

Neuronal networks of depression: Pushing the limits of brain stimulation technology

 openaccessgovernment.org

3 April 2023

A team of researchers at the University of Freiburg and Delft University of Technology have joined forces to explore a new focused ultrasound technology to tap into the Neuronal Networks of Depression

Major Depressive Disorder – background and current treatments

Major Depressive Disorder (MDD, or “depression”) is not a single disorder but a syndrome: a spectrum of associated behavioral symptoms that are defined (and re-defined with time) in the Diagnostic and Statistical Manual (DSM) of Mental Disorders, American Psychiatric Association. Key symptoms are anhedonia and hopelessness. Clinical depression is diagnosed if the person experiences five or more of the nine symptoms during a continuous 2 week period, with at least one of the symptoms being either reduced motivation or anhedonia (DSM-5 American Psychiatric Association, 2013). Given the nine main symptoms, the pairing with one of the two essential traits, the bi-directionality of many symptoms (increase or decrease), or their sub-symptoms, there are several hundred different individual symptom profiles possible that would qualify for depression diagnosis (Fried & Nesse, 2015).

Given this diversity in symptoms, it is not surprising that numerous co-existing theories try to explain the etiology of depression (Beck, 1967). According to some of these cognitive and behavioural theories, depressed people have never developed successful skills to cope with stressful experiences or traumatic events. Other theories focus more on biological components and consider changes in neurotransmitter systems, connectivity, hormones, epi/genetics, or inflammation to be the root cause of depression (Dean & Keshavan, 2017). The cognitive/behavioural and the biological-centred approaches are by no means contradictory, as the former can also be integrated and completed with the biological knowledge of anatomy, neurochemistry, and connectivity of the patient’s brain affected by depression (Disner et al., 2011).

Despite the diagnostic criteria, a significant number of people remain undiagnosed in the population. For clinically diagnosed patients, treatment strategies typically follow a sequential treatment optimization scheme depending on the medical system and healthcare providers who are following the patient (Kraus et al., 2019). First-line treatment involves psychotherapy and pharmacological dose-escalating therapies targeting monoaminergic brain systems, as well as non-invasive brain stimulation (NIBS) methods like repetitive transcranial magnetic stimulation (rTMS) and theta-burst stimulation (TBS). Non-responsive patients would go on to receive augmentation/ switch

therapy with additional or different category of drug combinations complementing their existing antidepressant treatment, vagus nerve stimulation, NIBS, and electroconvulsive therapy (ECT) and ketamine for patients with recurrent/ severe episodes with suicidal ideation. However, up to approximately one-third of the patients can end up being classified as Treatment Resistant Patients (TRD), that is to say, they stay refractory to all currently approved treatments (Ruhé et al., 2012). It is this cohort of patients who are eligible to participate in clinical trials of experimental and in part, invasive therapies such as Deep Brain Stimulation (Bewernick et al., 2017; Drobisz and Damborská, 2019).

Neuronal networks of depression is complex

Depression is a network disease with particular symptoms emerging as a consequence of disorderly network connectivity and not because of the dysfunction of a single given brain region. The neuronal networks of depression have been identified through preclinical, experimental work and, crucially, through an increasing number of non-invasive clinical imaging studies over the past decade. Better understanding of the disease's neural substrates and associated symptoms should lead to more precise diagnosis and classification of the patients into biotypes, leading to more rationale and “customized” therapeutic strategies (Goldstein-Pierarski et al, 2022). Four principle networks – and changes in their activities – have been identified and implicated in the clinical disorder:

hyper-connectivity is reported within the “default mode” and the ventral limbic “affective” networks giving rise to symptoms such as rumination and dysphoria, respectively, and reduced activity is associated within the dorsal “control/cognitive” and the frontal-striatal “reward” networks, producing disrupted cognitive control and anhedonia/ reduced motivation, respectively (Li et al., 2018; Coenen et al. 2020). Neurostimulation, in the form of NIBS or DBS, is already used in a limited way in psychiatric disorders, including depression, although the matching of the patient biotype and symptoms with the appropriate target has not yet been integrated into clinical design. Many of the current non-invasive neurostimulation modules, for example, rTMS, permit the shifting of the targets but require multiple repetitive sessions, cannot target precise areas and have low tissue penetration qualities (cannot target deep brain structures and fiber bundles); whilst more invasive approaches, for example, DBS, permit the chronic and continuous stimulation of well defined deep brain structures, but the selected target is pre-fixed as the implanted electrodes cannot be changed without additional extensive neurosurgery. In order to be able to modulate activity at several targets and networks, an optimal brain stimulation technique would need to merge the targeting flexibility of NIBS, with the capacity of DBS to deliver stimulation precisely to any cortical or subcortical brain structure.

Epidural-focused ultrasound as a promising therapy

In this context, CMOS (complementary metal-oxide-semiconductor) ultrasound 2D phased arrays transmitters have emerged as a promising technology for enabling chronic neuromodulation via an epidural ultrasound stimulator. CMOS ultrasound 2D phased arrays transmitters consist of a 2D array of tiny ultrasound transducers that can be

precisely controlled to generate a focused and steerable beam of ultrasound waves. This technology also enables wireless and remote control of the neuromodulation parameters, which can potentially improve the patient's comfort and reduce the risk of infection or other complications. In the clinic, precise targeting could be achieved by integrating the beam steering feature with an MRI-derived patient-specific 3D brain/ tractography atlas.

Perhaps the most considerable clinical contribution – and a major innovation – of the emerging epidural-focused ultrasound technology would be the post-implantation capability to shift or to have multiple simultaneous targets, including deep brain structure targets. In view of the discussion above concerning neuronal networks of depression, the chronic, long-term ability to target multiple regions on multiple networks (based on adaptive closed-loop feedback) would represent a paradigm shift in the therapeutic value of neurostimulation in depression and other psychiatric and neurological disorders.

However, there are still some challenges that need to be addressed before CMOS ultrasound 2D phased arrays transmitters become widely used in clinical settings. One of the main challenges is optimising the transducers' design and fabrication to achieve high efficiency and reliability while minimizing the power consumption and heating effects. This can be achieved by using advanced materials and fabrication techniques, such as MEMS (micro-electro-mechanical systems) or nanotechnology, and by optimizing the acoustic and electronic properties of the transducers.

[Click here for references](#)

Please Note: This is a Commercial Profile



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](#).