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Transcranial focused ultrasound: a new tool for non-invasive neuromodulation

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ABSTRACT

Ultrasound (US) is widely known for its utility as a biomedical imaging modality. An abundance of evidence has recently accumulated showing that US is also useful for non-invasively modulating brain circuit activity. Through a series of studies discussed in this short review, it has recently become recognized that transcranial focused ultrasound can exert mechanical (non-thermal) bioeffects on neurons and cells to produce focal changes in the activity of brain circuits. In addition to highlighting scientific breakthroughs and observations that have driven the development of the field of ultrasonic neuromodulation, this study also provides a discussion of mechanisms of action underlying the ability of ultrasound to physically stimulate and modulate brain circuit activity. Exemplifying some forward-looking tools that can be developed by integrating ultrasonic neuromodulation with other advanced acoustic technologies, some innovative acoustic imaging, beam forming, and focusing techniques are briefly reviewed. Finally, the future outlook for ultrasonic neuromodulation is discussed, specifically in the context of applications employing transcranial focused ultrasound for the investigation, diagnosis, and treatment of neuropsychiatric disorders.

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Introduction

Ultrasound (US) is a sound pressure wave that has an acoustic frequency higher than the range of human hearing. Unlike light, magnetic fields, or electrical currents, US can be focused across solid structures and transmitted long distances with minimal power loss in soft biological tissues, which have bulk acoustic properties similar to water (O'Brien, 2007). Due to these characteristics, its long history of safe use, and other attributes, US represents the most widely implemented biomedical imaging modality in the world. The physics governing how sound waves interact with biological tissues, as well as advances in engineering, have recently given way to a recent wave of technological breakthroughs demonstrating US and focused ultrasound (FUS) as extremely powerful tools for basic and clinical neuroscience. These breakthroughs cover broad embodiments, ranging from clinically performing non-invasive thalamotomies for the treatment of movement disorders to the investigational, precise, focal stimulation of neural circuits (Elias et al., 2016; Naor, Krupa, & Shoham, 2016).

It has long been known that US can produce a variety of thermal and non-thermal effects on cells and tissues, depending on several factors including frequency, intensity, duty cycle, and exposure time. The acoustic frequency of the US used in a particular application defines the spatial resolution. In soft tissues, like the brain, the diffraction-limited spatial resolution of 0.5 MHz US is ~3 mm, while it is ~15 μm for 100 MHz US. However, power loss due to absorption and scattering of US by tissues becomes greater as acoustic frequency increases. For instance, the optimal gain for transcranial transmission and brain absorption of US is between 0.2–0.65 MHz (Hynynen & Clement, 2007; Hynynen & Jolesz, 1998). Higher US frequencies (for example, 2–10 MHz) are routinely used in transcranial imaging applications because only nominal acoustic intensities are required for imaging applications. Thus, the greater power loss at these higher US imaging frequencies can be tolerated. In other non-imaging applications of transcranial US requiring higher acoustic intensities to be generated in brain tissues, lower US frequencies (<0.7 MHz) should be used.

High-intensity FUS (HIFU) is often delivered to tissues as a continuous wave having an acoustic intensity exceeding 200 W/cm^2. HIFU produces thermal effects on tissues and it is extremely effective at focally and rapidly heating tissues for ablative purposes.

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Lower intensities of US (0.5–100 W/cm^2) are less likely to produce thermal effects, but can still induce prominent mechanical bioeffects on cells and tissues, especially when delivered in a pulsed mode to further minimize the probability of tissue heating (Dalecki, 2004; Legon, Rowlands, Opitz, Sato, & Tyler, 2012; Legon et al., 2014). Methods of ablating tissues, like tumors or diseased brain circuits for therapeutic purposes are typically conducted using HIFU at intensities greater than 500 W/cm^2. Frequency, intensity, and other ultrasonic parameters influencing the interactions of US with biological tissues are further discussed in the context of brain tissues below.

The idea of using US to modulate biological activity can be traced back to the early part of the 20th Century when Harvey (1929) first demonstrated that US could influence the activity of frog and turtle neuromuscular activity. Almost 30 years later, F. Fry (1958) first demonstrated that HIFU targeted to the lateral geniculate nucleus of cats can reversibly modulate the amplitudes of light-evoked responses recorded in the visual cortex. This, and other work by W.J. Fry (1956, 1958) during the 1950s, culminated with their realization and demonstrations that HIFU could be used to treat human movement disorders, including Parkinson's disease by thermally modulating or ablating diseased deep-brain circuits. Because at the time transcranial focusing of HIFU was not readily possible, Fry's methods required major craniotomies and were, therefore, not adopted by the clinical community. With numerous advances in US transducers and focusing methods, electrical engineering, radiologic imaging, and computational modelling over the past 60 years, Fry's original ideas have recently come to fruition. The focal, thermal ablation of deep-brain circuits can be safely conducted in humans using transcranial MR-guided HIFU (tcMRgHIFU) to treat movement disorders (Elias et al., 2016). This tcMRgHIFU method of focally ablating brain circuits has also demonstrated feasibility as viable neuropsychiatric intervention. Jung et al. (2015) recently showed that bilateral capsulotomies performed using tcMRgHIFU provided clinical benefits for patients with treatment-resistant obsessive-compulsive disorder without producing psychological or neurological side-effects.

With the recent milestone approval of tcMRgHIFU by the United States Food and Drug Administration for the treatment of essential tremor, it can be expected that additional interventions involving ablative neurosurgery to treat neurological and psychiatric disorders with HIFU will begin to follow. In contrast to the high-intensity applications of FUS, which rely on continuous wave US to focally heat and ablate circuits, low-intensity US was first shown to be capable of directly stimulating brain circuits through non-thermal mechanisms about a decade ago (Tyler et al., 2008). The remainder of this review focuses on discussing the background and outlook for such non-thermal applications of low-intensity FUS in the rapidly emerging field of ultrasonic neuromodulation (UNMOD; Naor et al., 2016).

Development of ultrasonic neuromodulation

Since the early observations by Harvey (1929) and F. Fry (1958), several studies have investigated the effects of US on neuronal activity by pre-sonicating neural circuits before electrically stimulating them. Observations made in these studies showed US can differentially effect the amplitudes and durations of compound action potentials and field potentials evoked by electrical stimulation (Bachtold, Rinaldi, Jones, Reines, & Price, 1998; Mihran, Barnes, & Wachtel, 1990; Rinaldi, Jones, Reines, & Price, 1991; Tsui, Wang, & Huang, 2005). In other words, these studies showed US is capable of influencing electrically evoked activity, but not that it could directly stimulate neuronal activity or trigger action potentials. Through a series of *in vitro* studies, Tyler et al. (2008) provided the first evidence that low-intensity pulsed US could directly stimulate action potentials and synaptic transmission in brain circuits. Using optogenetic probes, whole-cell current-clamp recordings, and optical imaging of ionic transients in hippocampal slice cultures, we found these effects of US on brain activity involved non-thermal mechanisms acting, in part, upon endogenous voltage-gated sodium and calcium channels (Tyler et al., 2008).

Following the initial discovery that low-intensity US could directly stimulate action potentials, synaptic transmission, and brain circuit activity *in vitro*, we began developing methods for conducting non-invasive, transcranial stimulation of brain circuits using pulsed US. Using these methods we published a series of studies demonstrating *in vivo* stimulation of the motor cortex and hippocampus (Tufail et al., 2010), as well as the rapid attenuation (within seconds) of kainic acid induced electrographic seizure activity in mice (Tufail, Yoshihiro, Pati, Tauchmann, & Tyler, 2011). Since then our basic observations have been replicated in numerous experimental models and expanded into new applications and embodiments. For example, other groups have shown the non-thermal (mechanical) bioeffects of FUS can stimulate

the activity of intact cortical, thalamic, and hippocampal circuits in rodents (King, Brown, Newsome, & Pauly, 2013; Li et al., 2016a; Mehic et al., 2014; Yang et al., 2012), rabbits (Yoo et al., 2011), and sheep (Lee, Lee, et al., 2016). Targeting frontal eye fields, transcranial focused ultrasound (tFUS) has been shown to modulate visuomotor behaviours in behaving non-human primates (Deffieux et al., 2013). In addition to these collective observations made by targeting brain circuits with US, it has been shown that FUS can focally and precisely stimulate salamander retinal circuits at temporal resolutions faster than natural photic activation by circumventing the need for photochemical reactions (Menz, Oralkan, Khuri-Yakub, & Baccus, 2013). The spatial resolution in these studies was shown to be 90 µm using 43 MHz FUS (Menz et al., 2013). Other embodiments of US for neuromodulation have recently first demonstrated the feasibility of sonogenetics to stimulate and study previously uncharacterized behaviours in *c. elegans* (Ibsen, Tong, Schutt, Esener, & Chalasani, 2015). These observations, on all accounts, have provided evidence that such applications of FUS do not produce heating or tissue damage and can be applied safely for investigational purposes. In most cases the acoustic intensities that have been used in these studies to stimulate brain circuits are below the recommended upper limits ($<$190 W/cm^2) deemed safe for imaging applications.

The accumulation of safety observations gained through some of the aforementioned studies, other published animal studies, and unpublished pre-clinical studies supported recent translational investigations of UNMOD using transcranial focused ultrasound (tFUS) in humans. Using a pulsed US waveform having a fundamental acoustic frequency of 0.5 MHz at peak intensities $<$50 W/cm^2, Legon et al. (2014) first demonstrated that tFUS can physiologically and functionally modulate sensory-driven activity of the primary sensory cortex (S1) with a lateral spatial resolution of ~5 mm and an axial resolution of ~18 mm in healthy human volunteers. More specifically, Legon et al. (2014) first demonstrated functional UNMOD in healthy humans by showing that low-intensity tFUS can focally and specifically suppress somatosensory evoked potentials, as well as alpha-, beta-, and gamma-band EEG activity in response to median nerve stimulation. These neurophysiological changes produced by tFUS targeted to the crown of the postcentral gyrus (S1) and posterior wall of the central sulcus led to a functional enhancement in somatosensory discrimination thresholds (d'), as determined through psychophysical investigations. Follow-up work from these basic observations also showed that tFUS produces an effect on the phase distribution of intrinsic beta EEG activity when targeted to human S1 (Mueller, Legon, Opitz, Sato, & Tyler, 2014). Expanded studies have more recently shown that 0.35 MHz tFUS targeted to S1 can directly stimulate and evoke somatosensory potentials and thermal/mechanical/pain sensations in the hand and fingers of human volunteers (Lee et al., 2015).

Most recently, Lee, Kim, et al. (2016) replicated their basic findings to demonstrate that tFUS targeted to the primary visual cortex can elicit visual sensations and evoke sensory potentials in humans. Although the evidence to date has demonstrated convincingly that UNMOD is safe, appropriate safety precautions should always be taken when modulating brain or neural function with FUS, since the full spectrum of safe and effective parameters are still being identified, optimized, and refined. We, thus, caution the readers to realize strict exposure limits, standard operating procedures, and technical guidelines were imposed in the human studies conducted to date, as discussed in more detail elsewhere (Lee et al., 2015; Lee, Kim, et al., 2016; Legon et al., 2014). Presently, UNMOD is being advanced by a growing number of multidisciplinary groups around the world. With these efforts, the methods and devices will advance so that UNMOD becomes a more broadly accessible tool for clinical and basic neuroscience over the next few years. Similar to these translational efforts, there are an equally growing number of laboratories investigating the mechanisms of action underlying the ability of low-intensity, pulsed FUS to modulate and stimulate brain activity. With an increased understanding of these mechanisms, we will be able to better target and regulate the activity of brain circuits, including deep-brain circuits using tFUS.

Mechanisms of action underlying ultrasonic neuromodulation

The ability of pulsed US to stimulate and modulate neuronal activity challenges many of our conventional views regarding basic brain circuit function. It has been grossly under-appreciated in neuroscience that the brain is a soft material, with physical properties influencing its electrical characteristics and behaviours (Mueller & Tyler, 2014; Tyler, 2012). The brain is a viscoelastic or non-Newtonian material that displays complex mechanical behaviours across a range of factors (Tyler, 2011, 2012). Considering the physical nature and mechanical properties of the lipids,

proteins, and molecules that make up the brain (Tyler, 2012), there are several possible ways that US could influence cells and cellular networks (brain circuits) to activate or modulate neuronal activity (Tyler, 2011).

The most straightforward hypothesis accounting for the mechanisms underlying UNMOD is that the mechanical forces exerted by US act on the fluid mechanical properties of phospholipid membranes and the spring-like properties of membrane bound ion channels to alter neuronal membrane conductance and, thereby, neuronal activity (Tyler, 2011, 2012). Data in support of this hypothesis has shown that US stimulates brain activity through a non-thermal mechanism that involves the activation of voltage-gated sodium (tetrodotoxin-sensitive) and calcium transients, as well as intact SNARE protein signalling (Tyler et al., 2008). It has been well established that several voltage-gated ion channels, including sodium and calcium channels, as well as certain ionotropic neurotransmitter receptors, exhibit mechanosensitive properties that render their gating kinetics sensitive to mechanical forces (for review see Tyler (2012)). If and how the mechanical forces exerted by US are transduced into changes in ion channel activity has been the source of some debate. Recent experimental observations and models are beginning to provide further insights into these issues.

Using an artificial bilayer preparation and electrophysiological recordings combined with laser Doppler vibrometry it has been shown that the mechanical forces exerted by US produce changes in the area and capacitance of pure lipid membranes (Prieto, Oralkan, Khuri-Yakub, & Maduke, 2013). These data demonstrate that US can produce changes in the electromechanical properties of membranes that are not supported by an internal cytoskeleton, embedded with rigid membrane bound proteins, or stabilized by a meshwork of extracellular matrix. The inclusion of these biological elements, which also have specific electrical and mechanical characteristics, will influence the deformation actions of US on cell membranes, but how needs to be investigated. Findings from a series of electrophysiological recordings recently provided evidence that the mechanical pressures exerted by FUS can significantly influence the activity of potassium and sodium mechanosensitive ion channels, including channels of the two-pore-domain potassium family (K2P) TREK-1, TREK-2, and TRAAK, as well as NaV1.5 channels (Kubanek et al., 2016). Additionally, the influence of FUS-mediated pressure changes on ion channels was used to demonstrate the first functional and practical demonstration of sonogenetics by mis-expressing the pore forming region of the transient receptor potential (TRP) type 4 channel in neurons of *c. elegans* to trigger specific movement behaviours (Ibsen et al., 2015). Collectively, these observations demonstrate that the mechanical pressures and forces exerted by US exert actions on protein ion channels and membranes in a manner that can alter neuronal activity. Undoubtedly, however, there remain numerous unresolved and complicated issues.

Adding complexity to our ability to fully comprehend the mechanisms underlying UNMOD, FUS has been shown to differentially stimulate and modulate (excite and inhibit) brain circuit and neural activity across a broad range of acoustic stimulus parameters (frequency, intensity, duty cycle, pulse repetition frequency, and pulse duration), experimental models, and network conditions. For detailed discussions of the US parameters that have been used for UNMOD, we refer the reader to several other sources (Naor et al., 2016; Plaksin, Kimmel, & Shoham, 2016; Tufail et al., 2011). Recently, a unifying framework theorizing how US influences neuronal activity provided a set of baseline models and predictions that help explain many of the experimental UNMOD observations thus far (Krasovitski, Frenkel, Shoham, & Kimmel, 2011; Plaksin et al., 2016). At the core of the biophysical theory is the concept of intramembrane cavitation, which is produced by the effects of positive and negative pressures exerted by US on cells where small membrane regions (bilayer sonophores) experience expansions and contractions (Krasovitski et al., 2011). These bilayer sonophores and membrane deformations produce capacitive displacement currents that can lead to the accumulation of charge over the course of tens of milliseconds until an action potential threshold is reached, causing pyramidal neurons to fire (Plaksin et al., 2016). This basic convention of the theory is referred to as the neuronal intramembrane cavitation excitation (NICE) hypothesis (Plaksin et al., 2016). When the NICE model was extended to different types of neurons, it was shown that low threshold spiking (LTS) inhibitory cortical interneurons and major types of thalamic neurons, which express T-type voltage-gated calcium channels, experience a boost in charge accumulation in between bursts of US, making them more likely to be stimulated than pyramidal neurons when low duty-cycle (i.e. 5%) UNMOD waveforms are used (Plaksin et al., 2016). The NICE model explains the empirical observations in the cortex by showing preferential activation of LTS neurons expressing T-type calcium channels

when low duty-cycle (i.e. 5%) UNMOD waveforms are used. The preferential activation of these inhibitory interneurons in the cortex produces a net suppression of pyramidal neuron activity, whereas higher duty-cycle UNMOD waveforms (i.e. 50%) lead to the excitation of cortical pyramidal neurons (Plaksin et al., 2016).

Whether or not the general NICE model and its subsequent refinements will be able to accurately describe ongoing results and observations remains to be determined. Further, additional structural elements like microtubules and extracellular matrix proteins, glia, other neurons, and additional channels that comprise brain circuits will be influenced by US in a manner that also contributes to the effects observed on electrical activity. Therefore, more work is needed to expand these and other models attempting to explain the mechanistic underpinnings of UNMOD. For now, the NICE model and its associated hypotheses indeed provide the most detailed theory of how US can regulate activity and, critically, it serves as a useful framework for generating testable predictions by those interested in using or studying UNMOD.

It is important to realize that the past decade has seen a flurry of activity demonstrating US can stimulate and modulate activity. However, we are just at the beginning of an effort that will require decades in order to unravel how mechanical energy influences the electrical activity of brain circuits. In many cases, the basic observations that US can stimulate brain circuit activity simply do not fit with our conventional models of electrochemical neural activity (Mueller & Tyler, 2014). Therefore, the generation of new frameworks, such as the bilayer sonophore and NICE models that elegantly consider how mechanical forces can interact with conventional models of neuronal excitability, are required (Krasovitski et al., 2011; Plaksin et al., 2016). It has taken several decades to understand how electrical currents or pulsed electromagnetic fields influence brain activity, and these tools already fit within our existing working models of neuroscience. Despite more than a century of use, we are still grappling with how electrical neuromodulation effects brain function and behaviour. Thus, one can be certain that understanding the biophysical mechanisms of UNMOD poses a particularly difficult challenge that will require research by numerous multidisciplinary groups to solve. Large cross-disciplinary efforts aimed at solving these issues should be justified, however, since they will reveal some completely novel information about how mechanical forces act to regulate brain activity and plasticity.

Innovative acoustic technologies and materials useful for advanced ultrasonic neuromodulation applications

Other technologies that implement FUS to modulate brain function are related to blood–brain barrier (BBB) disruption for targeted drug, gene, or antibody delivery (McDannold et al., 2015; Meairs, 2015; Rodriguez, Tatter, & Debinski, 2015; Wang, Olumolade, Sun, Samiotaki, & Konofagou, 2015). It is imperative to recognize that these specific applications rely on the interaction of intravenously administered microbubbles (contrast agents) that serve as exogenous cavitation bodies in a continuous wave or a high-intensity pulsed FUS field, in order to generate sufficient pressure amplitudes capable of disrupting endothelial tight junctions forming the BBB (Meairs, 2015). It is further important to recognize that UNMOD of brain circuit activity does not require the use of exogenous agents. We see no reason for the intentional production of damage to tissues to deliver a therapeutic agent due to the risk of homeostatic disruption of multiple biological systems from such an event as BBB disruption and, thus, developed the core UNMOD method such that it did not require such insults. With the advances recently made in demonstrating the basic safety and feasibility of FUS-mediated BBB disruption and drug delivery, there are numerous opportunities for designing and developing biomolecular or synthetic cages and carriers that can release their contents in response to different thermal and non-thermal effects exerted by FUS. The rapidly advancing field of FUS-mediated drug and gene delivery is one that is poised to deliver impactful results over the next few years.

Recently there have been a number of significant innovations in the fields of physical acoustics, materials engineering, and ultrasonics that can be integrated with basic UNMOD approaches to advance state of the art neuromodulation and brain mapping tools. One of the most logical manners by which these advances can have a near-term impact on brain mapping is through combining recently developed ultrasonic-based imaging methods with neuromodulation applications. For example, new methods enabling functional US imaging have been demonstrated capable of imaging brain activity and functional connectivity at high spatial resolutions in real time (Mace et al., 2011; Osmanski, Pezet, Ricobaraza, Lenkei, & Tanter, 2014). Other imaging methods have recently

combined the physical interactions of light with matter, which, under certain conditions, can generate sound waves, to develop non-invasive photoacoustic imaging methods also capable of mapping brain activity at high spatial and temporal resolutions (Yang & Wang, 2008; Yang, Xing, Zhou, Xiang, & Lao, 2007). Besides functional imaging, US can also be used in certain imaging modes as a guidance tool to conduct navigated FUS treatments (Hynynen & Jones, 2016). As UNMOD joins forces with these different US imaging modalities, the precision and power of brain mapping and neuromodulation tools employing US will greatly expand.

As mentioned previously, the diffraction limited spatial resolution of tFUS is a function of the acoustic frequency or wavelength of a particular frequency in a tissue. For tFUS used in UNMOD and HIFU applications where US has had to be transmitted across intact human skull bone, the acoustic frequencies have ranged from 0.7–0.3 MHz, yielding theoretical spatial resolutions of ~2–7 mm, respectively. Quantitative measurements of HIFU-induced thalamic lesions in humans (Elias et al., 2013, 2016) and functional localization of cortical UNMOD in humans have shown the actual spatial resolution of tFUS to be ~4–10 mm (Lee et al., 2015; Lee, Kim, et al., 2016; Legon et al., 2014). It was recently shown that, when using mice as experimental models, higher US frequencies could be transmitted across their thin skulls, with power sufficient to stimulate brain circuits at functional spatial resolution of ~0.3 mm for 5 MHz tFUS (Li et al., 2016b).

Some other methods have been developed to improve upon UNMOD spatial resolutions. A particularly interesting method generated a beat frequency of 0.5 MHz by transmitting modulated higher, carrier frequencies such as 2.0 and 1.5 MHz US across rodent skulls to stimulate cortical activity (Mehic et al., 2014). This is an interesting approach to optimizing the spatial targeting of tFUS, which demonstrated feasibility in animals, and warrants further investigation in humans to understand the limits for using mixed combinations of high carrier frequencies in UNMOD applications that require US transmission across the skull. Advances in acoustic metamaterials and acoustic hyperlenses have enabled super-resolution acoustic imaging over the past decade by producing sub-diffraction US (Li, Fok, Yin, Bartal, & Zhang, 2009; Zhang, Yin, & Fang, 2009). Whether such advances in acoustic metamaterials (Zhang et al., 2009), hyperlenses (Li et al., 2009), sound bullets (Spadoni & Daraio, 2010), or propagation invariant acoustic field needle beams (Parker & Alonso, 2016) can enable super-resolution UNMOD by tFUS is not yet known, but is most certainly worth exploring, since such methods could enable totally unprecedented spatial control of both superficial and deep-brain circuit activity in a manner that is non-invasive.

One of the most interesting technical developments in acoustics recently has been the emergence and demonstrations of acoustic holography or holographic US (Melde, Mark, Qiu, & Fischer, 2016). This also brings us to perhaps one of the most fascinating embodiments of UNMOD, which involves the delivery of holographic US through an acoustic retinal prosthetic device capable of generating multi-focal, patterned neurostimulation of retinal circuits to convey fine spatial visual information (Hertzberg, Naor, Volovick, & Shoham, 2010; Omer, Yoni, Esther, Eitan, & Shy, 2012). Similarly, generating acoustic holograms with tFUS may enable the projection of structured US into brain circuits for the multi-focal, patterned neuromodulation of brain circuit activity. Imagine a situation where one may wish to non-invasively and precisely replicate the flow of somatosensory information throughout the brain. This would require that sparsely distributed regions of both deep and superficial brain circuits (for example, regions of the thalamus, somatosensory cortex, prefrontal cortex, hippocampus, and amygdala) be synchronously and sequentially stimulated and modulated in a precisely timed manner. In other words, FUS would need to produce effects on circuits in many different brain regions at exactly or nearly the exact same time. Such an embodiment of UNMOD seems conceptually possible by projecting dynamically structured acoustic fields or ultrasonic holograms into the brain. Whether or not acoustic holograms and other advanced acoustic technologies will be practically useful for UNMOD remains to be determined. Given the relatively early stage of the UNMOD field combined with the rapid advances being made in acoustic materials/technologies, the coming years will provide fertile ground for developing and advancing ultrasonic tools for non-invasive neuromodulation and brain mapping.

Potential for the use of transcranial focused ultrasound and ultrasonic neuromodulation in psychiatric medicine

There is a critical need for new neuromodulation-based therapies and diagnostics in neuropsychiatric medicine. Numerous non-invasive and invasive

neuromodulation methods have been used in the investigational or clinical treatment of almost every psychiatric disorder imaginable. For numerous practical and technical reasons, there have been many failures at demonstrating that neuromodulation treatment approaches can provide clinically significant benefits in psychiatry. In fact, electroconvulsive shock therapy remains one of the most effective neuromodulation-based approaches to treating debilitating psychiatric disorders like treatment-resistant depression (TRD). While transcranial magnetic stimulation (TMS) has been shown to be capable of treating TRD, the outcomes can certainly be improved upon. As discussed below, deep-brain stimulation of various brain targets has been used with mixed results, depending on the disorder being treated. Therefore, in this section, we outline several aspects discussing how UNMOD and tFUS can become a particularly useful new neuromodulation tool for neuropsychiatry.

It is widely becoming accepted that, in order for neuromodulation approaches to be effective treatments of psychiatric disorders, brain regions and circuits should be targeted using functional signatures rather than anatomical landmarks alone. For example, targeting functionally localized prefrontal brain circuits using subject-specific realistic simulations of the electric field distributions generated by TMS pulses would likely improve clinical outcomes when TMS is used for treatment of TRD. This is because subject-specific gyral curvatures and tissue-specific anisotropies cause the electric field produced by TMS pulses to be uniquely shaped and distributed throughout the cortex in a manner that cannot be easily or accurately predicted without knowing specific anatomical geometries (Opitz et al., 2013). This highlights one potential advantage of US in that the mechanisms of action underlying UNMOD are less affected by gyral curvature (shape) and mechanical anisotropy than the mechanisms underlying TMS are affected by curvature and electrical anisotropy. In other words, acoustic fields are not as greatly influenced by small differences in tissue shapes as electrical fields. This particular property of tFUS may prove an advantage by minimizing variability in outcomes arising from tissue/energy interactions. Another advantage of tFUS over TMS is that it is readily compatible with EEG, by not producing artifacts or saturating amplifiers. Perhaps the most obvious and biggest advantage of UNMOD over TMS and other non-invasive electrical-based neuromodulation methods is that US can be transmitted across the skull and focused to almost any location in the human brain including deep-brain targets. This advantage immediately opens the potential for exploring deep-brain targets using tFUS as a tool for neuropsychiatric interventions and diagnostics.

Deep-brain stimulation for psychiatric disorders has proven to be a difficult therapeutic platform to advance. This difficulty was most recently displayed when two different randomized clinical trials failed to demonstrate efficacy of DBS for the treatment of TRD (Bergfeld et al., 2016; Dougherty et al., 2015). These trials targeted the ventral capsule/ventral striatum (Dougherty et al., 2015) and the ventral anterior limb of the internal capsule (Bergfeld et al., 2016) with DBS electrodes to treat TRD. Other clinical trials and studies using DBS targeted to different brain regions including the nucleus accumbens, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundles for the treatment of TRD have also been wrought with similar shortcomings or lack appropriate controls to make reliable inferences (Morishita, Fayad, Higuchi, Nestor, & Foote, 2014). One of the major problems facing DBS therapies in psychiatry is that emotion and mood tend to be more diffusely localized in the brain, making target identification/localization difficult. Therefore, it has been proposed that DBS electrodes should be targeted to brain circuits that have been localized using functional neuroimaging approaches rather than anatomically localized (Keedwell & Linden, 2013; O'Halloran, Kopell, Sprooten, Goodman, & Frangou, 2016). One issue with this approach is that there may be some amount of functional localization jitter that occurs, depending on brain state and network dynamics, at any given time that neuroimaging may be conducted. In other words, one may expect the specific location of 'sadness' in the brain is likely to vary slightly from day to day, depending on several factors. Another issue is that different individuals with the same disorder, clinical manifestation, and severity may have identical functionally identified targets, but the patients may respond to DBS of that target in totally different manners.

The issues raised above highlight the critical need for a non-invasive neuromodulation method capable of reaching deep-brain targets with a high spatial resolution. As discussed above in this review, tFUS seems to fit the bill as it can be focused to deep-brain regions and since the spatial resolution is about the same size as the spatial extent of electric fields generated by standard DBS electrodes. Further, UNMOD is compatible with MRI, and has been used to focally stimulate and modulate human BOLD responses at both 3T and 7T (Ai, Mueller, Grant, Eryaman, &

Legon, 2016; Lee, Kim, et al., 2016). The most logical application of UNMOD for psychiatry is the use of tFUS to interrogate and modulate potential DBS targets during functional neuroimaging experiments combined with measures of behavioural outcomes and neurophysiological assessments. In such an embodiment tFUS could enable exhaustive pre-surgical mapping and surgical planning studies in order to identify the best targets for treating a particular psychiatric disorder in a highly-personalized manner. Whether or not such approaches will help improve the clinical outcomes of DBS-based psychiatric therapies or not needs to be thoroughly investigated, and our group is engaging in a series of studies to begin evaluating feasibility.

Another application through which UNMOD can provide clinical utility in psychiatric medicine would be in the development of new therapies. Certainly, tFUS and UNMOD have been considered as potentially viable treatments for psychiatric disorders, but there have been no clinical or pre-clinical studies to date to support such a possibility. It does appear that the field has matured to a point over the past decade where pilot and feasibility studies aimed at treating neuropsychiatric disorders should be planned and conducted. While there is a significant amount of work still required to ensure UNMOD reaches its full potential as a modern tool for psychiatric medicine, the field has finally reached a state where there is a critical mass of laboratories, scientists, companies, and engineers fully engaged in conducting this work. Therefore, new embodiments of tFUS and UNMOD will begin to emerge in neuropsychiatry soon.

Discussion

Ultrasound represents a fresh method of achieving focal neuromodulation. In particular, tFUS has emerged as a new method of non-invasive neuromodulation over the past decade. The observations made in the field thus far have demonstrated that low-intensity US can reversibly stimulate and modulate intact brain circuits through non-thermal mechanisms of action. More work is required to unravel the optimal UNMOD parameters for modulating and stimulating brain activity. Likewise, understanding the mechanisms of action will require additional multidisciplinary investigations conducted across a variety of experimental preparations and conditions. Continuing to identify the safe parameters for UNMOD applications is also imperative. Despite the efforts that remain ahead, the foundation has been laid, and it is anticipated the UNMOD field will continue to grow. If tFUS and UNMOD continue to advance, then they will eventually represent a powerful set of next generation tools for neuroscience and medicine.

Disclosure statement

WJT is the inventor and co-inventor on issued and pending patents related to methods, systems, and devices for electrical and ultrasonic neuromodulation.

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