

Review

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Review

Biomarkers: The Key to Enhancing DBS Treatment for Psychiatric Conditions

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Abstract: Deep brain stimulation (DBS) is currently a promising technique for psychiatric patients with severe and treatment-resistant symptoms. However, the results to date have been quite heterogeneous, and the indications for psychosurgery with DBS remain in an experimental phase. One of the major challenges limiting the advancement of DBS in psychiatric disorders is the lack of objective criteria for diagnosing certain conditions, which are often based more on clinical scales rather than measurable biological markers. Additionally, there is a limited capacity to objectively assess treatment outcomes. This overview examines the literature on the available biomarkers in psychosurgery in relation to DBS, as well as other relevant biomarkers in psychiatry with potential applicability for this treatment modality. There are five types of biomarkers: clinical/behavioral, omic, neuroimaging, electrophysiological, and neurobiochemical. The information provided by each biomarker within these categories is highly variable and may be relevant for diagnosis, response prediction, target selection, program adjustment, etc. A better understanding of biomarkers and their applications would allow DBS in psychosurgery to advance on a more objective basis, guided by the information provided by them and within the context of precision psychiatry.

Keywords: deep brain stimulation (DBS); psychosurgery; depression; obsessive-compulsive disorder (OCD); biomarkers; diffusion tensor imaging (DTI)

1. Introduction

1.1. Deep Brain Stimulation (DBS) and Psychosurgery

Psychosurgery refers to the neurosurgical treatment of severe mental illnesses that are resistant to conventional treatments, such as medication and psychotherapy. In society, about 20% of people are diagnosed with major depression, and 2% with obsessive-compulsive disorder (OCD). Of these patients, 10-20% will not improve with conventional treatments, which are based on subjective clinical diagnoses and "trial and error" treatments with psychotropic drugs and psychotherapy [1].

Psychosurgery, although controversial in the past, has experienced a resurgence thanks to technological advances and a better understanding of the neurobiology of mental illness. Approaches include lesion techniques and neuromodulatory therapies, most notably deep brain stimulation (DBS). DBS, initially approved in 2002 for the treatment of Parkinson's, has been used for other disorders such as dystonia, epilepsy, OCD, pathological aggressiveness, anorexia, Gilles de la Tourette, schizophrenia, and depression, although many of these indications are still experimental [2].

Mental illnesses present unique challenges that complicate the use of DBS. Symptoms include thoughts and behaviors that are difficult to quantify, making diagnostic criteria such as DSM-V or

ICD-11 not always effective. In addition, psychiatric illnesses often present comorbidities, such as 80-90% of patients with depression also presenting anxiety, which exacerbates refractoriness to conventional treatments [3]. Recent advances in neuroscience have led to a paradigm shift, understanding mental illnesses as alterations in neural networks rather than isolated dysfunctions of brain structures [4].

The concept of DBS has evolved from the stimulation of a specific nucleus to the modulation of complex neural networks, which has generated interest in connectome studies to correlate brain connectivity with patient clinical data and optimize treatments. However, identifying the optimal stimulation target remains a challenge, and the mechanisms of action of DBS in psychiatric patients are not yet fully understood [5]. A more personalized approach to DBS, based on the individual patient profile, might be the way forward.

1.2. Precision Psychiatry

Precision medicine focuses on treatment based on individual variability, considering each person's genetics, environment, and lifestyle. This approach has transformed disciplines such as oncology, where treatments are decided based on genetic and molecular biomarkers [6]. However, psychiatry has not advanced at the same pace due to the complexity of mental illness, where symptoms vary widely between patients with the same diagnosis [7].

The precision approach in psychiatry seeks to identify biomarkers for more personalized diagnosis and treatment. "Omics" techniques, such as genomics and proteomics, together with neuroimaging and clinical data, could contribute to the development of biosignatures for more accurate classification of mental illnesses. This would allow predicting response to treatments such as DBS and choosing the best stimulation targets. Although precision psychiatry is in its early stages, it promises better prediction of prognosis and treatment optimization [8].

1.3. Biomarkers in psychosurgery

In recent decades, there has been an increased interest in biomarkers in mental illness, raising the possibility that diagnosis based on clinical criteria, such as the DSM, lacks biological validity [9]. The use of biomarkers in diagnosis and treatment could revolutionize psychiatry, although their identification is not easy due to the high heterogeneity of results in the literature. Although biomarkers of response to antidepressants and psychotherapy have been proposed outside the field of DBS, in psychosurgery, the identification of these is more complicated due to the smaller number of patients treated and the lesser experience in the application of these modern techniques [10].

The ideal process to create a biomarker in psychosurgery with DBS includes four phases: identifying a phenotype that can be measured and modified with DBS, validating the biomarker intra and interindividually, associating it with the response to DBS through clinical trials, and conducting multicenter studies to confirm its usefulness. Biomarkers can provide diagnostic, response, monitoring, prognostic and safety information [5]. Biomarker-based precision psychiatry could transform the use of DBS in psychosurgery, allowing for more personalized neuromodulation tailored to the patient's profile.

1.4. Deep brain stimulation based on precision psychiatry

DBS treatment in psychiatric disorders has shown a large variability of results, influenced by several factors such as the selection of the stimulation target and the programming of the electrodes. The identification of biomarkers based on the patient's phenotype would allow treating individuals in a more personalized way, improving the prediction of the response to treatment. The development of connectome atlases, which correlate brain connectivity with the patient's symptoms, could help define a more precise neuromodulation [11]. Advancing in this concept, symptom networks, such as those defined in anxiety, depression and OCD, could guide the selection of stimulation targets more appropriate for each patient.

2. Objectives

In this work, we aim to review the existing literature on biomarkers related to deep brain stimulation in the treatment of psychiatric disorders, as well as other biomarkers already described in these diseases, which could have a possible future application in psychosurgery using this therapeutic method.

2.1. Materials and Methods

In this study, a literature review on biomarkers in psychosurgery with deep brain stimulation (DBS) was carried out.

The articles were obtained through searches in PubMed, Embase and Google Scholar. In addition, the search was expanded by reviewing the references cited in these articles. The time limit for the search was set on 09/12/2024.

Articles related to biomarkers in DBS applied to psychosurgery were selected, as well as those that, although not directly dealing with DBS, offered relevant information on biomarkers in psychiatric diseases, being considered useful for future studies and applications in this field.

Studies on DBS in movement disorders, non-invasive neuromodulation or psychosurgery with ablative techniques that did not provide relevant data on DBS in psychosurgery were excluded.

3. Results

Biomarkers related to DBS treatment can be classified into the following categories: clinical or behavioral biomarkers, peripheral biomarkers, neuroimaging biomarkers, electrophysiological biomarkers, and neurobiochemical biomarkers. Below, we will review biomarkers for DBS in psychosurgery within each of these categories.

3.1. Clinical/Behavioral Biomarkers

In the absence of objective biomarkers, subjective rating scales remain the standard in psychiatry to measure disease severity and monitor treatment [1].

These scales, however, have limitations for assessing outcomes in neurosurgery. An example is major depression where the most common scales (HAM-D and MADRS) are not ideal in psychosurgery for two reasons:

1. Patients undergoing neuromodulation are refractory to conventional treatment, and these scales were not designed to assess resistant depression or to monitor long-term outcomes [1].
2. They can be imprecise, influenced by external factors (such as recent stressful events), leading to variations in outcomes that do not reflect actual clinical effectiveness [12].

In addition, the scales do not break down key aspects of depression (anhedonia, emotional dysregulation), which may be more relevant to clinical response in DBS. This might have contributed to the failure of clinical trials in psychosurgery due to lack of adequate clinical biomarkers, rather than treatment inefficacy [1].

Regarding OCD, Rios-Lagos and colleagues (among whom the last author is included) has recently conducted a study in which we sought to investigate the hypothesis about processing speed in patients with treatment-resistant OCD and to clarify to what extent slowness is related to psychopathological symptoms. A clinical and neuropsychological examination was performed on 39 patients with resistant OCD, candidates for neurological surgery, and 39 matched healthy individuals. Principal component analysis revealed a three-component structure in the neuropsychological battery used, which included processing speed, working memory, and conflict monitoring. Comparisons between groups showed that OCD patients performed significantly worse than healthy individuals on speed measures, but no differences were found on executive tests not influenced by time. Correlation analyses revealed a lack of association between neuropsychological and clinical measures. The results suggest that patients with treatment-resistant OCD present a primary deficit in information processing speed, independent of clinical symptoms [13].

Finally, given the advance in knowledge of neural networks, it is suggested that clinical scales be adapted to measure changes in modulated networks, rather than focusing only on general pathology [1].

3.2. *Peripheral Biomarkers*

No peripheral biomarkers have been identified in psychiatric patients treated with DBS, but there are studies suggesting their possible future use in psychosurgery, which we will summarize below:

Serum biomarkers

Several biomarkers can be measured in blood (plasma), although many have limited evidence and low specificity. Most of them have been used with a diagnostic approach. Some of the most relevant biomarkers are broken down below for schizophrenia, depression and OCD [10,14,15]:

- Increased in schizophrenia: arachidonic acid, antigliadin IgA, anti-NMDAR antibodies, malondialdehyde, sIL-2 receptor.
- Decreased in schizophrenia: adiponectin, vitamin B6, NGF, TNF-alpha.
- Increased in depression: C-reactive protein, FGF-2, glutamate, IL-6, IGF-1, lipid peroxidation marker, sIL-2 receptor.
- Decreased in depression: BDNF, KYNA/3HK, KINA/QUIN, KINACID
- Increased in OCD: cortisol, glutathione peroxidase, superoxide dismutase, 8-hydroxydeoxyguanosine, malondialdehyde.
- Decreased in OCD: vitamin C and vitamin E.

Genomic biomarkers

Genetics plays an important role in mental illness, but its clinical applicability is limited by polygenic complexity. GWAS studies have generated polygenic risk scores (PRS) to predict the evolution of diseases such as schizophrenia or the response to lithium in bipolar disorder. Although promising, it is not yet clinically useful, but could be useful in the future to identify responses to DBS [16].

Transcriptomic biomarkers

In depression, changes in the expression of genes related to better response to antidepressants (MMO28 and KXD1 genes) have been identified [17]. MicroRNAs (miRNA-146a-5p, miR-146b-5p, miR24-3p and miR-425-3p) have also been linked to response to antidepressant treatment, suicide risk and substance abuse [18].

Proteomic biomarkers

Proteins related to neuronal transmission and other processes have been proposed as biomarkers in schizophrenia [19]. Zinc finger protein 729 was found to be decreased in patients with schizophrenia compared to controls [19]. GMF-beta, BDNF and RAB3GAP1 were also found to be decreased in this pathology [20]. In depression, acetyl-L-carnitine is a marker of severity and resistance to treatment [21]. In anorexia nervosa, neurofilament light chains (NF-L) have been associated with neuronal damage [22].

Metabolomic biomarkers

Small molecules of cellular metabolism are also considered potential biomarkers. In depression, certain levels of phosphatidylcholine C38:1 (absence of response) and hydroxylated sphingomyelin (increased response) in plasma have been associated with prognosis and recovery of symptoms after treatment [23].

Epigenetic biomarkers

Epigenetic modifications, such as gene hypermethylation, have been linked to depression, schizophrenia and post-traumatic stress. In addition, methylation of genes such as BDNF or FKBP5 could be a predictor of response to antidepressants [24].

3.3. *Biomarkers in Neuroimaging*

The use of imaging techniques, such as functional MRI and tractography, has been key to conceptualizing DBS as a modulation of neural networks, rather than a specific nucleus. These

techniques allow the analysis of both the local impact of stimulation and that of the anatomically and functionally connected regions [25].

Currently, neuroimaging plays a crucial role in presurgical screening, target selection, neurosurgical planning, electrode localization, therapeutic evaluation and analysis of clinical correlations [26].

Obsessive-compulsive disorder (OCD)

In OCD, alterations in volume, metabolism and blood flow are observed in structures such as the orbitofrontal cortex, anterior cingulate cortex, caudate, amygdala and prefrontal cortex, all members of the cortico-striato-thalamic-cortical network [27]. A larger volume of the nucleus accumbens (NAcc) has been proposed as a biomarker of response to DBS [28], and reduced connectivity between this nucleus and the medial/lateral prefrontal cortex has been associated with clinical improvement [29].

Connectivity with areas such as the middle frontal gyrus and the frontothalamic network correlates with good response to DBS. Furthermore, stimulation of the ventral anterior limb of the internal capsule (vALIC) improves anxiety and mood symptoms [30]. On the other hand, stimulation in targets such as the VC/VS activates several structures of the cortico-striato-pallidum-thalamus-cortical network, while connectivity with the hypothalamus can produce adverse effects, such as weight gain [31]. Given these findings, some authors advocate grouping the NAcc, VC/VS and ALIC targets as a “striatal region” given the structural and functional proximity [3].

The medial forebrain fasciculus (slMFB) has shown better results when stimulating areas close to the slMFB rather than the anterior thalamic radiations (ATR) [32]. In the subthalamic nucleus (STN), stimulation reduces metabolism in areas such as the cingulate and medial frontal cortex, although it may also increase impulsivity [33]. Measurements of the metabolism in those targeted areas might be a potential biomarkers for the selection of patients for DBS.

Simultaneous stimulation of amSTN and VC/VS has shown improvement without added effects from their combined stimulation. DBS in the amSTN improved cognitive flexibility, while in VC/VS an improvement in mood was observed [34].

A study on the structural connectivity of the bed nucleus of the stria terminalis (BNST) in OCD showed a relationship between connectivity in this area and a reduction in the Y-BOCS scale when stimulating subcortical pathways connected to the amygdala, hippocampus and stria terminalis, as well as cortical areas such as the prefrontal cortex, parahippocampus and extrastriate visual cortex [31].

Major depression

Depression involves dysfunction of several limbic networks connected to the DMN (default mode network) [35]. An increase in metabolism in the subcallosal gyrus has been proposed as a biomarker of response in depression, especially in stimulation of this region (Cg25) [36]. Reduced activity in the dorsal anterior cingulate cortex, posterior cingulate cortex and precuneus predicts clinical improvement [37].

The medial forebrain fasciculus is another target in depression, showing correlation between frontopolar/orbitofrontal volumes and clinical response, which could personalize treatment [38].

In patients with stimulation in the NAcc, an alteration of the frontostriatal network was observed, which is also involved in depression. Hyperactivation was identified in the dorsolateral prefrontal cortex, cingulate cortex, and amygdala, and hypoactivation in the ventromedial and ventrolateral prefrontal cortex, dorsal caudate, and thalamus [39].

Other target areas in DBS to treat depression include the ALIC and the VC/VS complex, which have shown improvement in depressive symptoms in patients with OCD. Due to their connections with the bed nucleus of the stria terminalis and the NAcc, these areas could influence stress regulation and reward and motivation management [40].

Complete remission of depressive symptoms has also been described in one patient after stimulation in the lateral habenula (LHb), in which hyperactivity is described in patients with depression [41].

Stimulation of the inferior thalamic peduncle has also shown a reduction in depressive symptoms, although in few patients [42].

Tourette Syndrome

Stimulation in the internal globus pallidus (GPi) improves tics based on its connectivity with limbic and associative networks [43]. Stimulation in the centromedian-parafascicular nucleus (CM-Pf) reduces motor and vocal tics by suppressing motor and insular hyperactivation [44].

The internal thalamic-centromedian-ventro-oral nucleus (CM-VOI) showed better results in patients with activation of fibers projected to premotor areas, especially Pre-SMA. Wider stimulations in Pre-SMA, SMA and M1 were associated with worse responses [45].

In a study using CM/VC/VS targets, patients who improved clinically showed increased connectivity with the precentral gyrus, while dizziness was related to cerebello-rubral fibers, paresthesias to thalamic and insular connections, and depression to fibers connecting the thalamus and amygdala [46].

Anorexia nervosa

DBS over the NAcc has shown a reduction in frontal, limbic, and insular hypermetabolism, while stimulation in Cg25 improves affective and body perception symptoms [47].

Addiction, schizophrenia, and post-traumatic stress disorder

In addiction, the NAcc is the main target due to its involvement in the dopaminergic reward system [48]. In PTSD, the basolateral amygdala has been proposed as a target [49], while in schizophrenia the NAcc and Cg25 have been explored without conclusive biomarkers to date.

3.4. Electrophysiological Markers

EEG is a useful tool as a biomarker in psychosurgery, providing preoperative, intraoperative and postoperative information, especially in closed-loop systems [49].

Preoperative markers

In patients with OCD, the surface EEG shows frontal asymmetry in alpha and beta ranges, increased ERN (error-related negativity) and REM sleep disturbances [50]. An elevated ERN correlates with limited success of the intervention. It has also been observed that a decrease in the beta band in the anterior cingulate cortex is a favorable indicator of response to treatment [51]. Decreases in the beta band in the anterior cingulate cortex and medial frontal gyrus have also been described for this entity as biomarkers of favorable response to medical treatment [52].

In depression, the EEG shows hyperactivity of the anterior cingulate cortex, detected by theta activity in areas such as Fz and FCz, using techniques such as LORETA for greater precision [53].

Intraoperative markers

In patients with OCD, intraoperative recordings reveal abnormal activity in the caudate nucleus and aberrant local field potentials in frontal electrodes [29]. In subjects with depression and DBS in the subgenual gyrus, autonomic phenomena such as tachycardia and increased skin conductance have been observed, correlated with a good response to stimulation [54].

Postoperative markers

In OCD, NAcc DBS shows reduced frontal delta oscillation, correlated with the severity of obsessions and compulsions [29]. Normalization of P300 amplitude is also observed in patients with a good response to serotonin reuptake inhibitors, which is associated with better results in working memory and attention [55].

In refractory depression, action potentials in the bed nucleus of the stria terminalis and subgenual alpha activity allow differentiation between OCD and treatment-resistant depression [56]. Alpha activity in the subgenual area has been found to correlate with the severity of depression, while beta desynchronization has an inverse correlation [57].

In patients with depression treated with DBS in the subgenual gyrus, changes in frontal theta and parietal alpha activity have been shown to be predictors of depression severity before and after treatment [27]. In addition, biomarkers such as low theta energy in the subgenual area and high parietotemporal alpha energy have been identified, although some results have not been replicated in other studies [58].

In Tourette syndrome, an increase in low frequency and alpha range has been observed in the thalamus and GPi, which serves as a biomarker of disease severity [59]. In another study, an increase in the gamma band in the median center of the thalamus has been shown after symptom improvement [60]. In patients with alcohol addiction treated with DBS in NAcc, the increase in ERN has been shown to correlate with clinical improvement [61].

3.5. Neurobiochemical Markers

Neurobiochemical biomarkers measure changes in extracellular neurotransmitters, providing key information about the disease status thanks to their high temporal resolution.

In OCD, DBS in the NAcc modulates the cortico-striato-thalamus-cortical network and regulates neurotransmitter levels. This includes an increase in dopamine, serotonin, and norepinephrine in the prefrontal cortex, an increase in dopamine in the striatum, and an increase in dopamine and GABA with a decrease in glutamate in the NAcc [62]. These changes are clinically relevant. Techniques such as voltammetry and biosensors allow the measurement of dopamine, serotonin, and glutamate with high precision, making them good candidates for closed-loop systems in OCD [62].

In depression, serotonin and dopamine play a crucial role in the pathophysiology and treatment, with alterations observed in the striatum and hippocampus, making them potential neurochemical monitoring regions (63, 64).

In Tourette syndrome, there are abnormal concentrations of dopamine, GABA and glutamate, with dopamine being the most promising biomarker. This is due to the positive response to dopaminergic antagonists and the observation of hypoactivity in the striatum, suggesting that measuring dopamine in this region is useful for future closed-loop systems in Tourette [62].

3.6. Closed-Loop Systems

Closed-loop systems adjust stimulation parameters based on specific biomarker recordings. These biomarkers must have high specificity, good signal-to-noise ratio, and high temporal resolution. The biomarkers used include electrophysiological (action and field potentials) and neurobiochemical (neurotransmitters), and allow determining when and how much to stimulate based on the patient's clinical status. However, due to the novelty of this technology, there are few published studies on its use in psychosurgery [62].

The difficulty of replicating results and the lack of uniform criteria for biomarkers in psychiatric diseases complicate the self-programming of closed-loop systems. Currently, these systems are contributing experimentally to the understanding of the circuits and electrical activity involved in mental disorders [65].

An example is the use of field potentials in the CM-Pf in patients with Tourette syndrome, where an increase in low-frequency and alpha-range activity was found [59]. In a case of refractory OCD and severe depression, the closed-loop system recorded activity in the BNST, where decreased gamma activity correlated with depressive symptoms. Stimulation in the ventral ALIC improved symptoms and increased gamma activity in the BNST [66].

Another interesting approach was presented by Scangos et al., who implanted electrodes in several brain areas of a patient with severe depression. They found that gamma activity in the amygdala indicated the severity of the disease, while the VC/VS was the area with the greatest symptomatic improvement. A connection was identified between the VC/VS and the amygdala, suggesting that the recording and stimulation areas may be different [67].

In the future, it is hoped to move towards more precise and effective closed-loop systems, based on reliable biomarkers for the treatment of psychiatric diseases.

4. Discussion

Psychiatric illnesses represent a major cause of chronic morbidity, with a major socioeconomic impact. Although conventional treatment includes psychotherapy and medications, up to 30% of patients are refractory to these therapies. For these severe cases, alternative treatments such as

psychosurgery, including deep brain stimulation (DBS), are considered. Despite technological advances, DBS in psychiatry is still in the early stages of development [68].

One of the greatest challenges in this field is the heterogeneity of psychiatric disorders, since clinical diagnoses are based on changing criteria (such as those of the DSM) and some symptoms occur in multiple diseases. This situation makes both diagnosis and treatment difficult [69].

Therefore, the goal is to move towards precision psychiatry, where biomarkers are identified that allow the treatment of each patient to be personalized according to their individual profile or “biosignature”. These biomarkers can be classified into categories based on the information they provide, such as diagnosis, prediction of effectiveness, prognosis, safety, susceptibility, response, and monitoring.

A precision psychiatry approach would apply a comprehensive analysis of these biomarkers in a patient to determine their diagnosis based on dysfunctional neural networks, rather than traditional clinical criteria. This would also allow predicting which patients will respond best to conventional therapies or DBS, and even help choose the best target for stimulation.

Furthermore, closed-loop neurostimulation systems, which adjust stimulation parameters in real time based on biomarkers, offer a promising approach to improve therapeutic response, but still require further research to optimize their implementation in psychiatry.

5. Conclusions

In conclusion, although numerous studies have been carried out to identify biomarkers in psychiatric diseases, there is currently no broad standardization or generalization in their use for deep brain stimulation in psychosurgery.

The growing knowledge of these biomarkers and their application could facilitate the advance towards precision psychiatry in the coming decades. In this context, identifying the biosignatures that best adapt to DBS treatment will be especially important.

It is crucial to advance in the personalization of the diagnosis of psychiatric diseases, focusing on the identification of dysfunctional neural networks that contribute to the patient’s symptoms and selecting the most appropriate treatment based on this. Establishing a “brain symptomatology” will be essential to direct DBS towards the correct pathological network.

In addition to being vital for the diagnosis and objective assessment of disease severity, biomarkers can also be valuable predictors of prognosis, providing more realistic expectations to the medical team, the patient and their relatives.

Future biomarkers in psychosurgery are also expected to play an important role in treatment monitoring and objective assessment of DBS response during follow-up. Closed-loop systems, which integrate disease biomarker recording with self-programming and stimulation, appear to be a promising technology for psychiatric pathologies due to the high clinical variability of these diseases and the need for continuous monitoring.

Although DBS in psychosurgery still has a long way to go, it offers great hope for patients with severe psychiatric diseases who do not respond to other treatments. In the future, joint analysis of clinical/behavioral, omic, neuroimaging, electrophysiological and neurobiochemical biomarkers is expected to allow the development of more personalized, precise and effective DBS treatments.

Conflicts of Interest: None.

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