persists during euthymia – and is not merely a question of severity. Treatment strategies have been shown to be effective and can be utilized in treating cognitive impairment in BD patients, including pharmacotherapy, psychotherapeutic and non-invasive brain stimulation interventions, but more research is needed to identify the effects of these treatments on BD cognitive outcomes [13]. Mood stabilizers, atypical antipsychotics and antidepressants remain the mainstays of medication-based techniques [14, 1]. Illustration of key treatment agents and their mechanisms of action for bipolar disorder. Figure reproduced under permission from Wolters Kluwer Health, Lippincott Williams & Wilkins [1]. The long-term effects of lithium have shown up to a 38 per cent decreased risk of manic symptoms, and 28 per cent of depressive symptoms [15], an example of the most quintessential mood stabilizer. Lithium is associated with its own limits, though, such as a low therapeutic index, a spectrum of adverse effects, and the potential teratogenic risk for congenital malformations in newborns whose mothers took lithium while pregnant, and a high nonresponse to treatment [3]. The next step in the progression of BD includes agents considered to be anticonvulsants used as mood stabilizers in BD, such as valproate and lamotrigine, which can lead to similar degrees of response to lithium, but with less robust proven effectiveness of long-term relapse prevention seen with lithium [15]. Atypical antipsychotics generally have well-demonstrated cases as necessary aspects of treatment for acute manic and mixed states [3], an example being quetiapine leading to superior improvements in outcomes compared with the rest of the treatment population. However, ills such as the induction of significant metabolic side effects make shopping a popular activity, including sedation and pronounced weight gain, a common adverse effect. Another class of medication, antidepressants, occasionally step in for the treatment of bipolar depression, despite its much-controversial use considering the relative lack of convincing evidence, due to the potential hazardousness of side effects, such as the risk of provoking a switch or cycle acceleration.

3.2. Challenges and Limitations

Nonetheless, these pharmacotherapeutic options remain limited because of high rates of treatment-resistance, recurrence and residual symptoms. Person-centered neuroimaging markers can help to identify resilience and vulnerability factors in BD, and can guide treatment decisions [16]. Our systematic review and network meta-analysis of maintenance pharmacological treatments in BD compared both efficacy and tolerability, with the aim of proposing treatment choices. This study showed that second- and third-generation antipsychotics [such as olanzapine and quetiapine (atypical antipsychotics)] were associated with a higher relative risk of relapse. However, the rate was still lower than that observed with placebo. Comparable results were also observed for lithium and anti-epileptic drugs. The most well-tolerated maintenance pharmacological treatments were mood stabilizers (lamotrigine and valproate), not antidepressants. Our network meta-analysis helps clinicians better define maintenance pharmacological treatments for BD [17]. The use of antidepressants in bipolar depression remains controversial. Their role is currently debated because of the possibility of increasing the risk of manic switch and the acceleration of the cycle. However, recent studies suggest that antidepressants can be useful and safe when added to mood stabilizers [18]. Simulating the results of randomized controlled trials, less than 50 per cent of BD patients achieve remission with pharmacotherapy, and the rates of response in the best responders remain high (above 80 per cent), but relapse rates remain very high, between 60 and 80 per cent [19, 1]. One of the crucial limitations of traditional medication-based treatments is the lack of specificity to the underlying pathophysiology of BD (e.g., neural circuit disruption and neuroplasticity impairment), which may explain such treatment outcomes in many patients. What's next? Findings still harbor new hopes for pharmacotherapeutic strategies that directly target and modulate the molecular mechanisms of mood disorders. As an example, a clinical trial establishes that modulations of glutamate transmissions through blocking of NMDA receptors could be promising as mood-stabilizing agents. Glutamate is the main excitatory neurotransmitter mediating synaptic plasticity and the function of neural circuits

in the brain. Glutamatergic dysfunction was detected in a meta-analysis of magnetic resonance spectroscopy studies of patients with BD, arguing for glutamatergic as the therapeutic target possibilities [11]. Despite promises of new "magic bullets", the development of novel pharmacotherapies for BD is far from unequivocal. The complex nature of BD pathophysiology emerging from interactions between genetic, environmental and neurodevelopmental risk factors could be the reason why it remains difficult to find the most specific molecular targets for intervention [9]. A decrease in neuroplastic capacity may further constrain the efficacy of pharmacological treatments intervening on the plastic processes [9]. The presentation of BD is sometimes so heterotypic (e.g., presenting with different features at different episodes and across the course) and often exhibits significant life-level heterochrony (e.g., diagnostic shifts between mood phases). Therefore, the development of an ideal personalized treatment will be a challenging process that still lacks reliable biomarkers capable of showing whether and when a given medicine will be effective for a particular patient [20]. Moreover, long-term use of lithium and atypical antipsychotics is associated with intolerable adverse metabolic effects (e.g., diabetes and obesity), which in some patients make it difficult to adhere to such medications in the face of adverse health consequences.

4. Neurotechnology-Based Interventions for Bipolar Disorder: Applying Neuroplasticity

Neurotechnology-based interventions constitute a fast-moving field with a growing range of approaches to modulate brain function and neuroplasticity [2]. The neurotechnology-based approaches to help reorganize the brain towards neuroplasticity and better recovery for bipolar disorder (BD) include two main approaches-neuromodulation and neurofeedback [1]. Neuromodulation techniques use external stimulation, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), to modulate brain activity and to lead to neuroplastic changes [21].

4.1. RTMS Overview

RTMS is a non-invasive electrical stimulation that can modulate neural activity, applying short pulse (usually 25 Hz; 0.5-second duration) of electrical currents (1.5-2 Tesla) from a magnetic coil to the specific cortical areas. Modulated electric currents transit electrically adjacent neurons, hence allowing to modulate its activity in a very precise and non-invasive way, thus improving cognitive and/or emotional function of the stimulated area [1]. For example, stimulation at dorsal prefrontal cortex (DLPFC) via rTMS can modulate executive and cognitive control. Several rigorous randomized clinical trials endorse the beneficial effect of TMS in reducing the depressive symptoms of patients [22]. Up to 60 per cent response rates were described in BD with rTMS. The mechanism by which TMS mitigates the symptoms of BD is still unclear, but it is most likely to improve neuroplasticity, stabilizing the dysfunction of neuronal circuits. TMS induces slow oscillations and can potentiate neuronal plasticity (long-term potentiation [LTP] and long-term depression [LTD]) via the modulation of cortical excitability [23]. Remodeling of cortical structure induced by repetitive neuronal activation has been suggested as a potential mechanism to explain electrophysiological markers of the depressive state in manic patients [2]. Further studies support the hypothesis that rTMS could modulate neurotrophic factors, especially the release of BDNF – a member of the neural plasticity suspects, which contributes to neuronal survival, differentiation and synaptic plasticity. Several issues are still open to inducing a meaningful use of rTMS in BD. Studies will be required to further optimize stimulation parameters (such as intensity, frequency, number of pulses, target area and duration of treatment) [24]; to identify predictors of treatment response and distress tolerance [21], and to better describe long-term beneficial effects [30]. Despite these encouraging results, episodes of side-effect such as headache and discomfort warn for the possibility of adverse effects of a new therapeutic intervention.

4.2. Overview of tDCS

tDCS, another exciting neuromodulation technique, targets human scalp with low levels of electrical current and modulates cortical excitability [22]. Both the rTMS and tDCS techniques are believed to have neuroplasticity effects such as facilitating BDNF expression, promoting synaptic plasticity and modulating neural network activity [23]. Studies show that rTMS could be an effective intervention for the treatment of bipolar depression, and multiple meta-analyses suggest that active rTMS is more effective than sham stimulation in improving depressive symptoms [24]. Skew or reduced alpha asymmetry in BD has been linked to disrupted lateralization and impaired EEG connectivity, and therefore a target abnormality for neurofeedback Beyond rTMS, another exciting neurotechnology-based approach – neurofeedback – has also been tested in the treatment of BD. Neurofeedback involves the real-time feedback of brain activity by external devices such a video screen or sound messages, and enables subjects to adapt their neural states, offer rewards for the desired brain activity, and ultimately induce adaptive neuroplasticity [25]. In the field of BD, neurofeedback training has been utilized to restore EEG abnormalities associated with disrupted lateralization or abnormal slow wave activities. For instance, skew or reduced alpha asymmetry in BD – and an imbalance of slow (theta/delta) and fast (beta/gamma) waves – has been linked to disrupted lateralization and impaired EEG connectivity, and therefore a target abnormality for neurofeedback [26]. Although the evidence for neurotechnology interventions in BD is promising, there are also several challenges and limitations that need to be addressed. First, optimal stimulation parameters for rTMS or tDCS, as well as the treatment protocols with different number of sessions and the right patients to respond to these interventions, still need to be established and validated by large, well-controlled trials [27]. Second, it is important to determine the long-term effects of these interventions in terms of their impact on brain function and neuroplasticity – there is a need for longitudinal studies to investigate their durability to prevent relapse.

5. Future Directions and Approaches

With a deeper understanding of the complex pathophysiology that underlies BD, we are at a critical point where we must develop innovative therapeutic approaches that can target the specific circuits involved, as well as have the capability to induce neuroplasticity. While pharmacotherapy is likely to remain an important component in the treatment of BD, the combined application of neurotechnology-based interventions with pharmacotherapy and psychosocial treatment could provide a more comprehensive management strategy. Future directions that may pave the way for a more personalized and efficacious approach to maintaining BD are the integration of neurotechnology-based interventions with pharmacotherapy and psychosocial treatments. By combining the benefits of specific approaches that complement each other and tailoring those approaches to the varying needs of individual patients, it may be feasible to achieve superior outcomes and a better quality of life for those affected by a disorder that is often functionally debilitating and resistant to current treatment approaches. One future direction is to develop personalized treatments based on individual variations in the interaction between neural circuitry, genetics and clinical features [5, 10]. Neuroimaging measures such as fMRI and diffusion tensor imaging may ultimately inform and guide treatment selection based on specific neural biomarkers. An additional future direction may include integrating neurotechnology-based interventions with pharmacotherapy and psychosocial treatments; for instance, while rTMS or tDCS may not be suitable as standalone approaches, it could serve as an adjuvant treatment to augment the effects of mood stabilizers or cognitive-behavioral therapy [28]. Final thoughts will consider the ethical and societal challenges related to the proliferation of neurotechnology-based interventions for disruptive psychiatric disorders. Such interventions will surely be developed to increasingly sophisticated levels as they are more readily available, and robust formal regulations will be critical to ensure appropriate uses and mitigate against potential misuses of these novel technologies [29].

6. Conclusion

The severe impact of BD on quality of life for millions of people globally, as well as substantial unmet needs regarding efficacy, treatment resistance, symptom recurrence and incomplete remission, highlight the urgent need for effective therapeutic approaches. Although pharmacotherapy has improved, treatment for BD remains a severe unmet need. Neurotechnology-based interventions afford a novel and transformative perspective for this purpose by directly targeting the much-broader neural substrates of the disorder while simultaneously leveraging the brain's innate capability for adaptive neuroplastic processes in service of therapeutic ends. Below, we explain why a treatment, combo or intervention that directly target the neural substrates of BD while leveraging adaptive neuroplastic processes represents a novel and promising perspective for achieving the goal of better BD treatment. We first depict the prevalent shortcomings of traditional pharmacotherapy for BD and the accompanying ridges for neurotechnology-based interventions in this domain, followed by a brief explanation for why neuroplasticity represents a promising new therapeutic construct for novel preventative, treatment, and combo approaches for this multifaceted neurological disorder. BD is a multifaceted neuropsychiatric disorder characterized by a number of shortcomings and comorbidities with substantial unmet needs regarding efficacy, treatment resistance, symptom recurrence and incomplete remissions, among others. As reviewed above, features of BD involve impaired neuroplasticity and atypical activation within circuits that regulate mood, cognition, and behavior. Treatments for bipolar illness to date have largely centered on pharmacological attempts to normalize these impaired features. Traditional pharmacological treatments – with lithium, anticonvulsants and antipsychotics – have been the mainstay of BD treatment for over 70 years. However, treating BD has many shortcomings, including high rates of treatment resistance, symptom recurrence and incomplete remission. Neuromodulation-based approaches, such as transcranial magnetic stimulation and transcranial direct current stimulation, have demonstrated promise as treatments for BD. As we continue to unravel the complex nature of BD and refine our understanding of the brain's capacity for change, neurotechnology-based interventions may revolutionize the way we approach the treatment of this debilitating condition, offering hope for a brighter future.

References

[1] Grande, I., Berk, M., Birmaher, B., & Vieta, E. Bipolar disorder. The Lancet, 2016, 387(10027), 1561-1572.

[2] Dome, P., Rihmer, Z., & Gonda, X. Suicide risk in bipolar disorder: a brief review. Medicina, 2019, 55(8), 403.

[3] Geddes, J. R., & Miklowitz, D. J. Treatment of bipolar disorder. The Lancet, 2013, 381(9878), 1672-1682.

[4] Frye M.A., Ha K., Kanba S., et al. International consensus group on depression prevention in bipolar disorder. J Clin Psychiatry, 2011, 72, 1295–310.

[5] Salagre, E., Dodd, S., Aedo, A., Rosa, A., Amoretti, S., Pinzon, J., ... & Grande, I. Toward precision psychiatry in bipolar disorder: staging 2.0. Frontiers in psychiatry, 2018, 9, 641.

[6] Vieta, E., Berk, M., Schulze, T. G., Carvalho, A. F., Suppes, T., Calabrese, J. R., ... & Grande, I. Bipolar disorders. Nature Reviews Disease Primers, 2018, 4(1), 1-16.

[7] Strakowski, S. M., Adler, C. M., Almeida, J., Altshuler, L. L., Blumberg, H. P., Chang, K. D., ... & Townsend, J. D. The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar Disorders, 2012, 14(4), 313-325.

[8] Hibar, D. P., Westlye, L. T., Doan, N. T., Jahanshad, N., Cheung, J. W., Ching, C. R., ... & Thompson, P. M. Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. Molecular Psychiatry, 2018, 23(4), 932-942.

[9] Machado-Vieira, R., Soeiro-De-Souza, M. G., Richards, E. M., Teixeira, A. L., & Zarate Jr, C. A. Multiple levels of impaired neural plasticity and cellular resilience in bipolar disorder: developing treatments using an integrated translational approach. The World Journal of Biological Psychiatry, 2014, 15(2), 84-95.

[10] Fernandes, B. S., Molendijk, M. L., Köhler, C. A., Soares, J. C., Leite, C. M. G. S., Machado-Vieira, R., ... & Carvalho, A. F. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Medicine, 2015, 13(1), 1-22.

[11] Gigante, A. D., Bond, D. J., Lafer, B., Lam, R. W., Young, L. T., & Yatham, L. N. Brain glutamate levels measured by magnetic resonance spectroscopy in patients with bipolar disorder: a meta-analysis. Bipolar Disorders, 2012, 14(5), 478-487.

[12] Passos, I. C., Mwangi, B., Vieta, E., Berk, M., & Kapczinski, F. Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatrica Scandinavica, 2016, 134(2), 91-103.

[13] Sole, B., Jimenez, E., Torrent, C., Reinares, M., Bonnin, C. D. M., Torres, I., ... & Martinez-Aran, A. Cognitive impairment in bipolar disorder: treatment and prevention strategies. International Journal of Neuropsychopharmacology, 2017, 20(8), 670-680.

[14] Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., ... & Berk, M. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disorders, 2018, 20(2), 97-170.

[15] Malhi, G. S., Gessler, D., & Outhred, T. The use of lithium for the treatment of bipolar disorder: recommendations from clinical practice guidelines. Journal of Affective Disorders, 2017, 217, 266-280.

[16] Frangou, S., Dima, D., & Jogia, J. Towards person-centered neuroimaging markers for resilience and vulnerability in bipolar disorder. Neuroimage, 2017, 145, 230-237.

[17] Miura, T., Noma, H., Furukawa, T. A., Mitsuyasu, H., Tanaka, S., Stockton, S., ... & Cipriani, A. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. The Lancet Psychiatry, 2014, 1(5), 351-359.

[18] Gitlin, M. J. Antidepressants in bipolar depression: an enduring controversy. International Journal of Bipolar Disorders, 2018, 6(1), 1-7.

[19] Caseras, X., Murphy, K., Lawrence, N. S., Fuentes-Claramonte, P., Watts, J., Jones, D. K., & Phillips, M. L. Emotion regulation deficits in euthymic bipolar I versus bipolar II disorder: a functional and diffusion-tensor imaging study. Bipolar Disorders, 2015, 17(5), 461-470.

[20] Li X., Frye M.A., Shelton R.C. Review of pharmacological treatment in mood disorders and future directions for drug development. Neuropsychopharmacol, 2012, 37, 77–101.

[21] Brunoni, A. R., Moffa, A. H., Sampaio-Junior, B., Borrione, L., Moreno, M. L., Fernandes, R. A., ... & Benseñor, I. M. Trial of electrical direct-current therapy versus escitalopram for depression. New England Journal of Medicine, 2017, 376(26), 2523-2533.

[22] Perera, T., George, M. S., Grammer, G., Janicak, P. G., Pascual-Leone, A., & Wirecki, T. S. The clinical TMS society consensus review and treatment recommendations for TMS therapy for major depressive disorder. Brain Stimulation, 2016, 9(3), 336-346.

[23] Cirillo, G., Di Pino, G., Capone, F., Ranieri, F., Florio, L., Todisco, V., ... & Di Lazzaro, V. Neurobiological after-effects of non-invasive brain stimulation. Brain Stimulation, 2017, 10(1), 1-18.

[24] McGirr, A., Karmani, S., Arsappa, R., Berlim, M. T., Thirthalli, J., Muralidharan, K., & Yatham, L. N. Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression. The World Journal of Biological Psychiatry, 2016, 17(6), 490-499.

[25] Sitaram, R., Ros, T., Stoeckel, L., Haller, S., Scharnowski, F., Lewis-Peacock, J., ... & Sulzer, J. Closed-loop brain training: the science of neurofeedback. Nature Reviews Neuroscience, 2017, 18(2), 86-100.

[26] Fernandes, B. S., Williams, L. M., Steiner, J., Leboyer, M., Carvalho, A. F., & Berk, M. The new field of 'precision psychiatry'. BMC Medicine, 2017, 15(1), 1-7.

[27] Kadosh, R. C., Levy, N., O'Shea, J., Shea, N., & Savulescu, J. The neuroethics of non-invasive brain stimulation. Current Biology, 2012, 22(4), R108-R111.

[28] Bueno, V. F., & Brunoni, A. R. Decision-making in the era of personalized psychiatric treatment based on non-invasive brain stimulation. Frontiers in Neuroscience, 2019, 13, 1040.

[29] Jauhar, S., & Nour, M. M. Brain stimulation as a treatment for depression: the need for informed consent. The British Journal of Psychiatry, 2019, 214(5), 248-249.