ISTU On-Air Webinar Series: October 22, 2020 Q & A

Wynn Legon, Ph.D. presenting "Human Applications of Low-Intensity Focused Ultrasound in Neuromodulation"

#	Question	Answer(s)
1	What was the F# of the 500-kHz transducer?	1.13
2	What is Ispta and Isp in tissue?	Roughly 10 W Isppa and 3W Ispta
3	Are there any specific challenges with ultrasound neuromodulation for clinical studies in humans?	No more than would be expected collecting healthy subjects.
4	Did you mention that FUS produced both stimulatory and inhibitory responses? If so, were those in the same areas of the brain at the same FUS frequency? How did that translate to the patient's behavior?	Our human studies so far only find inhibition. However, there are examples of inhibition and excitation in the literature in small and large animal. Kim et al. 2014; King et al. 2013; Yoon et al. 2019
5	The well known obstacle is passing through skull in which loss a huge amount of energy. Based on your experience, which frequency would be optimum and how percentage of intensity is able pass through skull? and how intensity you expect on focal point?	Frequencies between 200 - 700 kHz are optimal for acceptable loss through the skull (see White et al. 2006). 500 kHz is the best as it also limits standing waves as compared to lower frequencies for example. The loss through the skull is ~ 14-22 dB/cm/MHz and for our purposes depending on the individual skull anywhere from 3x - 8x. We look to achieve in vivo brain intensities around 6W Isppa.
6	Any estimation of the focal intensity and/or pressure applied in the deep brain stimulation study?	The thalamic study we estimate in vivo intensity to be 6W Isppa with pressures in the 120 kPa range.
7	Do you think it might be possible to change the phase of the ultrasound temporally (e.g. in each PRF pulse) so that the propagated sound energy would create nulls and peaks (interference patterns) spatially in a controlled manner, and achieve an even better focusing and beam forming?	That may be possible though we currently do not have a method to image this to phase with a single element.
8	In the FUS + TMS studies, what made the primary motor cortex behavior to increase at 20000 msec and then decrease after delivering FUS? Did you continue time tracking after 10 sec to see if the behavior continued to decrease?	We did not see any statistically significant increases in activity. At 2000 msec there looks to be a slight increase but this is not above baseline levels statistically. We are currently conducting experiments tracking the effect out to longer durations up to 10 minutes. The general finding is that FUS needs to be applied for longer durations to achieve longer effects.
9	Follow up question: perhaps a 3D printed model with the same acoustic properties may be used, in a closed-loop model for measuring the response inside the model and modifying the stimuli in the actual skull for precise targeting?	Yes, one of the current issues in the field of single element transducers for human neuromodulation is having real-time monitoring of the in vivo pressure and confirming targeting. We do not have a solution for this currently.
10	What are the challenges in terms of imaging ultrasound neuromodulation in humans? How do you see it evolving in the future?	Human brain neuromodulation imaging for conformation of pressure and targeting is a challenge for the field. Multi-element arrays could be used but these are not practical. Real-time acoustic modelling plus holographic lenses is the future of single element ultrasound.
11	How much we know about each membrane channel protein in brain response to acoustics?	I do not study this field so I cannot give you a definitive answer. Recent studies have demonstrated that traditionally voltage sensitive channels are also sensitive to mechanical forces. There are also
12	Based on your results on the effects of US on the motor cortex, what do you think US future might be in treating diseases such as epilepsy? In your studies, have you learned more about the differences between the mechanical and the thermal effects of US when applied to the human brain?	There is evidence that FUS can be used to inhibit seizure in animal models (Tufail 2011; Yang 2011; Min 2011; Hakimova 2015; Chen 2020 etc.) including a trial now in humans https://doi.org/10.1101/2020.04.10.20060855 so this may be a promising method for treatment. We try to avoid thermal rise in our experiments so that the mechanism of effect is restricted to mechanical means though there may be some heating in the range of 0.2 C. Certainly, thermally mediated effects are possible but this is not what we try to do.
13	It seems that FUS induce inhibitory effect on EP only. Or it can produce stimulatory effect also? What do you think is the keys to tune the parameters and predict the response after FUS stim?	Yes, we find FUS to inhibit the EP. Other groups propose that they can use FUS to induce an EP (Lee et al. 2015) but we have not shown this. To develop predictable FUS in humans rigorous parameters studies need to be conducted and validated. The parameter work in small and large animal is an excellent starting point but needs to be translated to humans for reproducibility that has not been done yet.
14	Can you summarize the optimal exciatatory and suppressive sonication parameter that you found out so far in humans?	We have not found any parameters to be good for excitation yet. Our most successful inhibitory parameters are: PRF 1kHz; duration 500 msec; DC 36%. 5 minutes of this protocol with an inter-stimulus interval of 3 seconds. See the parameter slide in the talk for some clarification if needed.
15	Do you have any concern about TMS broad activation activating unrelated neural areas as opposed to focused ultrasound?	TMS will certainly activate surrounding finger representations in M1. Does this then effect how FUS operates? If there are recurrent connections between the sub-areas of M1 onto the area we are targeting then this is possible.
16	If the spation reolution of ultrasound would affact the outcome of neuromodulation?	Yes, this is possible. A broader field similar to TMS or tDCS could be used if desired though this has not been tested. Scanning ultrasound where the transducer is run across the head is now being investigated (Hatch et al. 2016, Braitstein 2020)
17	What is the DFA-approved max. intesity range, if any, for these type of applications (transcranial brain stimulation)?	There are currently no explicit FDA energy levels for human neuromodulation. The field follows the thresholds for diagnostics as 190W/cm^2 Isppa and 0.72 W/cm^2 Ispta.
18	Seems from one of your last slides that duty cycle does switch from excitatory to inhibitory effects (30% vs. 70%) for joint TMS-FUS. Can you comment?	Yes, this is preliminary data investigating parameters and early results look to suggest that DC of 50 and 70% may be excitatory. We are currently collecting more data to confirm this.
19	Did you observed morphology deformations during ultrasound excitation ?	No
20	Did you shave the subject's head for placing the transducer?	This is done for the clinical studies but not for the healthy participants but should be.
21	What was the intensity at the focal point?	~ 6 W/cm^2 Isppa
22	Is LIFU neuromodulation still in the research phase or is it already used for clinical human treatment? Is the lack of knowledge on the relationship between parameters and effects an issue?	Yes, it is not 100% clear what certain parameter combinations do or what is most efficacious for the desired effect. There are many excellent parameter studies in animals that are a good starting point to understand what could be useful in humans but we do not know yet how well these translate.
23	Considering other modalities os NIBS, such as TMS and/or tES, it is necessary several sessions to reach a result. What about tFUS? Just one is enough to modulate the brain area?	We do not know this yet but we assume that FUS is similar to other NIBS and that several sessions would impart a longer lasting effect. We have not conducted these studies yet and I am not aware for any labs that have tested this in humans. I believe there are several small animal studies that have administered FUS over multiple days. For example, Zhou et al. 2019 delivered 7 days of FUS for the treatment of Parkinsons. https://doi.org/10.24132/2019/1748489