

The Prospect of Focal Ultrasound in the Treatment of Mental Disorders

Carlos Trenado *, Nicole Pedroarena-Leal and Diane Ruge *

Laboratoire de Recherche en Neurosciences Cliniques (LRENC), 34725 Montpellier, France

* Correspondence: carlos.trenadoc@gmail.com (C.T.); diane.ruge@gmail.com (D.R.)

Abstract: Mental disorders critically affect an individual's quality of life by disrupting cognitive abilities and emotional states and are a major health burden worldwide. At present, psychotherapy and pharmacological interventions are the main approaches to target the symptoms associated with such disorders; however, some patients become treatment-resistant and thus, alternative treatments are needed. Focal ultrasound (FUS) is an emerging non-invasive therapeutic technology that relies on the use of sound waves to target brain regions with high specificity and without the need for incision or radiation. As a result, FUS has been proposed as a potential treatment for mental diseases as it may help to overcome several issues of current neuromodulation approaches. Here, we discuss basic neuroscience and clinical studies on the application of FUS and highlight perspectives and challenges of the technology as well as opportunities, for instance, regarding stimulation of deep brain structures with potential implication in modulating brain neuroplasticity of relevant cortical and subcortical pathways.

Keywords: focal; ultrasound; plasticity; psychiatric; diseases; neuromodulation; intracortical; neuromodulation; invasive; non-invasive



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1. Introduction

Mental disorders such as anxiety and depression are mental illnesses that disrupt cognitive abilities, behavior, and mood states. They represent a global concern, which has been aggravated in recent years due to world health events such as the COVID-19 pandemic as well as political, economic, and social instability in different regions of the world [1–3].

Among the most common types of mental disorders are anxiety disorders that have a world prevalence of 26.9%, depression of 28%, post-traumatic stress symptoms of 24.1%, stress of 36.5%, psychological distress of 50%, and sleep problems of 27.6% [4].

Invasive treatments such as neurosurgical interventions lesioning specific brain structures, (lobotomy, thalamotomy, etc.) thought to be involved in specific mental illness symptoms, have been used in previous decades [5]; however, the risk of side effects prompted medical research to look for alternative and safer non-invasive approaches. Focusing on non-invasive treatments, pharmacological (antidepressants and antipsychotics) and psychotherapy interventions represent the most common approaches to deal with mental disease symptoms. Psychotherapy comprises cognitive behavioral, interpersonal, and other techniques that show benefit for the patient's recovery [6]. While such treatments have proven to be effective for many patients, a subset of them remain treatment-resistant and thus alternative treatments to ameliorate their symptoms are needed. Neuromodulation is an emerging approach with the potential to change the neural activity of neurobiological brain substrates related to refractory psychiatric symptoms. It comprises techniques such as deep brain stimulation, vagal nerve stimulation, transcranial magnetic and electrical stimulation [7], as well as new emerging approaches such as focal ultrasound (FUS).

FUS involves acoustic waves with a frequency higher than 20 KHz and requires a physical medium in order to support its propagation. For a fluid, FUS's propagation

is mainly longitudinal, i.e., the particle displacement is in the direction of the wave's propagation, which occurs in the case of soft tissue due to a small shear modulus. However, for elastic materials and tissues such as bones, particle displacement may be perpendicular to the propagation direction, thus giving place to transverse waves [8]. Importantly, due to the inhomogeneity of the skull, FUS waves targeting a specific brain region may be subject to acoustic reflection, refraction, and distortion, which represent aspects of ongoing research given the medical prospect of this technique [9].

With regard to the mechanism of action, it has been proposed that FUS enables modification of the neural membrane gating kinetics through the action on mechanosensitive voltage-gated ion channels or neurotransmitter receptors [10–12]. Importantly, previous computational modeling studies suggest that this effect may not be sufficient to explain the induction of neural excitation [13,14], implying occurrence of additional mechanisms. Through the so called “bilayer sonophore” model, it has been proposed that the ultrasound may also affect membrane permeability resulting from cavitation into the cellular membrane by means of membrane pore formation [15].

It is worth emphasizing that the use of FUS for therapeutic purposes dates back to the seminal work of Lynn et al. [16], who devised a method to deliver sound stimulation non-invasively in soft tissue, while also demonstrating its physiological and behavioral effect in animal models. The fact that ultrasound waves can be focused using either single element transducers or electronically controlled phased arrays, thus enabling energy concentration into small volumes ($\sim 2 \times 7$ mm) with varying intensity fields, makes FUS a viable approach not only for ablation purposes but also for the modulation of deep neural pathways. It has only been in the last decades that the use of FUS as a treatment for mental and neurologic disorders proliferated from basic neuroscience studies through clinical trials, reporting the benefits of such treatment.

Depending also on the stimulation intensity, FUS applications range from healing physical therapies [17] to tumor ablation [18]. State-of-the-art MRI-guided FUS (MRg-FUS) is the current standard for image-guided FUS treatment, especially for non-invasive treatments of the brain. The use of MRI enables higher-resolution soft-tissue imaging for accurate treatment planning.

Clinically approved applications include low intensity, non-focused exposure for healing in physical therapy and higher-intensity FUS for ablating a variety of benign and malignant tumors [19].

In this work, we first describe the basic neuroscience and clinical studies reporting the use of FUS for the treatment of mental diseases including the prospect of FUS as a tool to modulate deep brain structures. Secondly, we discuss perspectives and challenges on the application of FUS by emphasizing key aspects such as the interaction between ultrasound and tissue, the need for standardization of stimulation protocols as well as safety measures.

2. Application of FUS in Mental Disorders

2.1. Obsessive-Compulsive Disorder (OCD)

Obsessive-compulsive disorder (OCD) is a debilitating condition that involves stress and anxiety-provoked thoughts and often leads to comorbid depression. OCD may be partly evoked by anomalies in the serotonin pathways and dysfunctional circuits in the orbito-striatal area and dorsolateral prefrontal cortex [20]. Importantly, recent clinical trials have been directed to determine the safety and efficacy of FUS as a treatment for OCD by considering consecutive weekly sessions of transcranial low-intensity focused ultrasound (LIFU) and targeting the caudate of the basal ganglia (<https://clinicaltrials.gov/ct2/show/NCT04775875> (accessed on 1 January 2020)). MRI-guided FUS (MRgFUS) has been proposed as an effective tool to generate precise focal thermal lesions in the internal capsule with the capability to ameliorate OCD symptoms with mild side effects, such as headache and vestibular symptoms [21,22].

Other MRgFUS studies targeting the bilateral anterior capsulotomy in patients with refractory OCD and major depressive disorder (MDD) reported no major adverse effects with only mild effects such as headaches and pin-swelling in seven out of twelve patients and a response rate of four out of six and two out of six in the OCD and MDD cohorts. Based on normative diffusion MRI-based structural connectome, it was revealed that FUS mainly affected the frontal pole, medial thalamus, striatum, and medial-temporal lobe. PET analysis revealed widespread decrease in the metabolism bilaterally in the cerebral hemispheres 6 months post-treatment, as well as in the right hippocampus, amygdala, and putamen. Overall, MRgFUS capsulotomy resulted in both targeted and widespread changes in neural activity, and neuroimaging may hold potential for the prediction of outcomes [23].

Moreover, recent studies on MRgFUS have been directed to optimize the stimulation target by addressing the relationship between the lesion location and long-term outcome in patients with OCD [24]. As indicated by the authors in [22], the application of MRgFUS for treating mental disorders has been limited in patients with a low skull density ratio, which impedes acoustic energy transmission across the skull, and with lateral targets on which it is difficult to achieve a focal ultrasound application. Thus, efforts need to be directed to overcome such limitations.

2.2. Major Depression

Major depression is a medical illness involving feelings of sadness or loss of interest, loss of self-esteem, changes in appetite, trouble sleeping, and suicidal thoughts. These symptoms can range from mild to severe and must last for at least two weeks to qualify for the diagnosis.

With regard to treatment, previous studies have been directed to investigate the feasibility and potential mechanisms of low-intensity pulsed ultrasound (LIPUS) in the treatment of depression in animal models. In particular, it was shown that four weeks of LIPUS was effective in improving depression-like behaviors in rats with chronic unpredictable stress (CUS) as mediated by enhancement of the BDNF/extracellular signal-regulated kinase (ERK)/mammalian target of rapamycin complex 1 (mTORC1) signaling pathways in the prefrontal cortex (PFC) [25]. As inflammatory processes may likely affect brain neurochemical pathways, which leads to depression-like symptoms, recent studies targeted the prospect of FUS in suppressing inflammation and improving depression-like symptoms in mice. Specifically, FUS of the PFC significantly and safely improved depressive-like behaviors in the tail suspension test (TST) and forced swimming test (FST), accompanied by an improvement of anxiety-like behaviors in the elevated plus maze (EPM). Such results were attributed to the downregulation of inflammatory cytokines in the PFC [26].

A case study of low-intensity FUS was carried out in an individual with treatment-resistant generalized anxiety disorder (trGAD) and treatment-resistant major depressive disorder (trMDD). The subject was reported to be the only true non-responder to previously administered treatments: pharmacological interventions; psychotherapy, ECT (electroconvulsive therapy) including two rounds, 24 sessions; diet, exercise, and sleep interventions; acupuncture, massage therapy; and meditation. Prior to FUS, the individual underwent sessions of rTMS (repetitive transcranial magnetic stimulation) to target depression symptoms, which exacerbated his anxiety symptoms. After FUS, the individual underwent another session of rTMS which resolved both the depression and anxiety. Thus, the authors hypothesized that FUS targeting the amygdala produces very specific symptom relief in anxiety, but not in depression and obsessive thinking [27].

2.3. Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the presence of β -amyloid-containing plaques and tau-containing neurofibrillary tangles. AD disrupts cognitive abilities with special emphasis on memory, speech, visuospatial processing, and executive functions [28].

Previous studies using whole-brain low intensity FUS in mice models of dementia reported improvement of cognitive dysfunction (Y-maze test and/or passive avoidance test) associated with improved cerebral blood flow (CBF). The results suggested that low intensity FUS is an effective therapy with the potential to activate specific cells corresponding to the pathology [29]. Moreover, clinical studies targeting the hippocampus or substantia nigra in AD patients during eight consecutive, weekly, 1 h sessions wherein sleep was encouraged naturally or pharmacologically, reported an improvement of cognitive and motor scores without adverse events [30]. MRgFUS has also been shown to reversibly disrupt the brain–blood barrier (BBB), which is known to interfere with effective therapeutics in AD. Although such intervention did not promote any amelioration of the AD pathology, participants did not experience worsening of cognitive abilities and adverse effects. The authors pointed out that treatment of different brain regions along with the effect of MRgFUS on AD needs to be properly characterized [31]. In addition, recent clinical AD studies based on transcranial pulsed stimulation (TPS), which consists of short (3 μ s), repetitive ultrasound shockwaves, reported scarce side effects as well as improvement in the Alzheimer’s disease Assessment Scale (ADAS) and the ADAS cognitive scores [32], and improvement of depression scores (BDI-II) accompanied by effects in functional connectivity after one session of TPS [33]. Furthermore, TPS enabled induction of neuroplasticity changes up to one week after the last stimulation within a three-week experimental longitudinal protocol [34].

2.4. Addiction

Drug addiction is a chronic relapsing disorder characterized by compulsive drug seeking and affects people worldwide. Glial cell-derived neurotrophic factor (GDNF) has been suggested as a potentially effective strategy for the treatment of addiction. With regard to this treatment, low-frequency ultrasound in combination with GDNF microbubbles were used to target the blood–brain barrier opening in the ventral tegmental area (VTA) region of rats under the influence of morphine. The results indicated that such intervention significantly increased GDNF, destroyed morphine-induced conditioned place preference (CPP), namely, disrupted the preference of the animals for a drug-paired compartment versus other compartments involved in a conditioning task, and reduced the withdrawal symptoms of morphine addiction in rats [35]. Another low frequency FUS study targeting the nucleus accumbens of rats under morphine reported no rise in morphine-induced place preference in comparison to a control group, although with no significant reduction of morphine preference [36].

2.5. Anorexia Nervosa

Anorexia nervosa (AN) refers to an eating disorder that leads to abnormal low body weight and anxiety related to gaining weight accompanied by distorted self-perception of one’s own body. With regard to treatment, AN has been commonly targeted through psychotherapy, physical exercise, and pharmaceutical interventions as a joint intervention [37,38]. Interestingly, deep brain stimulation (DBS) of the subcallosal cingulate has been well tolerated and shown to be associated with improvements in mood and anxiety in patients with treatment-refractory AN [39]. Nevertheless, at the present time there are no clinical trials recruiting patients for FUS treatment for anorexia. Further investigation as to the potential application of FUS in this group of patients is pertinent; however, most patients likely do not have the sufficient or minimum muscle and adipose tissue reserve necessary for hardware implantation into the thoracic cavity or for tolerance of potential side effects, such as chronic fatigue.

2.6. Aggressive Behavior

Aggressive behavior includes actions such as tearing, kicking, banging, or breaking objects, furniture, or even windows. It is characteristic, for example, for individuals suffering from autism spectrum disorder, intellectual disability, or AD. The mentioned

behavior represents debilitating conditions that impair an individual's social skills and thus are normally treated via behavioral and psychological treatment.

Alzheimer's disease is often associated with neuropsychiatric symptoms that include agitation and aggressive behavior. Focusing on approaches for treatment-resistant patients, FUS combined with anesthetic-loaded nanodroplets (nanoFUS) targeting the amygdala (a key structure in the neurocircuitry of agitation) has recently been proposed as a novel minimally invasive tool to modulate local neural activity that was able to reduce agitation and aggressive behavior in the TgCRND8 AD transgenic mice [40].

3. Low-Intensity FUS as a Tool to Modulate Deep Brain Structures

In order to understand the function of cortical and subcortical neural pathways, invasive and non-invasive neuromodulation approaches rely on perturbation of specific brain regions/pathways via a stimulus (electrical, magnetic, sound, light) and the observation of the physiological effect and corresponding behavioral implications. In particular, deep brain stimulation (DBS) is one of the most effective neuromodulation techniques that provides modulation of cortico-subcortical pathways by targeting specific deep brain structures via high frequency electrical stimulation. The DBS implantation procedure is invasive and entails surgery and optimal placement of electrodes, often resulting in adverse effects for patients and the possibility of neural inflammation. As an alternative, transcranial focal ultrasound stimulation (tFUS) or transcranial ultrasound stimulation (TUS) is a minimally invasive approach that has the potential to provide stimulation of deep brain structures for long time periods in a reversible way. For instance, macaque studies in which the amygdala and the anterior cingulate cortex (ACC) were targeted with tFUS and stimulation effects measured through fMRI, reported that in conditions without sonication, neural activity in a given area was related to activity in interconnected regions, while such relationships were reduced after the application of tFUS, with special emphasis on the target area [41]. Moreover, a subsequent study presented a protocol to modulate brain activity in macaques for more than one hour after 40 s of stimulation, while circumventing auditory confounds. Regionally specific tFUS effects were observed for the supplementary motor area and frontal polar cortex. Independent of these site-specific effects, tFUS also induced signal changes in the meningeal compartment. Importantly, such effects were temporary and not associated with microstructural changes [42].

4. Perspectives and Challenges

Based on the studies already discussed, FUS represents a promising approach with the potential to modulate the neural activity of barely accessible brain areas and circuits non-invasively. However, there are several challenges that need to be addressed in order to fully realize the potential of FUS. Some of the main challenges are as follows:

Ultrasound–tissue interactions: Ultrasound waves are attenuated by tissue, specifically they are subject to acoustic reflection, refraction, and distortion due to inhomogeneity of the propagation medium, which limits their penetration depth and makes it difficult to focally target deep brain structures, such as the thalamus or basal ganglia, which are important for a wide range of neurological and mental disorders. To deal with this issue, current efforts include the development of novel approaches to address time shifting of constituent single ultrasound waves, by taking into account the related tissue acoustical properties to ensure the proper alignment of waves reaching the target [43,44]. Another avenue for improving our understanding of ultrasound–tissue interactions includes computational modeling [45] as well as the use of experimental results based on tissue phantoms. For instance, previous work addressed the attenuation and dispersion effects of fatty tissue when applying ultrasound as an imaging tool [46]. Moreover, efforts have been directed toward developing mimicking phantoms of the human brain, for instance, by using a polyvinyl alcohol-based tissue-mimicking phantom with properties approaching those of human brain tissue, allowing control of backscatter and attenuation properties. It was

indicated that the ultrasonic properties of the phantom best matched the ones of the brain tissue in the frequency range of 1–3 MHz [47].

Standardization of protocols: There is currently no standard protocol for focal ultrasound neuromodulation, which makes it difficult to compare results across studies or to establish safe and effective clinical applications. In this respect, recent efforts have been directed toward collecting and summarizing protocols and parameters on the effect of ultrasound-mediated BBB in animal and clinical studies, by also considering the efficacy, safety, and their associated outcomes [48]. We also recommend the creation of a worldwide open source database that encompasses ultrasound protocols, stimulation parameters, demographic characteristics of subjects considered in studies, and basic results, all gathered through metadata descriptions that would facilitate data collection through the internet.

Side effects and tissue damage: Although focal ultrasound is a non-invasive technique, there is still a risk of inducing side effects such as pain, nausea, dizziness, or hearing loss as well as microhemorrhages or tissue damage, particularly if the ultrasound is applied at high intensity or over a long duration. To cope with this, proper experimental and theoretical characterization of the ultrasound's parameters in relation to thermal and biomechanical effects in different patient and healthy subject populations is required concerning the safety of the technique. In this direction, current FDA guidelines for adult and children cephalic ultrasound stimulation include $I_{\text{sspa}} \leq 190 \text{ W/cm}^2$, $I_{\text{spta}} \leq 94 \text{ mW/cm}^2$, and a mechanical index ≤ 1.9 . I_{sspa} denotes the intensity, spatial-peak pulse-average; I_{spta} denotes the intensity, spatial-peak temporal-average; and the mechanical index (MI) is directly proportional to the ultrasound beam's peak negative pressure and inversely proportional to the frequency of the beam [49].

Emerging applications of FUS: While focal ultrasound has shown promising results in neuromodulation for certain disorders, such as Parkinson's disease, essential tremor, and depression, its potential applications are still limited. Further research is needed, for instance, to explore its potential in the treatment of cognitive deficits. In this direction, recent studies in animal models reported a long-lasting effect (7 weeks) of FUS-mediated blood barrier opening on increasing long-term potentiation (LTP) at Schaffer collateral–CA1 synapses in the hippocampus, while ameliorating cognitive dysfunction and working memory [50]. Other application pertains to the use of ultrasound as an imaging technique for tissue recognition and visualization [51] as well as examination of age-related-changes in soft tissue [52]. Other emerging applications of ultrasound include treatment of brain tumors and neurodegenerative diseases through gene-delivery therapy [53].

Optimizing the efficacy of FUS: In order to maximize the efficacy of FUS for specific mental diseases and symptoms, more studies are needed to characterize not only the effect of stimulation intensity but also the stimulation of different brain targets as well as patient-specific side effects that may differ depending on the underlying disorder and associated comorbidities. In addition, proper characterization of the timeframe of the effects of FUS is required to determine its prospective chronic use as a future replacement of invasive neuromodulation techniques such as DBS.

Understanding the neuromodulatory mechanisms of FUS: due to its high spatial specificity and focused penetration depth, low-intensity focal ultrasound (LIFUS) has been developed as a non-invasive neuromodulation technology. In this respect, LIFUS has shown suppression effects as reflected, for instance, by a change of spectral power of EEG activity at frequencies corresponding to epileptic bursts in animal models of epilepsy, which translates to a reduction of epileptic crisis [54,55], and further as significant power changes in the intracranial EEG of epilepsy patients [56]. Likewise, LIFU has been shown to affect the excitability in the motor cortex of Parkinsonian mice [57] and facilitates an increase of dopamine release in the striatum [58]. However, proper characterization of the mechanisms that mediate suppression and excitatory effects of LIFUS are the subject of ongoing research. The following mechanisms have been suggested: (1) A neurophysiological–mechanical coupling mechanism relying on membrane conformational states (membrane displacements possibly voltage induced) and mechanosensitive ion channels (based on the transduction

of mechanical energy into neural signals). (2) A microtubule resonance mechanism, which proposes that the frequency of LIFUS may be in a resonant state with the frequencies of microtubules, which in turn would allow for vibratory effects modulating the electrical signals of membranes and plasticity. It is worth emphasizing that although LIFUS may only be able to produce small thermal changes, which are less likely to contribute to its neuromodulatory effects, thermal mechanisms still need to be considered when dealing with the definition of sonication parameters intended to achieve a specific effect [59]. Future experimental and theoretical studies need to be directed to clarifying the mechanisms involved in the neuromodulatory effects provided by LIFU and the sonication parameters required to achieve such effects with special emphasis on mental disorders. To accomplish such goals, extensive characterization of the neuroimaging biomarkers of LIFUS is highly relevant.

Advantages of FUS include: (1) FUS has the potential to reach almost inaccessible brain areas without damaging the surrounding tissue; (2) FUS is a non-invasive neuromodulation technique that is suitable for patients at any age.

Overall, focal ultrasound is a promising technology for neuromodulation, but its limitations highlight the need for further research to optimize its parameters, establish safety guidelines, and expand its potential applications.

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