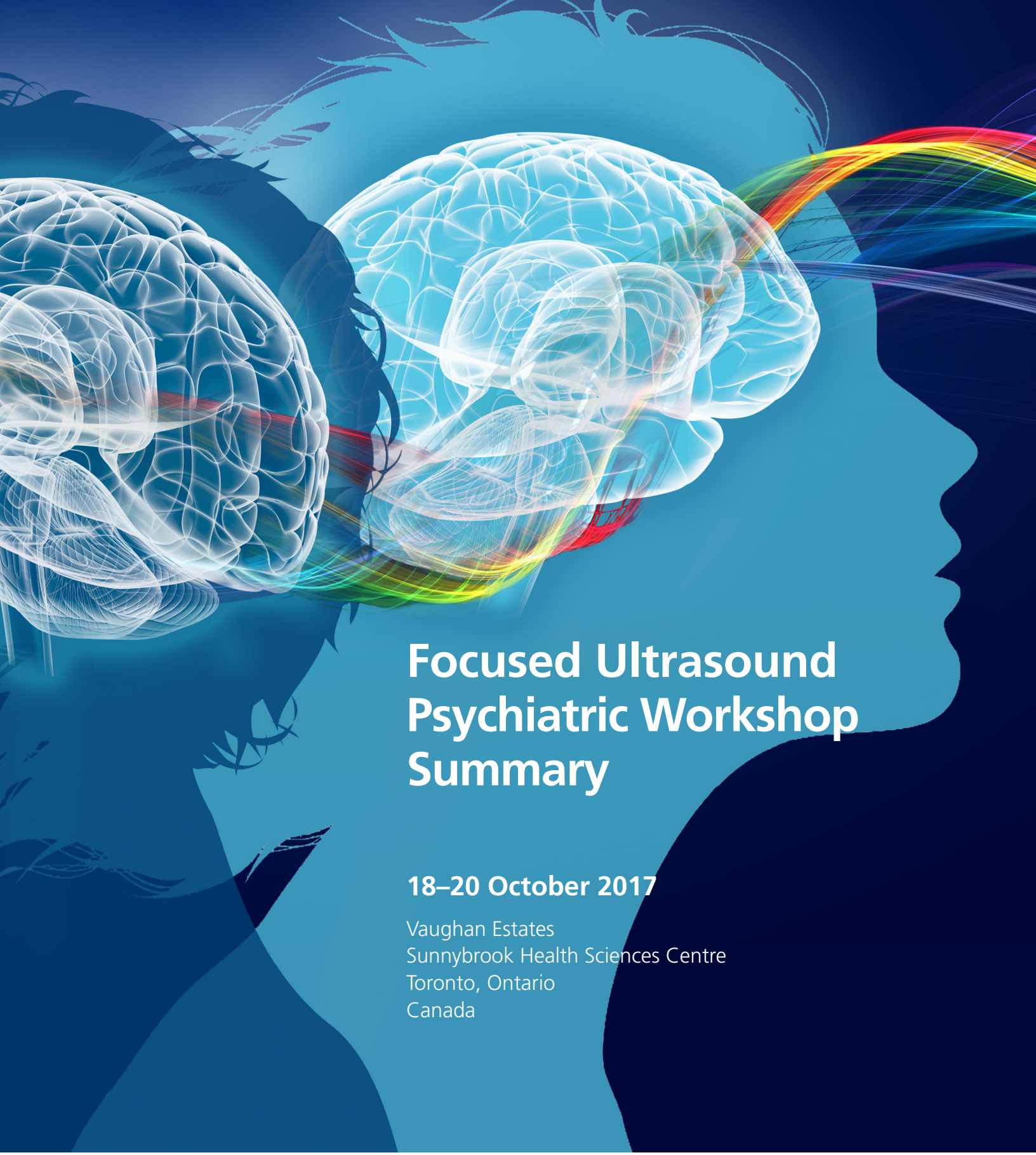

Focused Ultrasound Psychiatric Workshop Summary

18–20 October 2017

Vaughan Estates
Sunnybrook Health Sciences Centre
Toronto, Ontario
Canada

Sponsored by

Focused Ultrasound Foundation

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Focused Ultrasound Psychiatric Workshop

October 18–20, 2017

Executive Summary

Focused ultrasound (FUS) is an early-stage, disruptive, noninvasive therapeutic technology that has the potential to improve the lives of millions of patients with a variety of medical disorders by providing an alternative or complement to existing techniques. The Focused Ultrasound Foundation (FUSF) convened a multidisciplinary group of experts, including neuroscientists, neurosurgeons, psychiatrists, neurologists, neuroradiologists, and representatives from industry to address topics relating to the best path forward for FUS and psychiatric disorders.

The event occurred on October 18–20, 2017, at the Vaughan Estates of the Sunnybrook Health Sciences Centre and the Westin Prince Hotel in Toronto, Canada. Thirty attendees were present for the meeting.

As initial FUS treatment of patients with obsessive-compulsive disorder and depression has been promising, the goal of this 2-day meeting was to create a roadmap for further progress in patients with psychiatric illnesses by addressing the following key questions.

- What are additional novel indications for ablative focused ultrasound in psychiatric disorders?
- What other mechanisms of action with FUS (such as neuromodulation or blood-brain barrier (BBB) opening) should be investigated?
- Are there any technical or other limitations to pursuing new indications?
- What preclinical steps are needed next?
- What clinical studies should have the highest priority?

The group listed over a dozen potential clinical conditions that could benefit from FUS and gave top priority to anorexia nervosa, bipolar disorder, and addiction. These illnesses along with other disorders that have depression as the dominant symptom should also be considered for possible study.

In addition to the most common use of FUS for tissue ablation, other mechanisms of action were discussed such as neuromodulation of tissues with or without concurrent medication, and opening of the BBB for drug delivery.

At present, the clinical trials need to target tissue within the currently available treatment envelope, which is deep in the brain. The group felt that further refinement of the FUS treatment for obsessive-compulsive disorder (OCD) and depression could be considered when technical advances in the device allow for the treatment envelope to expand to more superficial areas of the brain. This will also enable consideration of additional indications and targets which are currently outside of the treatment envelope.

There was much interest in the preclinical work on neuromodulation; specifically, on the ability to better understand the circuitry for stimulation, inhibition, and modulation, most of which is unknown. There was interest in discussing the reversibility of FUS-mediated

local delivery of propofol, and potential learning that could come from its use. All agreed that as the reproducibility of the neuromodulation data improves, the added knowledge could offer significant improvements in knowledge and in patient care.

When considering study design, it was noted that a longer period of follow-up would likely be needed to ensure capturing delayed improvement patterns that has been seen with other treatment modalities. The importance of combining psychosocial rehabilitation with the FUS treatment was also felt to be important for optimal success.

The following is the list of next steps.

1. Identify and support clinical trials using FUS to treat anorexia nervosa, bipolar disorder, and addiction. Consider additional indications that are depression dominated.
2. Identify and support additional research on using FUS for neuromodulation, which may be preclinical or clinical.
3. Continue efforts to expand the treatment envelope.
4. Ensure that key protocol components, such as longer periods for clinical assessment and the use of psychosocial rehabilitation, are considered in future protocols.

The group was thoroughly engaged in discussion from the beginning of the workshop until departure. The attendees were asked to continue thinking and collaborating on these issues, and to share any additional thoughts with their colleagues and the FUSF.

Background

What is Focused Ultrasound and Current Applications

There is a tremendous need to develop new therapeutic options for psychiatric disorders. Psychiatric disorders are common, complex, and expensive disorders to treat. Brain circuit disorders account for a large proportion of morbidity worldwide, and are projected to increase in the coming decades. One of the challenges for developing treatments for brain circuitry disorders is balancing benefit with risk. Treatment options have not developed at the same pace as advances in our ability to diagnose psychiatric illnesses. There is also a history of failed neuropsychiatric treatments, such as frontal lobotomy, that contributes to emotional obstacles and recruiting difficulties for clinical research.

FUS is an emerging, noninvasive, surgical technique that uses real-time MRI coupled with multiple high-energy transducers to focus high frequency acoustic energy onto discrete brain regions with sub-millimeter accuracy. The effects depend on the amount of energy used. For example, high-energy application leads to a thermo-coagulative lesion. Lower frequencies combined with microbubbles allow for disruption of the BBB.

FUS for brain surgery has been in existence for over 75 years, with the first mention in the literature dating back to the 1940's with preclinical study using acoustic energy to lesion the brain. Several technical challenges, such as the need to remove part of the skull and bone overheating, prohibited further development. The introduction of MRI and MRI thermometry allowed visualization of the lesion and surrounding structures including bone in real-time. Phased-array technology now allows energy to be re-focused after passing through the skull, which can also alleviate some skull heating.

Currently, brain applications of FUS (lesions) are available for essential tremor, dystonia, Parkinson's disease, medication-induced dyskinesia, obsessive-compulsive disorder (OCD), and depression. A stereotactic frame is necessary for spatial accuracy of the acoustic energy. The procedure requires head shaving to ensure that the ultrasound beam passes into the brain without refocusing or reflection.

The advantages of FUS include real-time feedback, the ability to visualize the lesion immediately after the procedure, and to assay in real-time (such as movement improvements with essential tremor). The maintenance of lesions over time (months to years) is an area of active investigation. A 2016 randomized trial showed that lesioning for essential tremor was reproducible and effective in a multicenter trial.[1] Given the success with lesioning the thalamus, FUS is now being investigated to treat OCD and depression. These disorders are associated with abnormalities to key limbic structures of the brain thought to underlie many refractory mood and anxiety disorders. Some of the target areas include capsulotomy, cingulotomy, sub-caudate tractotomy, and limbic leucotomy.

Another consideration for the use of FUS for psychiatric disorders is neuromodulation through low frequency FUS combined with BBB opening. The majority of pharmacotherapy does not cross the BBB. Currently FUS combined with BBB opening with or without targeted agents is under investigation for the treatment of Alzheimer's disease, brain tumors, and in numerous preclinical studies.

Current Status of Focused Ultrasound for Neurological and Psychiatric Disorders

Jin Woo Chang from Yonsei University described his research using FUS to treat neurological and psychiatric disorders including essential tremor, Parkinson's disease, OCD, and depression. Advantages of FUS for neurosurgery include exact targeting (without damage adjacent brain structures).

Thalamotomy of the ventralis intermedius nucleus with FUS for the treatment of essential tremor is an established treatment modality. A functional network analysis was carried out with resting-state functional magnetic resonance imaging (rs-fMRI) combined with magnetic resonance-guided focused ultrasound (MRgFUS).[2] Focal lesions resulted in both remote and global changes to the brain network, suggesting that thalamotomy affects not only the motor system, but also the global brain circuitry. Chang also highlighted the issue of skull-related factors that create challenges for FUS.[3] Retrospective analysis of MRgFUS treatment for essential tremor revealed that both skull volume and skull density ratio (SDR) in the treatment field were related to temperature increase during sonication. A higher SDR, meaning a higher ratio of bone marrow to cortical bone, results in higher energy transmission. Skull volume and SDR may be important considerations when selecting patients for FUS treatment.

Bilateral thermal capsulotomy with MRgFUS for OCD has been developed and implemented in human clinical trials.[4] The results of the treatment showed a gradual improvement in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score. The mechanisms that underlie improvement in the Y-BOCS score for OCD are unknown. A preliminary trial for the treatment of major depressive disorder with MRgFUS is underway. A recently published case report found that bilateral anterior capsulotomy via MRgFUS resulted in improvement of depressive symptoms (Hamilton Depression Rating Scale (HAMD)).[5] Low frequency MRgFUS is also being evaluated for the treatment of OCD, but there are similar patient challenges regarding SDR.

Open Discussion

There was a question on why FUS is not a good technology for targeting the anterior cingulate.

- Low frequency (220 kHz) targeting of superficial regions is difficult. Skull factors (SDR, thickness, geometry, and marrow thickness) present challenges; the closer the target is to the skull, the harder it is to control heating of bone.
- The anterior cingulate is outside of the treatment envelope.

Specific anatomic targets might dictate the optimal treatment for the patient (deep brain stimulation (DBS) versus lesioning via FUS).

- If the patient has an optimal SDR, FUS is usually recommended for essential tremor. However, for bilateral treatment, DBS is may be preferred.

There was some discussion on the role of cognitive behavioral therapy (CBT) in combination with lesioning or DBS for OCD.

- There was consensus that CBT plays an essential role for treatment when combined with other treatment modalities.
- Patients with OCD may have had a long lifetime history of disability, and their needs may extend beyond just CBT. For example, occupational therapy, or psychosocial rehabilitation.

Workshop Presentations

Several brief presentations provided an overview of FUS, the history of psychiatric surgery, and the potential role for FUS to create focal lesions or induce neuromodulation.

Peter Giacobbe from the University of Toronto discussed the current status of neuromodulation for psychiatric disorders. Modalities that were discussed included electro-convulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), transcranial direct stimulation (tDCS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS). Approximately 40% of patients with major depression are treatment resistant. ECT is the oldest form of neuromodulation, known to be safe, and can be performed in the post-anesthesia care unit. ECT can increase neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and can increase brain volume in certain regions such as the hippocampus. It was noted that there are no assays for psychiatric surgery that are predictive. Canada released guidelines for neuromodulation in 2016.[6] The field needs to optimize the sequencing of available treatment options (pharmacotherapy, neuromodulation, etc.). There is an emerging subspecialty in psychiatry to look at underlying circuitry for mood disorders. Over the past few decades, research into techniques such as rTMS and DBS has increased exponentially, but many clinicians may not be comfortable with these modalities. Rapid advances in research should be matched with education for the medical community to make newer treatments more widely available to patients.

Clement Hamani from the University of Toronto discussed how preclinical models can be used to study lesioning and neuromodulation for psychiatric disorders. Each modality, DBS or lesioning for example, affects the brain through different circuitry. There are a variety of animal models that mimic depression, such as the forced swim test and chronic unpredictable mild stress. DBS stimulates the brain at high frequencies (100 Hz) and shuts down neuronal firing where the device is implanted. Activating axonal pathways near the electrode may induce changes in the neuronal firing of structures and tracts projecting either to or away from the target, change the release of neurotransmitter and neurotrophic factors, and/or induce neuroplasticity. Preclinical behavioral testing revealed that lesions and neuromodulation have differing effects in the rodent prefrontal cortex. Interestingly, implanting DBS electrodes (without stimulation) produces an anti-depressant effect in rodent models. There is a complex cascade of events that occur in the brain after DBS that may take months to years to occur. DBS has been shown to increase brain levels of serotonin and serotonin receptors (5-HT1B). Preclinical research in animal models with FUS can induce region-specific activity. DBS and FUS have very different mechanisms in the brain, but the preclinical research for FUS is still in the very early stages.

Leo Sugrue from the University of California at San Francisco discussed imaging studies of neural circuitry. Symptom-based categorization for mood disorders is an outdated method. There have been suggestions to rework how we conceptualize these disorders and to focus on a more circuit-driven approach.[7] Therefore, new treatment approaches for psychiatric disorders should focus on ways to modulate neurocircuitry. The imaging technology to study spatial and temporal anatomy at the network level doesn't yet exist. Lesioning the brain for treatment-resistant psychiatric disorders, such as OCD has historical effectiveness. Basic neurobiology can be leveraged to develop imaging biomarkers of OCD. Imaging studies in primates using a dynamic value-based decision-making task has been used to study brain circuity[8] There is a lot of research underway to determine imaging biomarkers for psychiatric disorders, but little definitive evidence to date.

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Renana Eitan from Brigham and Women's Hospital discussed challenges with DBS in psychiatry. DBS has been refined to not only select patients that will most likely benefit, but to also identify more definitively the specific anatomic brain target for the electrode placement, and to determine the amount of stimulation necessary. Electrophysiology recordings during the DBS procedure can be used to pinpoint the appropriate location within the target area for DBS. Using the Medtronic Activa® PC+S system, electrophysiological recordings can be done both intra-operatively (micro- and macro-electrodes) and post-operatively (macro-electrodes). Beta oscillatory activity was observed at the dorsolateral (motor) subthalamic nuclei (STN) in OCD patients, similar to patients with movement disorders. Theta oscillatory activity at ventro-medial (emotional-cognitive) STN appears only in patients with OCD, and is negatively correlated with symptom severity. Additional research is needed to determine the role of the theta oscillatory circuit in OCD.

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Rees Cosgrove from Brigham and Women's Hospital discussed ablative surgery for psychiatric disorders. Cosgrove discussed the historical perspective of surgery for psychiatric disorders, such as the prefrontal lobotomy. With the arrival of stereotactic surgery in the 1950's additional surgeries were developed including cingulotomy, anterior capsulotomy, subcaudate tractotomy, and limbic leucotomy. Psychiatric surgery decreased with the development of psychotropic medications. However, the available evidence at the time suggested that approximately 60 to 70% of patients that underwent psychiatric surgery had a response to a surgical intervention. A prospective study of patients with treatment-resistant major depression had a 75% response rate to ablative stereotactic procedures (dorsal anterior cingulotomy followed, if necessary, by subcaudate tractotomy).[9] Similar results were also found for patients with OCD.[10] Patients were more likely to show a response to treatment during longer follow-up periods. DBS and anterior capsulotomy are both effective treatments for OCD.[11] There is a role for ablative surgery in psychiatric disorders, but brain targets are not well-defined or understood.

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Raag Airan from Stanford University discussed FUS for neuromodulation. Preclinical research has investigated a range of effects in several models for a variety of behavioral endpoints. Continuous wave ultrasound for ~80 ms directed to dorsal cortex can elicit muscle twitch. Transcranial FUS can also be used to modulate the activity of the primary somatosensory cortex in both humans and rodents.[12,13] The exact mechanisms of FUS neuromodulation are unknown at this time. Intravenous (IV) microbubbles can induce pores in the BBB to allow particles to enter the brain.[14,15] Phase-change nanoparticles can be used for targeted neuromodulation. Nanoscale perfluorocarbon droplets encapsulated by biodegradable polymer can be combined with FUS to induce droplet vaporization and release of drug only in the sonicated region. Potential applications for ultrasound neuromodulation include either direct or drug-mediated neuromodulation for pre-surgical brain mapping, target validation, or as an adjunct to psychiatric therapies.

Airan also outlined several practical considerations that will help advance the field of FUS for neuromodulation. New FUS systems designed specifically for neuromodulation are necessary. The currently available systems are repurposed ablation devices. The ideal neuromodulation FUS system will have:

- Targeted accuracy without the need for a stereotactic frame
- A tracking system that removes the need for continuous MRI monitoring.
- An expanded treatment envelope that will allow targeting of brain regions near the skull such as the hippocampus, amygdala, dorsolateral prefrontal cortex, and nucleus accumbens.
- A safety profile similar to transcranial magnetic stimulation (TMS), so that a technician can perform the procedure.
- A method to verify sonication focus site such as acoustic imaging or acoustic radiation force impulse imaging (ARFI)
- A protocol that makes shaving a patient's head unnecessary.
- Protocols that deliver predictable and reproducible neuronal activity

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Mor Dayan from Insightec discussed the technical challenges of FUS for psychiatric disorders from the industry perspective. One of the most challenging issues is the limitation of the treatment envelope. High incident angles are created when the target is not near the center of the skull, and result in undesirable off-target effects. Phase correction algorithms and other methods can help, but cannot overcome these problems. Absorption, reflection, and scattering of the beam all play a role in focal accuracy. Low frequency (220 kHz) results in insufficient temperature rise at the focus, and energy is more attenuated in the mid-frequency range (650 kHz). In a series of simulation experiments they found that the anterior cingulate was an unfeasible target as it is too close to the skull, the anterior limb of the internal capsule (ALIC) and subcaudate regions were within the treatment envelope (considering adequate SDR), but the proximity of the subcaudate region to the skull base may be a limitation. Insightec's 650-kHz transducer can provide thermal

ablation to targets that are within the treatment envelope (ALIC and subcaudate). The 220-kHz transducer is being studied to determine the feasibility of creating thermal ablation in the presence of microbubbles, opening the BBB for drug delivery, and inducing neuromodulatory effects. Improvements are being made to increase the ability to perform reproducible lesions (volume, shape, and alignment), and are estimated to be ready for clinical use by mid-2019. A 3T MR imaging coil is also under development, but there is no timeline for clinical use. Software changes have been implemented to reduce total treatment time, particularly for bilateral and larger treatment volumes, and will be released in future software updates.

Discussion from Presentations

Preclinical issues:

- Questions about the utility of current rodent models for depression or other psychiatric disorders
  - The problem with many anti-depressant models is that they can be useful to screen drugs, but are not useful to study mechanisms.
- Questions about the feasibility of using FUS combined with BBB opening and microbubbles to deliver a cytotoxic agent to create a focal lesion.
  - This is theoretically possible, similar research has been done using anesthetics, such as propofol.
- Preclinical research suggests that there do not appear to be cumulative effects of repetitive BBB opening such as petechial hemorrhage or apoptotic neurons.
  - In preclinical animals, BBB opening daily for 7 days was safe. However, this is not practical in humans with the current FUS systems.

Clinical issues:

- Reimbursement for neuromodulatory procedures is a limitation for all patients.
- Psychiatric surgery is a politically sensitive issue.
  - Potential reluctance on the part of funding agencies and difficulty recruiting patients to clinical trials
- Real-time imaging during surgery is an important advantage for FUS compared with current surgical techniques.
- Patient selection is very important. Selecting the optimal subtype of OCD along with appropriate biomarkers to predict the patients most likely to respond will improve the utility of the FUS-induced lesions in this population.

Overall Discussion and Evidence Gaps

Open Discussion

Given that both OCD and depression research with FUS are already underway, what are additional psychiatric disorders that could be potentially treated with FUS?

Anorexia nervosa

- There is a high mortality and few treatment options.
- The participants discussed the appeal of lesioning to this population and considered the fact that DBS may not be optimal for this group of patients because they are usually very young.

Bipolar disorder

- A classic circuitry disorder known to be controlled by anti-epileptic agents.
- Most patients (75%) are in the depressive phase. There was some concern that lesions could increase the risk for a severe manic episode.
- Suggested targets for bipolar disorder were capsulotomy or cingulotomy.
- There was a recommendation to look at the literature for depression versus mania for lesioning.

Addiction

- Complex because there are also many behavioral components.
- Most of the published literature originates in Russia or India (cingulate) and China (nucleus accumbens), but the publications lack important follow-up information such as comorbidities, cognitive function, rehabilitation efforts, etc.
- There was a suggestion to look at the hypo-reward functioning circuitry; the exact target may have large individual variability.
- The circuitry in addiction is well-known, but translational work is necessary; DBS has not worked well for these patients.
- The participants were divided on whether addiction was a good target for FUS at this time.

Pain

- There was discussion that FUS research is ongoing for chronic pain in the central lateral thalamic nucleus for clinical use.

Self-mutilation

- Small population, but they require many healthcare interventions and are a large burden on the healthcare system in general.
- Surgical lesions (limbic leucotomy or capsulotomy) have been used to treat these patients with some success.

Fear and anxiety/post-traumatic stress disorder (PTSD)

- The circuitry is well-known, but the target is unclear. Some work with lesioning the amygdala has been done for PTSD.

  - There was a comment that, in the US, veterans are monetarily compensated for having PTSD. There is no incentive for these patients to receive treatment or make a recovery.
- There were a few psychiatric disorders that were briefly mentioned by the participants, but did not garner much enthusiasm from the group. These included binge-eating, body dysmorphic disorder, hoarding, and tardive dyskinesia.
- There was discussion that the utility of lesions for psychiatric disease in general hasn't been proven, and FUS may be a good tool to investigate that question.
  - Focus on refining FUS for OCD and depression before targeting other disorders.
  - Patients that are candidates for lesions need to have life-threatening illnesses, therefore the high risk of death due to addiction and anorexia, may make these appropriate indications.

Given the limited treatment envelope at this time, can we look at specific regions of interest to treat within that envelope. For example, if the anterior capsule can be targeted, should we consider any disorder that involves this region, such as generalized anxiety. Is this a helpful way of looking at priorities?

- The group agreed that FUS should focus on high-risk patients. Patients with generalized anxiety are not heavy users of the healthcare system.
- It might be useful to target underlying symptomatology instead of a disorder. It is necessary to treat underlying depressive symptomatology first in many of the disorders discussed.

Participants were asked for their thoughts on experimental designs for early phase clinical studies with FUS for psychiatric disorders.

- Clinical trials should be designed for the brain targets currently available.
- Feasibility studies with a small number of patients might be useful to look at recruitment methods and shape of the lesion.
- There was some discussion on a reasonable length of time for follow-up in patients that receive sham treatment.
  - The participants were divided on whether 12 or 18 months was adequate for sham procedures. There was concern that potential efficacy could be missed in studies that only last 12 months.
  - There was a comment that patients are accustomed to waiting many years for surgical treatments. In Canada, it is typical to wait 2 to 3 years for DBS. Studies could be designed so that sham-treated patients receive the intervention after a specified period of time, and this may be comparable to the real-world experience at this time.
  - The participants cautioned that lesion trials with long follow up are difficult to recruit, and they will need multicenter trials.
- There was a suggestion to include resting-state electroencephalograms (EEGs) and other cognitive tasks before and after the FUS procedure to try to classify responders versus nonresponders.
  - There was also a suggestion to use FDG-PET scans before and after the procedure to determine responders.

- Depression and OCD are the most common disorders treated with lesions. However, these populations also have comorbid disorders and subpopulations within the major disorders that could be analyzed to identify additional patient groups that might benefit from FUS.
- Psychosocial rehabilitation is also an important consideration.

The participants were asked what kinds of preclinical studies could help to inform future clinical work.

- Rodent work is not useful for lesion studies because the fiber tracts are different.
- Participants suggested that preclinical work in neuromodulation is key.
  - Reversible lesions with agents like propofol are interesting.
  - Preclinical models can be used to figure out the circuitry for stimulation, inhibition, modulation; mechanisms are mostly unknown.
  - There was a brief discussion on the utility of studying FUS-induced neuromodulation in brain slices. Some participants cautioned that this model allows the study of cytoarchitecture, but is not useful for studying brain circuitry.
  - Research teams produce the most useful data when there are experts in both FUS and neuroscience involved in the studies.
- Primate research could be useful for studying underlying brain circuitry changes because of focal neuromodulation and defining corresponding behaviors that match to a brain region of interest.
- Future proof-of-concept studies determining safety in humans are also needed.
  - Similar to the TMS literature, FUS could be applied to the somatosensory cortex with a paired pulse technique to measure the intensity and duration of effect.

Outcomes and Next Steps

Participants were encouraged to reach out to the Foundation with any research ideas or project proposals in this area. FUSF will continue engagement with this community to move the research forward.

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References

1 Elias WJ, Lipsman N, Ondo WG, et al. A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. *N Engl J Med.* 2016;375(8):730–739.

2 Jang C, Park HJ, Chang WS, Pae C, Chang JW. Immediate and Longitudinal Alterations of Functional Networks after Thalamotomy in Essential Tremor. *Front Neurol.* 2016;7:184.

3 Chang WS, Jung HH, Zadicario E, et al. Factors associated with successful magnetic resonance-guided focused ultrasound treatment: efficiency of acoustic energy delivery through the skull. *J Neurosurg.* 2016;124(2):411–416.

4 Jung HH, Kim SJ, Roh D, et al. Bilateral thermal capsulotomy with MR-guided focused ultrasound for patients with treatment-refractory obsessive-compulsive disorder: a proof-of-concept study. *Mol Psychiatry.* 2015;20(10):1205–1211.

5 Kim M, Kim CH, Jung HH, Kim SJ, Chang JW. Treatment of Major Depressive Disorder via Magnetic Resonance-Guided Focused Ultrasound Surgery. *Biol Psychiatry.* 2017.

6 Milev RV, Giacobbe P, Kennedy SH, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments. *Can J Psychiatry.* 2016;61(9):561–575.

7 Insel TR. Faulty circuits. *Sci Am.* 2010;302(4):44–51.

8 Sugrue LP, Corrado GS, Newsome WT. Choosing the greater of two goods: neural currencies for valuation and decision making. *Nat Rev Neurosci.* 2005;6(5):363–375.

9 Shields DC, Asaad W, Eskandar EN, et al. Prospective assessment of stereotactic ablative surgery for intractable major depression. *Biol Psychiatry.* 2008;64(6):449–454.

10 Sheth SA, Neal J, Tangherlini F, et al. Limbic system surgery for treatment-refractory obsessive-compulsive disorder: a prospective long-term follow-up of 64 patients. *J Neurosurg.* 2013;118(3):491–497.

11 Pepper J, Hariz M, Zrinzo L. Deep brain stimulation versus anterior capsulotomy for obsessive-compulsive disorder: a review of the literature. *J Neurosurg.* 2015;122(5):1028–1037.

12 King RL, Brown JR, Newsome WT, Pauly KB. Effective parameters for ultrasound-induced in vivo neurostimulation. *Ultrasound Med Biol.* 2013;39(2):312–331.

13 Legon W, Sato TF, Opitz A, et al. Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. *Nat Neurosci.* 2014;17(2):322–329.

14 McDannold N, Zhang Y, Power C, Arvanitis CD, Vykhodtseva N, Livingstone M. Targeted, noninvasive blockade of cortical neuronal activity. *Sci Rep.* 2015;5:16253.

15 Airan RD, Meyer RA, Ellens NP, et al. Noninvasive Targeted Transcranial Neuromodulation via Focused Ultrasound Gated Drug Release from Nanoemulsions. *Nano Lett.* 2017;17(2):652–659.

Abbreviations

ALIC	Anterior limb of the internal capsule
ARFI	Acoustic radiation force impulse imaging
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
CBT	Cognitive behavioral therapy
DBS	Deep Brain Stimulation
ECT	Electro-convulsive therapy
EEG	Electroencephalogram
FDG-PET	Fluorodeoxyglucose position emission tomography
FUS	Focused ultrasound
FUSF	Focused Ultrasound Foundation
OCD	Obsessive-compulsive disorder
PTSD	Post-traumatic stress disorder
SDR	Skull density ratio
STN	Subthalamic nucleus
TMS	Transcranial magnetic stimulation
US	United States
VNS	Vagus nerve stimulation

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