Neuromodulation Workshop

March 3-4, 2014, Charlottesville, VA

Introduction

Neuromodulation – reversible stimulation or suppression of neural activity – can be induced by a range of energies and technologies, including electrical (e.g. deep brain stimulation), chemical, thermal, cryogenic, mechanical and magnetic (e.g. transcranial magnetic stimulation). Neuromodulation could potentially enable a range of therapeutic benefits including: targeting of regions in the brain for ablative procedures; suppressing epileptic seizures or symptoms of psychiatric disorders; reversible nerve blocks to treat pain; and brain mapping. Although less widely used, focused ultrasound can also induce neuromodulation, depending on the parameters of the energy applied to neural tissue. This is achieved through either pulsing of focused ultrasound using various sequences, or by subtly raising the temperature of the tissue.

Studies have shown that the mechanical effects of pulsed focused ultrasound can reversibly decrease the functionality of targeted neurons. This allows for the temporary blocking of neural signals from targeted locations within the brain or spinal/peripheral nerves. Such techniques hold promise in the treatment of epilepsy or chronic pain.

Conversely, pulsed focused ultrasound can also be used to stimulate targeted neurons. Ultrasound energy with specific pulse parameters can trigger the activation and propagation of neural signals that could excite muscle contractions or stimulate specific areas of the brain; thus, focused ultrasound may potentially be used for precise brain mapping, to enable a better understanding of how the brain works by identifying how individual cells and complex neural circuits interact (also a primary focus of the President's recent BRAIN Initiative).

Finally, the thermal effects of focused ultrasound can also induce neuromodulation. When brain tissue is raised to a slightly elevated temperature—lower than that required for thermal ablation—neural signals may be reversibly suppressed in that area. This technique can be used to confirm the precise target in the brain during neurofunctional treatments (e.g. essential tremor), before delivering the therapeutic dose of ultrasound energy to permanently ablate the targeted neural tissue.

The field of neuromodulation using focused ultrasound is growing, with many academic sites directing their research towards a wide range of clinical applications. The Focused Ultrasound Foundation has recognized the promise of this field and the need for collaboration to most effectively drive the field towards clinical utility. To this end, the Foundation convened a workshop on March 2-3, 2014 which included participation from several luminary investigators within the field. This document presents the goals and outputs of the workshop, including a detailed roadmap to achieve the first clinical use of focused ultrasound neuromodulation for targeting prior to thermal ablation.

Goals

- Collect an inventory of current state of the field.
- Identify important clinical indications for focused ultrasound neuromodulation.
- Develop a roadmap which will achieve the first clinical use of focused ultrasound neuromodulation.

Participants

- Luminaries in transcranial focused ultrasound, ultrasound physics, MR imaging, medical device manufacture, neurology, and neurosurgery
- Academia, industry, FDA and FUSF represented.

Presenters

Jeff Elias (University of Virginia)

Jeff Elias provided a clinical background for the workshop by describing some of the historical uses of neuromodulation and by suggesting some near term clinical applications. He described neuromodulation as the reversible inhibition or excitation of neurons or neuronal circuits. Historically this has been achieved by a variety of means, including electrical, chemical, thermal, cryogenic, mechanical and magnetic [Dallapiazza 2014].

Neuromodulation (NM) with focused ultrasound has a number of potentially important indications both acute and chronic, including pre-ablation brain mapping, diagnostic mapping of deep circuits, acute seizure interruption and chronic treatment for psychiatric disorders.

Stereotactic ablation targets of immediate interest are the ventralis intermedius nucleus of the thalamus (Vim) for tremor, the globus pallidus for dystonia/dyskinesia associated with Parkinson's disease and the subthalamic nucleus for Parkinson's disease tremor and dyskinesia. These nuclei are not defined on MR and require clinical guidance. These targets are surrounded by regions that can be tested with NM to verify the target location prior to ablation. Heating to approximately 50°C with FUS produces NM and is used in the context of ongoing movement disorder trials for clinical targeting guidance. However, it was discussed that heating to this temperature approaches the

threshold for damage. Therefore the relatively low energy , non-thermal regime of FUS NM is highly interesting as a safer, more repeatable physiological target verification tool. Even with improvements in imaging, it will likely always be the case that clinical guidance via NM will be required for targets within the thalamus. Anatomical mapping is insufficient and functional mapping will be required for a number of indications, particularly those without immediate therapeutic effects. NM could play an important role clinically and scientifically as a functional brain mapping tool.

Yoav Levy (Insightec)

Yoav Levy discussed the current Insightec technology and future plans. Insightec's immediate priorities beyond neurofunctional lesioning are drug delivery and neuromodulation. Insightec is part of the Brain Monitoring and Stimulation Toolkit (BMST) consortium working to integrate brain neuromodulation and monitoring platforms. Consortium members include commercial, academic and clinical partners. These include Brainsway, ElMindA, InSightec, Ornim, Alpha Omega, Technion, Ben Gurion, and Bar Ilan. Insightec has academic partnerhship for neuromodulation with Technion and Sheba.

Levy stated that the state of the field is immature, but with a lot of activity. Currently, clinical requirements and the technical specification of sonication parameters are not well defined. The most important early application of FUS neuromodulation is the verification of neurofunctional lesion targeting, beginning with movement disorders (Essential tremor and Parkinson's disease) and eventually addressing other indications including neuropathic pain, obsessive compulsive disorder, depression and epilepsy. Interesting targets are deep brain targets for now.

The current goal is to determine parameters for safe neuromodulation. Small animal models have and are being used to investigate FUS NM, with transition to large animal models in progress. The group discussed anesthesia and monitoring methods for conducting preclinical investigation of NM. Anesthesia remains a challenge for animal studies. Better monitoring methods need to be developed. The group discussed the use of EEG and fMRI in addition to evoked potential monitoring.

Mark Schafer (Sonic Tech) – Dosimetry and Standards

Mark Schafer introduced Sonic Tech, which works with companies to bring US products to the market. They do transducer design, work with the FDA and participate in standards work. He discussed the issues involved with dosimetry and standards with FUS NM. There are several challenges including the wide range of US frequency and exposure levels and the lack of a unified

standard for characterization and reporting. It is important to understand how standards are developed and who approves them.

Characterization and reporting are critical. Mechanisms need to be identified so that experiments can be controlled and replicated. Mechanical Index (MI) is one of the most misapplied parameters and was intended for characterizing diagnostic US pulses only. "Derating" to determine safe exposure is complicated. The derating scheme is based on an average of tissues and does not provide actual pressures and intensities:

$$Intensity_{derated} = Intensity_{water} * exp^{-F*d*0.669}$$

where ***F*** is frequency and ***d*** is depth in tissue.

FDA limits are regulatory limits, not safety limits. Standards are developed to promote commerce and should always follow technology development. Conformance to a standard is easier than conducting a clinical trial. The FDA and EU work with the IEC standards body. IEC TC87 in ultrasonics covers a range of US applications. Working group 7 specializes in US surgical and therapeutic equipment and meets annually. High Intensity Therapeutic Ultrasound (HITU) standards were published in July 2013.

The concept of dose is not yet defined for FUS NM. We don't yet understand which mechanical factor is important. Dose also needs to be defined for cavitation.

Jeff Anderson (University of Utah) – Neurodiagnostics

Jeff Anderson discussed work toward the neurodiagnostic uses of NM. His group is using a preterm lamb model to investigate whether it might be possible to develop functional biomarkers ventilator induced brain damage. In order to determine functional connectivity it would be valuable to be able to stimulate at a point in the brain while measuring function everywhere. This would go beyond the concept of a connectome by describing a causal network. In a mouse model it was possible to cause activation and see the propagation of activity. This has not yet been successfully demonstrated in the lamb model. BOLD effect was seen throughout the brain which was correlated with the FUS

pulsing scheme, but without evidence of activated functional networks. Might be attributed to MR artifact due to water motion, but additional experiments are needed. Anesthesia is also a potential issue contributing to the lack of definitive NM results. The successful combination of targeted FUS NM with fMRI could have powerful scientific and clinical applications.

Jean-Francois Aubry (Institut Langevin, Paris)– Neuomodulation in Rats

A recent rat stimulation study [Medical physics 40:082902, 2013] was presented and discussed. A 250 kHz, 64 mm diameter transducer operating at 320 kHz was used. The animals were lightly anesthetized with Ketamine (66 mg/kg) and Xylazine (13 mg/kg). The anesthesia allowed only a limited working time and results proved variable from one experiment to the next on the same animal. It was possible to stimulate discrete gross motor movements (eyes, whiskers, etc.) but the effects were unpredictable. Heterodyne interferometer measurements of the pressure field inside the skull showed a complex pattern. It was mentioned that Pierre Mourad's group (University of Washington) recently published good results at 2 MHz.

Pierre Pouget (ICM, Paris) – Neuromodulation in awake behaving monkeys

Pierre Pouget summarized a recent paper on NM in alert macaque monkeys. The monkeys were trained to look away from a moving visual target (antisaccade) using juice reinforcement. The FUS NM (320 kHz, 0.6 MPa, 100 ms) was targeted to the frontal eye field (FEF). The latency of eye movement was measured with and without ultrasound stimulation. Latency was reduced with ultrasound, similar to previous optogenetics results and superior to a transcranial magnetic stimulation (TMS) study by the same group. Ipsilateral sonication reduced latency and contralateral sonication showed no effect. The group is currently investigating the superior colliculus as a target.

Alexander Korb (UCLA) – Preparing for Low Intensity Focused Ultrasound Pulsation (LIFUP) first in human trials

Alexander Korb described work ongoing at UCLA to develop a non-invasive clinical neuromodulation system for reaching deep cortical structures. Intended therapeutic indications for the device include epilepsy, depression and anxiety. There may also be brain mapping applications for presurgical planning and scientific inquiry. The device incorporates a single element 650 kHz ultrasound transducer. Sonication parameters for stimulation and excitation build on the work of Seung-Schik Yoo (Brigham and Women's Hospital). The effects of transmission through bone were examined finding the expected strong attenuation. However, the focus appeared to be maintained, but with a 2-3 mm shift in focus location. Bone heating is not significant at expected exposure levels. Experience with transcranial magnetic stimulation (TMS) shows NM effects only last for milliseconds beyond the exposure, but it is hoped that chronic application of low intensity, pulsed focused ultrasound may produce longer lasting effects. UCLA is nearing FDA IDE approval for an initial clinical study on epilepsy patients.

Kim Butts-Pauly (Stanford) – Neuromodulation group

Kim Butts-Pauly reviewed a number of related research projects within her group at Stanford. They are investigating retinal stimulation. A FUS NM study in a mouse model showed specificity of motor stimulation via FUS NM between neck and tail muscles, but not between left and right sides of the

animal. Acoustic radiation force imaging (ARFI) is being developed to maximize signal to noise ratio (SNR). The group discussed application to non-thermal localization of the focal spot for NM applications. The clinical scenario for lesion making would be to verify the prescribed focal spot location with ARFI, followed by neurophysiological verification of the target with NM, concluding with thermal ablation to create a permanent lesion. A study was suggested to investigate potential long-term effects of FUS NM exposure. Ultra short TE (UTE) MRI could be used to take skull bone in to account. ARFI capability will be available soon on the GE/Insightec platform.

Matthew Meyers (FDA) – Neuromodulation and traumatic brain injury

Mattew Meyers discussed the FDA's goals for internal research: understanding mechanisms and parameters for different bioeffects of ultrasound in order to give insight for the review of devices related to ultrasound ablation, neuromodulation and traumatic brain injury (TBI).

Specific work toward understanding non-thermal, non-cavitational effects of pressure waves on blast-induced TBI was discussed. A HIFU pulse train can be modulated to produce an envelope similar to the shape of blast overpressure. T radiation force profile is also similar to blast overpressure exposure. In a mouse model mild TBI (mTBI) produced BBB disruption, inflammation, immune responses and behavioral disturbance, including disrupted sleep patterns. The HIFU model looks promising as a simulation of blast-induced TBI. His group is currently studying the use of electrophysiological sensors for monitoring effects on mice. These include miniature implanted electrode arrays. Going forward, monitoring devices will be used in concert with FUS to study the effects of mTBI on mice.

An earthworm model for NM was presented. Suppression of action potential seemed to correlate with cumulative radiation force impulse across multiple parameters and the number of pulses.

Eitan Kimmel (Technion) – Cell membrane dynamics

Eitan Kimmel presented 20 year old data from fish skin studies where spaces in cell membranes were observed after US exposure. Other in vitro studies observed similar effects. These bilayer spaces or sonophores could not be explained with radiation force, cavitation or streaming. Eitan proposed that the pressure difference during US exposure between membrane components can result in a variety of effects related to non-thermal mechanisms. A model of neuronal bilayer sonophores (NBLS) has been developed which suggests that US stimulates neurons by changing membrane capacitance.

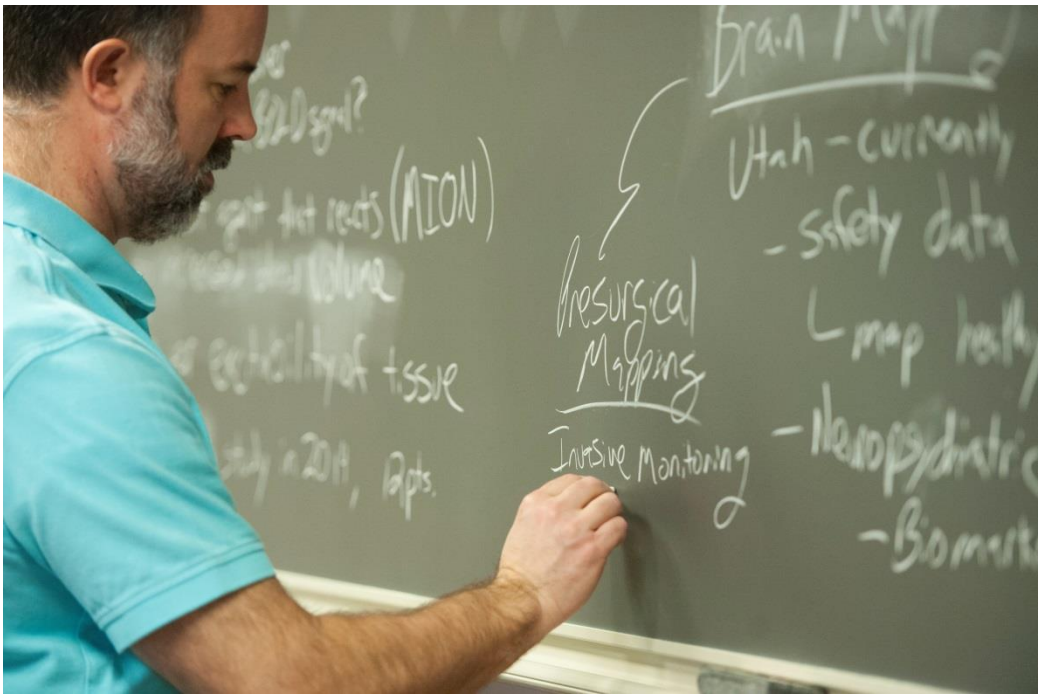
Shy Shoham (Technion) – neuronal bilayer sonophore model

Shy Shoham continued the previous presentation with additional discussion of the NBLS model (recently published in Phys Rev. X) and some applications. The NBLS model appeared to predict results presented by King et al. The model suggests that with specific parameters, one can stimulate inhibitory neurons . The Technion group has built an interface between Matlab and an NBLS simulation they have created.

The group is working to develop methods to excite continuous patterns with an US phased array. An application of this project is US image generation via retinal stimulation.

Zion Zibly (Sheba) – Clinical translation

Zion Zibly discussed clinical projects being planned at Sheba Medical Center. They are developing a large animal model for showing feasibility and safety of MR guided HIFU neuromodulation. The first indication will be the treatment of pain in end-stage cancer, with the ventral caudal (Vc) nucleus as the target. Other indications to follow include dystonia, OCD, epilepsy and Alzheimers disease.



Outcomes

- Neurofunctional ablation target verification was selected as the first application for development.
    - Initial indication is thalamotomy for Essential and Parkinsonian tremor, or neuropathic pain.
    - Roadmap created with timeline, milestones and responsibilities.
    - A goal was set to demonstrate neuromodulation successfully during a patient treatment before the end of 2014.

- An inventory of potential high impact clinical indications was created.
- A preliminary list of current research sites and investigators was drafted.

Next Steps

- Create and publish a whitepaper detailing the workshop (draft and final).
- Collect and publish an inventory of neuromodulation sonication parameters.
- Follow up on first preclinical roadmap steps in two animal models (BWH: monkey, UVa: pig)
- Define and announce specific details on a clinical neuromodulation prize, given to the first investigator to illicit transient sensory symptoms or tremor suppression using focused ultrasound neuromodulation during a patient treatment (ET, PD or Pain).
- Establish a neuromodulation investigator group email list.
- Schedule breakfast at the FUS symposium.

Neuromodulation Parameter Inventory

Authors	Model	Neural Response	Target	Intensity	frequency	total duration	PRF	pulse duration	duty cycle	
Yoo et al. 2011	rabbit	muscle contraction	motor cortex	12.6 W/cm^2 SPPA 6.3 W/cm^2 SPTA	690kHz	>=1 s	10 Hz	50ms	50%	
		fMRI activation	motor cortex	3.3 W/cm^2 SPPA 1.6 W/cm^2 SPTA	690kHz	>=1 s	10 Hz	50ms	50%	
		p30 VEP component	visual cortex	3.3 and 6.4 W/cm^2 SPPA	690kHz	>=7-8 s	100 Hz	0.5 ms	5%	
		fMRI suppression	visual cortex	3.3 W/cm^2 SPPA 0.160 W/cm^2 SPTA	690kHz	>=7-8 s	100 Hz	0.5 ms	5%	
Yoo et al. 2011	rat	waking from anesthesia	thalamus	6 W/cm^2 SPPA	650kHz	20 mn	100 Hz	0.5 ms	5%	
Min et al. 2011	rat	suppressing seizures	thalamus	2.6 W/cm^2 SPPA 0.130 W/cm^2 SPTA	690kHz	3 min	100 Hz	0.5 ms	5%	
Min et al. 2011	rat	increased dopamine increased serotonin decreased GABA (unpub)	thalamus	3.5 W/cm^2 SPPA 0.175 W/cm^2 SPTA	650kHz	20 min	100 Hz	0.5 ms	5%	
Kim et al. 2012	rat	eye abduction	abducens nerve	8.6 W/cm^2 SPPA 4.6 W/cm^2 SPTA	350kHz	200 ms	1.5 kHz	0.36 ms	54%	10 sets @ 1 Hz
King et al. 2013	mouse	muscle contractions	motor cortex	0.01-10 W/cm^2 SPTP	250-600kHz	80 ms	CW		1	Figure 10
		parameters		0.1-16.8 W/cm^2 SPTP	500kHz	80 ms	CW		1	Figure 5
				4.2 W/cm^2 SPTP	500kHz	20-320 ms	CW		1	Figure 7
				0.1-100	500kHz	80 ms	1.5 kHz	0.2 ms	30%	FIgure 11

				W/cm^2 SPPA 0.1-30 W/cm^2 SPTA						
				4.2, 16.8, 29.8 W/cm^2 SPPA	500kHz	40 ms - 10.9 s 120 pulses	11-3000 Hz	0.2 ms	0.22-60%	Figure 12
Menz et al. 2013	salamander	retinal stimulation	retina	10-30 W/cm^2 SPTA	43MHz	1-5 min	0.5 Hz	500 ms	0.5	
King et al.	mouse	muscle contractions	motor cortex		500kHz	80 ms	CW		1	
		localization								
Deffieux et al. 2013	monkey	antisaccade latency	FEF	4 W/cm^2 SPPA	320kHz	100 ms	CW		1	
Legon et al. 2014	human	refined 2 point discrimination	somatosensory cortex	5.90 W/cm^2 SPPA	500kHz	500 ms	1 kHz	360 us	0.36	
Fry et al., 1958	cat	partial VEP suppression	lateral geniculate nuclueus	not shown	not shown	20-120 sec	CW			Figure 1
Ballantine et al.1960	cat	functional respond of eye pupil	Edinger-Wesrpal nucleus	1700 W/cm^2 peak intensity	2.7 MHz	1-13 pulses	3 s pulse period	0.14 sec		Figures 7-11
Ballantine et al.1960	cat	reversible enhancement	spinal cord reflex	350 W/cm^2 peak intensity	2.7 MHz	3 pulses	1 s pulse period	0.3 s		Figure 13
"		following by depression				17-185 pulses	3 s pulse period	0.3 s		
Younan et al. 2013	rat	muscle contractions	motor cortex	7.5 W/cm^2 => 17.5 W/cm^2 SPPA corrected w/ standing waves	320kHz	250 ms	2 KHz	0.23 ms	50%	
Deffieux et al. 2013	monkey	antisaccade latency	Frontal Eye Field	4 W/cm^2 SPPA	320kHz	100 ms	CW		1	
Legon et al. 2014	human	refined 2 point discrimination	somatosensory cortex	5.90 W/cm^2 SPPA	500kHz	500 ms	1 kHz	360 µs	0.36	

Vykhodtseva et al.,	cat	VEP suppression	optic tract/lateral gen.	7- 63 W/cm^2	0.975 MHz	10-60 sec	0.5-50 Hz	5-50 msec		Figure 1
1984			nucleus junction							
		partial VEP suppression	"	7 W/cm^2	0.975 MHz	20 s	10 Hz	30 ms		
		complete VEP suppression	"	25 W/cm^2	"	40 s	10 Hz	50 ms		
		temporal amplitude decrease	"	7 W/cm^2	"	60 s	10 Hz	30 ms		
		complete VEP suppression	"	7 W/cm^2	"	60 s	20 Hz	30 ms		
		irreversible VEP suppression	"	63 W/cm2	"	60 s	50 Hz	10 ms		
Vykhodtseva&	rat	direct current potential (DC) (DC)changes	cerebral cortex	2.75 MPa	4.6 MHz	25 s		CW		
Koroleva1986, 2006		changes and spreading	hippocampus	1.59 MPa	"	10-40 s	5 Hz	100 ms		
		depression (SD) induction	thalamus	1.59 MPa	"	"	5-10 Hz	10 -100 ms		
			nucleus caudatus	2.24 MPa	"	5 s +5 s +5 s	5 Hz	100 ms		
Vykhodtseva	rat	suppression of	cerebral cortex	1.8 W total acoustical power	4.89 MHz	20- 30 s	2 Hz	40 - 200 ms		
et al., 2007		electrocorticogram (ECoG)								

Indications

Functional target verification for lesioning (ET, PD, Pain)
Brain Mapping

- Neurodiagnostic biomarkers
    - Autism
    - Schizophrenia
    - Bipolar disorder
    - ADHD

Presurgical Mapping

- Replacement for invasive monitoring in epilepsy
- Eloquent area mapping for tumor or AVM resection

Epilepsy Therapy

- Lower excitability of tissue

Psychiatric Indications

- OCD
- Depression
- Obesity

Effectiveness of pharmacotherapy
Wada test replacement

- Memory localization

Cancer pain treatment

- Thalamic neuromodulaiton

Stroke

- Neuro rehab, plasticity stimulation

Multimodal stimulation (TMS + FUS neuromodulation)
Retinal Prosthetic

Research Sites

Bolded sites have access to clinical transcranial focused ultrasound systems

Sheba Medical Center
Technion – Iraeli Institute of Technology
Brigham and Women's Hospital
ICM/Institut Langevin, Paris
Stanford University
Sunnybrook Health Sciences Center - University of Toronto
Saint Mary's Hospital, Korea
University of Virginia
Zurich University Children's Hosptal
University of California, Los Angeles
Virginia Tech Carilion Research Institute
University of Washington
University of Arizona
University of Utah
Chang-Gung University, Taiwan
FDA

Attendees

Name	Organization
Nathan McDannold	Brigham and Women's Hospital
Natalia Vykhodtseva	Brigham and Women's Hospital
Seung-Schik Yoo	Brigham and Women's Hospital
Jean-Francois Aubry	Institut Langevin, Paris
Matthew Myers	FDA-OSEL
Jessica Foley	Focused Ultrasound Foundation
Arik Hananel	Focused Ultrasound Foundation
Neal Kassell	Focused Ultrasound Foundation
Pierre Pouget	ICM, Paris
Eyal Zadicario	InSightec
Yoav Levy	InSightec
Jeff Elias	University of Virginia
Rob Dallapiazza	University of Virginia
John Snell	Focused Ultrasound Foundation
Dana Berneman	Sheba Medical Center
Zion Zibly	Sheba Medical Center
Dana Berneman	Sheba Medical Center
Zion Zibly	Sheba Medical Center
Mark Schafer	Sonic Tech
Kim Butts-Pauly	Stanford
Patrick Ye	Stanford
Eitan Kimmel	Technion
Shy Shoham	Technion
Alex Korb	UCLA
Jeff Anderson	University of Utah
Dennis Parker	University of Utah

FUS Neuromodulation Neurophysiologic Target Verification Roadmap

1. Inventory previous sonication parameters

Survey of the literature (inhibiting, thalamic NM parameters):

- Carrier frequency
- Duty cycle
- Pulse duration
- PRF
- Exposure duration
- Intensity(sppa)
- Peak negative pressure (may not be available in all papers)

[JF group, Seung-Schick, Alex Korb (2011 review), Jamie Tyler review]

Start with Natalia's optimal parameters from previous cat studies

2. Modify device to enable parameters (Insightec)

3. Preclinical Safety/Efficacy Studies

Models

- UVa: somatosensory/visual evoked potentials in pig
- BWM: Nathan's monkey model VEP

Preclinical safety data

a. Imaging and histology from pigs (monkey if available).
b. Preclinical efficacy for thalamic NM

Fast track pathway: Natalia's best parameters (cat) and Nathan/Natalia monkey VEP model (efficacy/safety with functional testing and imaging) [needs to be done no later than April since device is being moved for clinical work]

Parallel pathway: Jeff/Rob pig model (efficacy/safety histology) [can be completed April/May timeframe]

4. Regulatory pathway decision

a. Amendment of an existing protocol
   PD tremor crossover patients

5. Clinical protocol & PI responsibility

- (Jeff/Rob) – PD study amendment (use in a crossover patient)?
- Chang?
- Rambam?

6. Regulatory approval (Insightec)

Roadmap Goal

12/31/14 Milestone: Illicit transient sensory phenomenon in thalamus in a patient (or tremor suppression) [or October 12, 2014 for bigger prize]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