NON-INVASIVE FOCUSED STIMULATION OF NEURAL ACTIVITY USING THE ACOUSTOELECTRIC EFFECT

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BACKGROUND TO PROJECT:

There is a huge unmet clinical need for focused, low risk brain stimulation techniques. Invasive Deep Brain Stimulation (DBS) has had great impact, helping treatment-resistant patients with disorders such as Parkinson's disease[1] and obsessive–compulsive disorder[2], with great potential for other disorders such as depression[3] and Alzheimer's disease[4], though being a surgical procedure, it bears the risks for serious complications that limit its therapeutic impact[5].

Dr. Nir Grossman's previous work[6] in non-invasive deep brain stimulation has shown it's possible to recruit neurons deep in the brain using only current sources on the outside of the skull opening up new potential therapeutics in the field of non-invasive DBS. This technique shows great promise but is limited by its poor focality at depth.

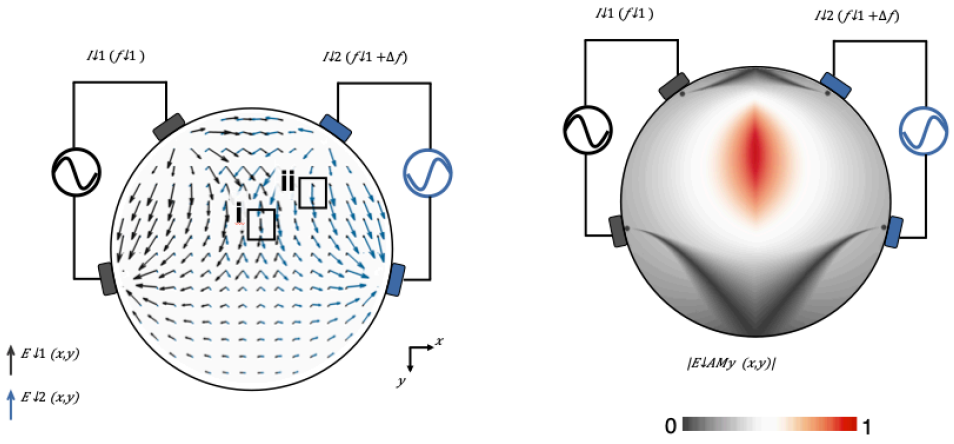

Figure 1 Color map of Temporally Interfering field (TI) stimulation, in this case f1 is 2kHz and f2 is 2.01kHz, modulating the envelope in red at a beat frequency to induce coherent neural oscillation at 10Hz.

This PhD project aims to address the poor spatial focality problem so that non-invasive DBS may rival invasive techniques in its specificity, thus decreasing the risk profile for treatment, and expanding its use into new therapeutic treatments for neurological disorders. The novelty of our approach involves using ultrasound, to tightly control the focality.

ACOUSTOELECTRIC EFFECT:

The core new innovation of our proposed stimulation approach involves using ultrasound to control the focal size of an electric field through use of the Acoustoelectric effect. Ultrasound has much smaller wavelengths than electric fields, bringing back the ability to utilize beam forming and phased arrays which have much higher focality than current-only neuromodulation methods. The best focality of ultrasound to date is using High Intensity Focused Ultrasound(HIFU) which can yield 1mm focal areas in sub-cortical regions[7].

The acoustoelectric effect modulates electric current by changing the conductivity in the region of applied acoustic pressure. The acoustic focal spot experiences periodic cycles of mechanical compression and rarefication inducing a change in local conductivity only at the focal spot. An Acoustoelectric electric field is generated at the same frequency as the ultrasound and only at the focal spot by applying a small lead current across the area. The generated electric field is proportional to the acoustic pressure at the focal point as well as the applied lead current. The theory was predicted in

1953 by Parmenter[8]. Its first experimental observation was reported in 1957 by Weinreich and White[9]. An in depth review of the materials science behind the acoustoelectric effect using solid mechanics theory was written by Xizi Song[10].

PhD Hypothesis:

I hypothesize that neural activity can be non-invasively stimulated at a precise focal point deep in the brain by utilizing the acoustoelectric effect in combination with temporally interfering fields.

Preliminary Data:

I plan to generate the first current source f1 via the acoustoelectric effect, with the second interfering current source f2 matching Nir Grossman's previous TI field stimulation work. The spatial overlap between the current path of the classic field and the acoustoelectric conductivity modulation will be where a 10Hz beat frequency occurs, stimulating neurons only at the focal point of the ultrasound. A suitable name for this technique would be acoustoelectric temporally interfering (ATI) field stimulation.

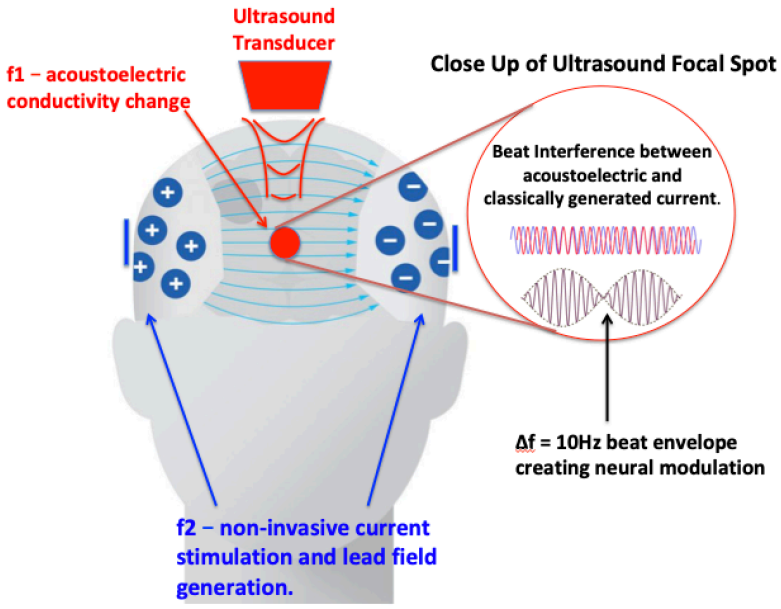

Figure 2 Proposed Experimental set up for Acoustoelectric spatially localized deep brain stimulation. The focal area of the beat frequency effect is limited to the ultrasound focal size.

To determine if this proposal is feasible, we must determine if the acoustoelectric field generated is of comparable size to the field size already known to generate TI stimulation. Nir Grossman's previous work has shown we need to generate a field of intensity E_{TI} = 0.9-3.7V/m. We can relate this electric field E to conductivity via:

$$\sigma = \frac{J_{TI}}{E}$$

Where σ is conductivity of the medium in Siemens per meter, J_{TI} is the magnitude of the current density in A/m^2 and E is the electric field in V/m. We can also obtain the change in conductivity ($\delta\sigma$) at the ultrasound focal spot from the acoustoelectric equation shown below:

$$\frac{\delta\sigma_{AE}}{\sigma} = kP$$

Where k is estimated as 4.10x10^{-8}[10] experimentally modelled by the beam width, frequency, focal area of the ultrasound transducer, the conductivity(σ) of the medium is estimated as white matter at 0.52 Siemens per meter, P is the applied pressure assuming 0.6MPa which is below the limit for proven safe clinical use imaging in humans.

In the specific case of the electric field E being in the range of neuromodulation at 1V/m, we can estimate the ratio of the acoustoelectric current density to the TI current density to give us an idea of the relative strength of the acoustoelectric effect, knowing that $\delta\sigma_{AE} = \frac{J_{AE}}{E}$ we can substitute into the acoustoelectric equation to obtain the ratio:

$$\frac{J_{AE}}{J_{TI}} = \frac{\sigma * k * P}{\sigma} = k * P = 0.0246 = 1{:}40$$

The ratio between J_{AE} and J_{TI} is 1:40. This means to obtain the same electric field used in TI stimulation using the acoustoelectric effect, we will need to either elevate the applied ultrasonic pressure, or increase the lead field to obtain an equivalent acoustoelectric current density. Since non-invasive focused ultrasound studies have recently shown that neuromodulation can be achieved at pressures at or above 0.6MPa[11] we will limit ourselves to this pressure and below, indicating that we'll need to increase the lead field by a factor of 40 to obtain an equivalent acoustoelectric field. Another advantage of limiting the ultrasound pressure is that we stay within the safe standards already used in clinical ultrasound imaging.

To generate an equivalent acoustoelectric field at the focal point we will increase the applied amplitude of the electric lead current. The safest way to obtain a larger field according to the IEC60601-1 Guidelines for biofeedback safety is to use a higher AC frequency. A company called Novocure has used fields at 200kHz applied at +50V and -50V to generate fields deep in the brain between 1-2V/cm[13]. If we divide this by our acoustoelectric conversion factor of 40 we obtain a field of 0.025-0.05V/cm or 2.5-5V/m which is sufficiently above the proven TI stimulation threshold. The Novocure device represents our upper threshold of field application yet has already successfully passed the FDA Guidelines and is currently in clinical use in humans. Thus, the acoustoelectric effect coupled with temporally interfering fields remains a strong candidate for improved focal applications of non-invasive neural stimulation within ranges that are safe for use in humans.

AIMS:

To non-invasively stimulate at a location defined by the ultrasound focal point size:

1. Characterize via computational modelling and phantom experiments, the parameter space of acoustoelectric temporal stimulation, so that improvements can be built on solid scientific grounding.
2. Develop the acoustoelectric stimulation hardware with improved focality at depth and test it with tissue phantoms, eventually tuning to mouse acoustic and electrical impedance parameters in preparation for testing in the live mouse brain.
3. Validate the performance of the acoustoelectric temporal stimulation developed in a live mouse brain, by characterizing how various regions of clinical interest are recruited by the stimulation.

PLAN OF INVESTIGATION:

Phase I: (14 months): Aim 1. Theoretical and Acoustoelectric phantom investigations.

I will systematically characterize, using finite element method (FEM) and neurophysiological and acoustic modelling, the response of different neuronal models to ATI stimulation to gain initial mechanistic understandings and guide the experimental investigation. The theoretical investigation will be performed using the Sim4Life platform (IT'IS Foundation, Zurich) and its integrated NEURON environment (Yale University). I will also systematically characterize the acoustoelectric parameters required, in a homogenous phantom model using an ultrasound transducer to generate an electric field. The focal size of the transducer will be adjusted to match the computer simulation until we can accurately predict the scale of the acoustoelectric effect in a known model. This will allow the parameters of the computer simulation model to be refined and the ATI stimulation proposal to be verified in a phantom model.

Phase II (9 months): Aim 2. Electrical hardware design and testing in tissue phantom.

I will revise and optimize the design of the existing electrical circuit for ATI stimulation to support Aim 1. I will test the revised hardware in tissue phantom. The ultrasound focal size, and ATI effect will now be optimized for testing in a live mouse using known acoustic and electric impedance data. To maintain focus on the key challenges of the project, some of the laborious design and assembly undertakes will be outsourced to industrial experts. During this period the I will be trained in immunohistochemistry techniques to facilitate the subsequent PoC experiments.

Phase III (12 months): Aim 3. in-vivo PoC validation in live mouse.

I will apply the new stimulation strategy transcranially, to clinically relevant cortical and sub-cortical brain regions, including the subthalamic nucleus (STN), of living mice. Mice will be anesthetized and head-fixed during the stimulation.
I will then use immunohistochemistry techniques, such as c-fos labelling and CLARITY, to globally map the focality of the resulting TI stimulation. In addition, I will characterize cell survival and health, using whole-brain staining and clearing. All analyses will involve comparisons against positive controls (TI stimulation only) and negative controls (no stimulation).
Phase IV (6 months): Write-up of thesis results.

Impact:
If we can control the spatial specificity with ultrasound using the acoustoelectric model detailed above in an animal model, we will have demonstrated a new method to non-invasively control the spatial specificity of deep brain stimulation. We anticipate that it might rapidly be deployable into human clinical trials, as both AC fields and Ultrasound have well-understood safety guidelines. The implications of being able to control the spatial focus of non-invasive DBS will enable many new therapeutics that can more safely be deployed in patients, as well as opening new lower-risk areas for exploratory DBS research.

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