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Neuromodulation for Treatment of Psychiatric Disorders: State of the Art

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Introduction

In the 1950s and the 1960s systematic researchers studied the effect of Direct Current (DC) on cortical excitability applied for the treatment of depressive or manic symptoms. The interest on "brain polarization" and electroconvulsotherapy declined during the 70s emerging psychopharmacology. In the last years, DC stimulation delivered transcranially (tDCS) demonstrated that could induce prolonged cortical neuroplastic changes with functional effects contributed to applied as potential approach for the treatment of several psychiatric disorders, such major depressive disorder, schizophrenia, obsessive-compulsive and also neurological disorders.

Brain stimulation can induce significant currents in cortical areas and modulate neuronal excitability without triggering action potentials. The long-term effects on post-synaptic connections generate long-term potentiation (LTP) and long-term depression (LTD) through NMDA-depended mechanisms. Different areas of cortex can be stimulated but last investigations have demonstrated the critical role of Orbito Frontal Cortex (OFC) in many of the complex functions that are essential to healthy human cognition, affect regulation and behavior. The psychiatric disorders emerge when these functions are disrupted from the point of view of neural basis the OFC to plays an important, role in the pathophysiology of mood, anxiety, psychotic and other major psychiatric disorder. A lateral orbitofrontal cortico-striatal loop circuit constitutes one of the five functional basal ganglia loop circuits. Multiple OFC loops, or OFC-interacting loops, may therefore serve as neural substrates for distinct dimensions of psychiatric illness [1-4].

Neuromodulation in Psychiatric Disorders

Current Neurostimulation modalities

Nowadays we have six neurostimulation modalities: 1) transcranial direct current stimulation (tDCS), 2) repetitive transcranial magnetic stimulation kn (rTMS), 3) electroconvulsive therapy (ECT),4) magnetic seizure therapy (MST), 5) vagus nerve stimulation (VNS), and 6) deep brain stimulation (DBS). When motor cortex neurons were stimulated with tDCS their excitability remains after stimulation stopped. The potential therapeutic benefit is clear because neurophysiological effect of current applied during a single session is durable in time.

tCS has been investigated as a treatment approach for schizophrenia, some found active stimulation improved cognition, reduced negative symptoms and hallucinations but unfortunately clinical effects disappear and currently available data does not support use of tCS for schizophrenia, dementia or cognitive deficits.

Randomized Controlled Trials of tCS for Treating Substance Use Disorders indicate that there are very few clinical trials, and several suggest potential harms, such as increased relapse ,greater risk-taking and heightened craving. Neurostimulation treatments using electrical or magnetic stimulation targeting specific brain regions with noninvasive techniques, such as transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), and magnetic seizure therapy (MST) as well as invasive surgical techniques, such as vagus nerve stimulation (VNS) and deep brain

stimulation (DBS), have been studied and are used in patients with treatment-resistant depression (TRD) who have failed to respond to standard treatments. The Canadian Network for Mood and Anxiety Treat-ments (CANMAT), a not-for-profit scientific and educational organization, published a revision of evidence-based clinical guidelines for the treatment of depressive disorders. There is increasing evidence for efficacy, tolerability, and safety of neurostimulation treatments. rTMS is considered now a first-line recommendation for patients with Major Depressive Disorders (MDD) who have failed at least 1 antidepressant. ECT remains a second-line treatment for patients with treatment-resistant depression, although in some situations, it may be considered first line. Third-line recommendations include tDCS and VNS. MST and DBS are still considered investigational treatments [5-8].

Deep brain stimulation for psychiatric disorders and closed-loop approaches will help in understanding the underlying biology of psychiatric disorders. Every closed-loop device is based on neuroscience creating and storing detailed snapshots of the patient's brain at very high resolutions. The past have seen the debut of two new devices for chronic implantable human use, and new developments in this area of neuromodulation are increasing.

For example, two targets in particular are very well studied: the "ventral capsule/ ventral striatum" (VC/VS) and subgenual cingulate gyrus (Cg25). DBS was first tested for refractory obsessive-compulsive disorder (OCD) at the anterior limb of internal capsule, which evolved into VC/VS as the target itself shifted more posteriorly. Comorbid depression also improved, and patients met depression remission criteria. On the other hand, Cg25 was selected as a possible target for psychiatric DBS based on neuro-imaging studies. Closed-loop systems are able to continuous brain recording, providing information about effects of neuromodulation in the the brain . In the present there are hardware platforms available for psychiatric disorders.

Future Neuromodulation Modalities

Optogenetics is a new neuromodulation device which provides control of brain and behavior through light. With high precision, Optogenetics uses genetic tools to introduce non-mammalian ion channels, making specific cells or pathways sensitive to light. Pulses of laser light excite or inhibit specifically those cells. In animal models has demonstrated changes in behavior that can be translated to humans. Brain Machine Interface (BMI) and Explainable Artificial Intelligence (XAI) are the future step on Neuromodulation of Psychiatric Disorders. Some Brain Stimulation (BS) studies in psychiatric patients focuss on anatomy others have both functional and anatomical components. This point of view including function and anatomy is the best aproach for the circuit/network level in psychiatric disorders. Modern imaging technologies, such as diffusion tensor imaging (DTI) and functional connectivity MRI can better study structural and functional networks. For that computational studies can be rigorous at a network level and applicable on neuromodulation by DBS.

It has been demonstrated that BS restores the less-variant activity of the brain and reduces excess of information between network nodes in a mathematical sense resulting in better network function. In terms of oscillatory activity there are rhythmic waves which could be aligned with the phase of frequency of band such as frontal theta in anxiety disorders or beta band in PD. In fact, psychiatric symptoms are finally changed through the improvement of network function providing neuroplasticity. For example, recent studies show BS of ventromedial prefrontal cortex, a putative rodent homologue of human subcallosal cingulate, increased synaptic density promoting neuroplasticity.

Intelligent computational approaches able to sense, interpret, and modulate large amount of data from behaviorally relevant neural circuits at the speed of thoughts. New approaches such as computational psychiatry (CPs) or Machine Learning (ML) are emerging. Explainable Artificial Intelligence (XAI) combines sophisticated AI and ML algorithms with effective explanatory techniques. Explainable Artificial Intelligence for neurostimulation in mental health can be seen as an extension in the design of Brain Mechine Interface (BMI). BMI are combinations of hardware and software systems designed to transfer information between one or more brain area and an external device. On the other hand Biomarkers, defined as biological measurements that give the ability to predict, detect, and diagnose, can be key targets of XAI approaches. Mental health conditions, and the Research Domain Criteria (RDoC) are of particular interest, because they focus on understanding the nature of mental illness in terms of varying degrees of dysfunctions in general psychological/biological systems [9-12].

Conclusion

In the future, XAI techniques for close-loop neurobehavioral modulation over complex neural circuits pertaining to mental disorders including electrical or magnetic stimulations, optogenetics, genome editing or pharmacological compounds and dynamic automatic adjustments can make the dream of efficient treatment of mental disorders come true. Probably in next few years it will provide knowledge on the basic principles about normal and abnormal brain functions and generate translational approaches to manage large multi-modal datasets.

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