FUS PULSE

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Toronto, ON

SYMPOSIUM 2026

FOCUSED ULTRASOUND in PSYCHIATRY

Sponsored by

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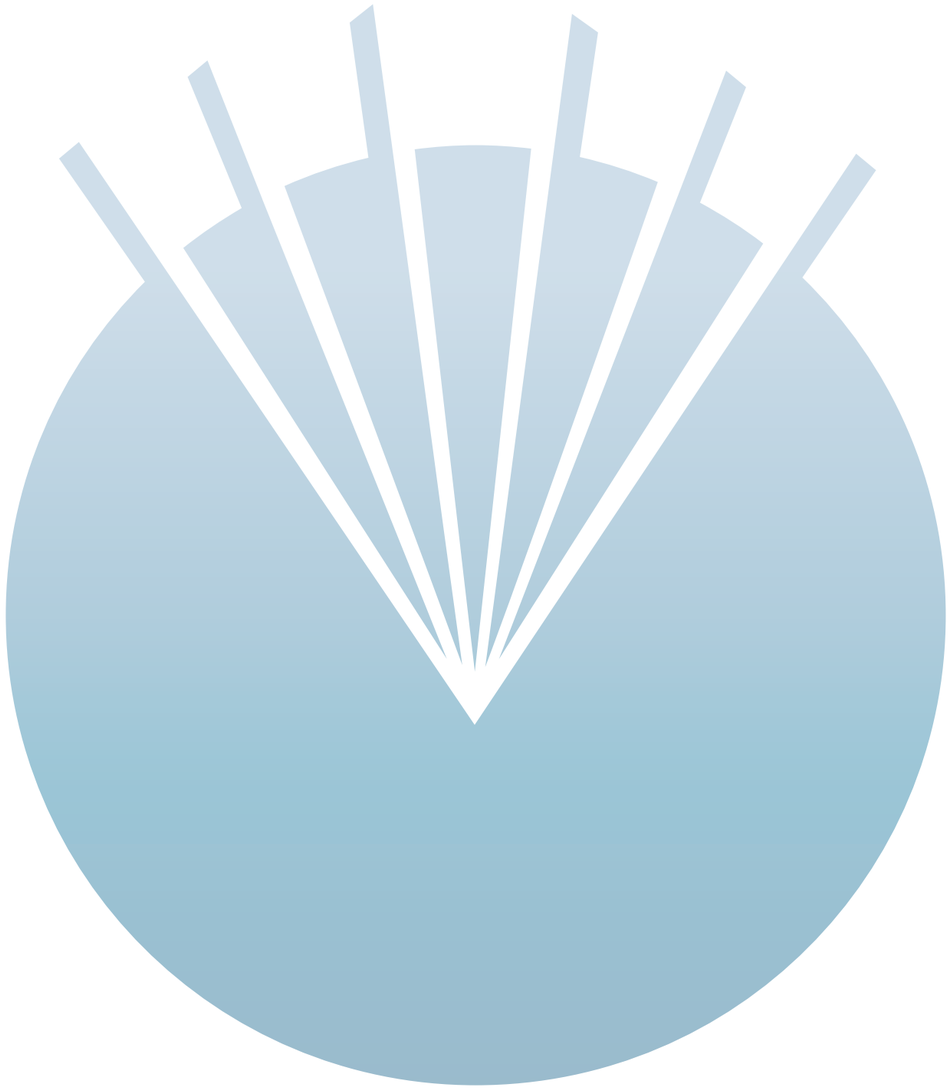

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EXECUTIVE SUMMARY

This white paper summarizes the second symposium on Focused Ultrasound in Psychiatry (FUS-PULSE), held in Toronto from June 24–26, 2026. The inaugural meeting in June 2024 was summarized in a white paper and subsequently published as a roadmap in Brain Stimulation.1 FUS-PULSE is now established as a biennial meeting. The third edition is being planned for June 2028.

The meeting was convened by co-chairs Nir Lipsman and Benjamin Davidson, and members of the steering committee, Rees Cosgrove, Renana Eitan, Clement Hamani, Susie LeBlang, Noah Philip, and Ali Rezai. As in 2024, attendance was by invitation, making for an intimate setting with approximately 80 attendees. The organizers acknowledge that the meeting has reached an inflection point deciding whether to expand substantially or preserve the small format that makes extended, candid discussion possible. For 2026, the latter was chosen: 5 sessions spanning the breadth of the field featuring 19 presentations, long moderated discussions, and networking time.

The first session, "Psychiatry and FUS Update: What Has Happened in the Last Two Years?" reflected on progress since FUS-PULSE 2024. The 2024 meeting was largely aspirational: a field describing what FUS might accomplish in the field of psychiatry. The 2026 meeting was defined by progress and data. Speakers presented completed crossover trials, active-controlled target-engagement studies, soon-to-be-published exciting results, pilot studies with novel devices including wearable and outpatient device platforms, and visions for incorporating real-time closed-loop parameter optimization.

In the second session, "Mechanisms of FUS Neuromodulation", an important theme emerged: the field should ask what the mechanisms are rather than the mechanism of FUS neuromodulation. The parameter space and associated mechanisms remain a central unsolved problem, but excitingly, the field has begun to address it systematically.

Session three, "FUS Clinical Results and Safety" addressed safety, detailing a serious unanticipated adverse device event from the NAc FUS neuromodulation trial, the specific device and protocol modifications that followed, and the patient's ongoing recovery. The repeated lesson: low intensity does not mean no risk, and protocols should be designed in advance to retain and study affected participants rather than simply withdraw them for the field to learn.

The fourth session, "Other Uses of Focused Ultrasound", pushed the boundaries further on emerging applications, with drug uncaging, glymphatic modulation, expanding ablative targets, and a vision for novel indications in the emergency setting. Preclinical studies pointed to an emerging, possibly dominant, non-neuronal mechanism of FUS neuromodulation, acting through effects on microglial, astrocytic, endothelial, extracellular matrix and glymphatic pathways.

Session five, "Bridging the Field Together" identified outcome measurement and implementation as rate-limiting steps equal in importance to the physics. Validated symptom scales may diverge from lived improvement, so the field needs both alongside objective biomarkers which would bring commercial interest. With professional and cultural barriers to interventional psychiatry, patients ultimately drive uptake. The Toronto experience of obtaining provincial funding for FUS capsulotomy for OCD through patient and family testimony was offered as hope that implementation is achievable.

The program included a moderated dinner panel on the history and future of neuromodulation with Helen Mayberg, Michael Fox and Andres Lozano, moderated by Nir Lipsman.

The closing discussion asked participants to identify next steps for the field. Consensus formed around validated, rapid target-engagement biomarkers, standardized reporting of parameters, durability data, a shift from open-label feasibility to adequately powered sham-controlled trials in the most mature applications, and composite outcome frameworks that pair symptom scales with functional improvement, patient-defined goals, and objective biomarkers.

WELCOME & INTRODUCTION

Nir Lipsman opened the meeting on behalf of the co-chairs and the Harquail Centre, thanking the steering committee and the Focused Ultrasound Foundation for the leadership and funding that helped bring the community together, and Leila Harwood for the organization of the symposium.

Greetings were extended to the symposium by the Premier of Ontario, the Deputy Premier and Minister of Health, the Mayor of Toronto and the Member of Parliament for Don Valley West. The meeting coincided with the tenth anniversary of Sunnybrook's designation as a Centre of Excellence in Focused Ultrasound by the Focused Ultrasound Foundation.

He explained the origin of the name FUS-PULSE, coined to "take the pulse" of focused ultrasound in psychiatry, and framed the meeting around two driving forces: opportunity and urgency. Psychiatric illness remains a leading global cause of suffering, morbidity, mortality, and disability worldwide, and despite substantial advances in understanding, many patients remain inadequately treated. In parallel, FUS has emerged as a less invasive, targeted, circuit-based intervention that has advanced rapidly, especially in the two years since the last meeting. What seemed aspirational and theoretical in 2024, is now taking shape around the world, much of it through work done by people in the room.

He noted that the field will not be built by a single institution, device, or mechanism. With that in mind, he set out one hope and one request for the meeting. The hope: that participants leave with new ideas, collaborations, and partnerships. The request: as attendees listened to the talks, they should identify the questions they wanted answered before the next edition of the meeting in 2028.

Benjamin Davidson welcomed participants and described the design of the program: a series of short talks designed to set the stage for longer, moderated discussion related to each session. He noted the organizers' awareness that the meeting topics have grown well beyond its original scope, a sign of how much momentum the FUS community has built.

PRESENTATIONS

Session 1: Psychiatry and FUS Update: What Has Happened in the Last Two Years?

Discussion moderated by Rees Cosgrove

James Mahoney, PhD presented on *"Focused ultrasound neuromodulation for addiction"*. Dr. Mahoney was recruited to the University of Virginia School of Medicine to establish the Center for Neuromodulation Research. He is also affiliated with the WVU Rockefeller Neuroscience Institute.

The scale of the problem remains severe despite recent progress. Overdose deaths have declined, attributable in substantial part to naloxone access, but still remain near 80,000 annually in the US alone, where approximately 28 million people are affected by drug and alcohol addiction each year, with substantial overlap between the two.

Polysubstance is commonplace in the substance use disorder cohorts. For instance, opioid use is typically accompanied by methamphetamine or cocaine use. However, this fits well with a circuit-based neuromodulation approach: engaging a core reward network and that can therefore address multiple addictive behaviours simultaneously.

Only a small proportion of people with substance use disorder ever receive treatment, and relapse rates remain high even among those who receive guideline-concordant care. FUS should therefore be conceptualized as adjunctive, another tool in the toolbox to complement the standard of care of medication and behavioural treatments.

The NAc sits at the core of reward circuitry, connected to insula and prefrontal cortex with craving and cognitive control circuits both implicated.[2,3] Dysfunction in the NAc is a principal driver of continued use and relapse. A recent review from the group in *Biological Psychiatry* tabulated ongoing and planned FUS trials for addiction. The number of registered studies has grown from a small handful in 2024 to at least 20 on ClinicalTrials.gov, spanning multiple targets within reward circuitry and multiple substances.[4,5]

Participants view substance-related images through goggles in the MRI and complete craving ratings before and after, allowing craving response to be brought "online" so that any reduction attributable to FUS can be measured. The procedure lasts approximately one hour.

Treatment context matters and must be reported. Dr. Mahoney described the West Virginia COAT (Comprehensive Opioid Addiction Treatment) program in detail as the ecosystem within which the RNI results should be interpreted: over 650 patients in clinic, buprenorphine prescribing, psychiatrist, case manager, group and individual therapy, a phase-based structure moving from weekly to biweekly visits as patients sustain 90 days of abstinence, escalating levels of care for those who relapse, and a 28-day residential dual-diagnosis unit (the Center for Hope and Healing). He argued that multi-site trials will need to standardize treatment regimens as far as regional availability permits.

Dr. Mahoney also described a NIDA-funded UG3/UH3 study targeting the anterior insula in cocaine use disorder at the University of Virginia. Of 25 participants enrolled, 22 completed the study, a notably high retention rate for this population. The design was a crossover study. After screening, participants were randomized to a single session of active FUS or sham, returned

2 weeks later for the opposite condition, and were followed for 4 weeks thereafter. Results were presented as safe and feasible, with significant decreases in percentage of days used comparing pre-screening to post-FUS, in both randomization orders. These were non-treatment-seeking individuals, not enrolled in behavioural or medication treatment and not interested in stopping. That they nonetheless reduced use suggests that a treatment-seeking cohort might show a stronger effect. The UH3 phase will recruit treatment-seeking participants, optimize follow-up timing and extend the follow-up period.

Future directions will include comparisons across devices and other neuromodulation modalities (TMS, VNS, tDCS) with an emphasis on scalability, optimization of target location beyond the accumbens including the insula, determining whether repeated sessions have additive or more durable effects, and whether maintenance sessions are required when craving returns.[124,125]

Bomin Sun, MD, presented a *"Pilot clinical study of high-intensity focused ultrasound in Alzheimer's disease"*. Dr. Sun (Ruijin Hospital, Shanghai Jiao Tong University School of Medicine) presented results from an open-label, single-arm pilot of high-intensity focused ultrasound in moderate-to-severe AD, a severity range for which he noted there is essentially no effective treatment. His group has also recently reported HIFU ablation in alcohol use disorder.[6]

Their pilot study in AD was conceptualized while treating an 89-year-old woman for medication-induced tardive dystonia using FUS pallidothalamic tractotomy. Although the dystonia improved only marginally, surprisingly, 1-month post-treatment her cognition improved markedly and by one year her cognitive ability had reached age-matched norms. This was a highly unexpected finding, because a PTT lesion itself is an unlikely explanation; the pallidothalamic tract is not a plausible AD target, however the mechanism remains unknown. The working hypothesis is that widespread cortical and subcortical tissue receives high-intensity ultrasound exposure over the course of the procedure.

Based on this hypothesis, Dr. Sun described an open-label trial which had enrolled 16 patients with AD, including baseline assessment, treatment, and 3-month follow-up. The majority of the cohort has now reached 6 months. The cohort was severely affected at baseline: mean baseline MMSE was 5.5, with many patients scoring 0–2, and only 3 patients above 10. Dr. Sun explained that this reflected the fact that only families of the most severe patients were willing to enroll.

The trial employed sonication parameters similar to those used for ablative procedures, although at lower intensities. 10-12 sonications were delivered per patient, with the target moved each time to explicitly allow wide cortical exposure to ultrasound rather than to create a lesion. No temperature rise was seen and no abnormal signals (or lesions) were observed on post-treatment MRI. Unfavourable skull density ratios in this population make lesioning difficult in any case.

Dr. Sun reported that the MMSE improved from a baseline mean of 4.4 to 7.3 at 3 months, and the MoCA improved from 2.3 to 3.6. Neuropsychiatric Inventory scores improved from

26.6 to 19.1 with reductions in hallucinations and behavioural disturbances. ADCS-ADL quality-of-life measures also improved. Substantial quality-of-life gains occurred only in less severe patients. In the most severe patients, improvements in cognition by ~30% did not translate to quality-of-life improvement, suggesting that future studies should prioritize less severely affected patients. Hippocampal volume predicted treatment response with lower volumes associated with poorer response. On PET, amyloid-beta changes were not significant, though some patients showed significant reductions in tau.

Interestingly, the first and most severely affected patient in the study awoke the day after treatment able to recognize family and friends by name, prompting a celebratory family dinner. The improvement then substantially receded over the following days. Dr. Sun argued that this transient recovery implies that memory content is not lost but access to it is blocked, and that even a single day of recovery is informative about potential mechanism.

Tommaso Di Ianni, PhD presented on *"Efficient closed-loop optimization of ultrasound neuromodulation protocols"*. Dr. Di Ianni (University of California San Francisco) discussed preclinical work from his group addressing the field's ongoing parameter problem.

Dr. Di Ianni framed his talk around 3 challenges for the field:

(i) Auditory and other peripheral confounds. LIFU stimulates not only the target but auditory and other sensory pathways as well.[7,8] Reporting standards for these controls are now formalized.[9,10]

(ii) Mechanisms are poorly understood, though he argued this is not necessarily rate-limiting. The precise mechanisms of TMS and DBS also remain unclear, yet those fields still have a general starting point that LIFU currently lacks.

(iii) The parameter space is poorly characterized.

His group has developed lenses for use with the NeuroFUS system that defocus the field so that the same pressure is deposited in skull and skin with no build-up at the target as an active sham. Similar lenses have been developed by other research groups such that participants cannot reliably distinguish active LIFU from active sham. In rodent studies, running visual, auditory, visual+auditory, and LIFU blocks shuffled within a single session, auditory stimulation alone activated auditory structures but did not change the visual response, indicating the LIFU effect at the dorsal lateral geniculate nucleus and downstream V1 was not an auditory artifact.

On (iii), he quoted the 2024 FUS-PULSE proceedings on the wide and poorly defined parameter space, underscoring that two years later, the field is still wrestling with the same problem. He emphasized four compounding difficulties: 1) Dose-response relationships are frequently non-linear, so more is not necessarily better, simply different. 2) The same protocol applied to different targets within the same individual can produce different responses. 3) Different protocols work best for different patients, suggesting group-level optimization may

be suboptimal at the individual level. 4) Finally, neuroplastic adaptation may reduce efficacy over time, similar to drug tolerance, implying that optimization may need to be repeated per subject, per target and longitudinally.

Bayesian-Enhanced Adaptive Control of Ultrasound Neuromodulation (BEACUN). Dr Di Ianni introduced BEACUN, an approach his group has developed for closed-loop optimization of FUS parameter space, explaining that it works in stages.[11] First, a planning phase identifies the stimulation-response measure or surrogate biomarker and safety limits. The search is initialized with randomly distributed points in parameter space. Than, a Gaussian process iteratively models the unknown stimulation-response function. An acquisition function described as the heart of the method selects the next parameter set to test. A probabilistic stopping criterion terminates the search once further gains become minimal.

In a rodent model, a ground truth was established by combining LIFU with functional ultrasound imaging at the dorsal lateral geniculate nucleus, examining only inhibitory online responses. Through BEACUN, they then shuffled pulse repetition frequency, duty cycle, and pressure across sessions to build a response map. His group selected a high frequency deliberately, not because rodent-derived parameters are expected to transfer to humans, but because the optimization method itself is meant to transfer, and the high frequency yields a focal-volume-to-brain-volume ratio closer to the human case.

In live optimization, with pressure up to 1 MPa and PRF and duty cycle both treated as continuous variables, BEACUN converged in a mean of 23 stimulation-response evaluations, compared to approximately 90 required to build the ground-truth map in each animal. Allowing the search to continue to 45 evaluations did not change the parameter landscape. BEACUN converged to a better solution than random search. Human testing is the next step. though of course it will depend on the presence of a reliable biomarker.

Pierre Mourad, PhD, presented on *"A view from inside a major funding agency"*. Dr. Mourad (University of Washington) was recently a program manager at ARPA-H, and he presented his experience developing a program over three year which reached the point of near-launch, but ultimately did not go live. His experience offered the room a rare view of how such programs are constructed.

Dr Mourad highlighted the ARPA-H philosophy is to address a very large problem with an idea ambitious enough that almost nobody would fund it, and yet, the problem must be plausible. The proposal must satisfy a program manager first, then every level above, ending at the Office of the Secretary of Health and Human Services. Improvements should be framed as large integer multiples and budgeted generously.

Beginning in March 2023, the target indication shifted from pediatric treatment-resistant depression to nociplastic pain. Chronic back pain without a structural lesion and fibromyalgia together represent roughly 60% of chronic pain cases. The field moved fast over those 3 years, and Dr. Mourad credited researchers Jan Kubanek, Wynn Legon, and Keith Murphy as being among those who advised him throughout the process.

Chronic pain, like many neuropsychiatric disorders, represents dysregulation of brain circuits. Sufficient acute pain sustained for long enough dysregulates circuits such that pain becomes suffering, thought becomes rumination, and the system becomes hypersensitive. The goal was normalization of circuit function in a personalized way.

Three technical areas anchored the ARPA-H proposal:

(i) Modulate. Steer focal modulatory energy to each candidate target without patient-specific MR or CT, which would save considerable time and cost. For chronic pain he identified emotional, sensory and attentional centres, each with 1-5 candidate targets to inhibit or activate.

(ii) Monitor. Generate a marker that identifies which target or targets matter for a given patient and at what dose. He cited Wynn Legon's demonstration that heart-rate variability rises with anterior insula targeting as the kind of real-time biomarker required[100], adding that one must also know when one is off target.

(iii) Scale. A device that can actually be purchased or leased with the successful device being positioned to submit an FDA claim within five years.

Success criteria were set deliberately high (approximately 80% response rate), exceeding TMS or ECT, on the reasoning that an ARPA program must promise, and plausibly deliver a revolution in both technique and patient care.

The budget totalled just under $100 million over 5 years across 5 academic and industry groups, with attrition built in by design. Teams were cut at the end of phase one and again in subsequent phases. Phase one required proof of concept in healthy subjects. Phase two required plausible integration. Phase three required a trial demonstrating efficacy. Considerable effort also went to ethical, legal and societal issues, including device cybersecurity, and human factors.

Jay Sanguinetti, PhD presented on *"Personalized amygdala neuromodulation in generalized anxiety disorder"*. Dr. Sanguinetti (co-founder and CEO, Sanmai Technologies and co-director of the SEMA Lab, University of Arizona) traced a decade-long arc from a hand-held single-element transducer to a deployable closed-loop clinical system.

In 2016, the device used a transducer held by hand, encountering exactly the coupling and targeting problems later catalogued in the 2024 FUS-PULSE proceedings.[1,12] Superficial targets were used because targeting capability at the time made anything else untenable, though there was always a hint of an effect, particularly in clinical populations.

The company's first prototype, an EEG-plus-ultrasound closed-loop system, produced strong signals on measures such as individual alpha frequency. However, the first clinic to use this device handed it back, noting that a system requiring the insertion of several needles into the scalp would be too invasive and complicated for patients already suffering from anxiety

disorders. The lesson was that a scientifically sophisticated system can fail entirely on clinical usability and the experience prompted a deliberate pivot to a minimum viable product.

The Lotus system. The Lotus device is deployable in 5 minutes, with sessions lasting 30 minutes, using a headset developed with a VR company for comfort. Individual skull correction is derived from a T1 MRI using deep neural networks to extract a geometric skull model, motivated in part by evidence, including recent work from Dr. Di Ianni, that existing simulation tools such as k-Plan and BabelBrain diverge substantially from one another and within patients.[13,14] Machine-vision segmentation of brain regions then yields voxel-wise estimates of pressure, intensity and heating.

During stimulation the system displays estimated delivered energy against the clinician's plan and will warn or shut off if the value drifts out of range, or if the patient displaces the helmet. A post-session toolbox analyzes delivered energy within and across sessions against safety guidelines and allows cross-patient comparison. In a PD trial now heading to the FDA, energy delivered to the basal ganglia predicts symptom reduction and a comparable relationship was seen in the anxiety cohort. Parameters are entered through a simplified interface built around ITRUSST-style reporting so that a non-expert can deploy the system and later report the parameters used.

Amygdala neuromodulation for anxiety using the Lotus system. This study was designed to replicate earlier open-label work targeting the right amygdala with the BrainSonix device.[15] The prior study delivered one session weekly for 8 weeks, whereas this study compressed treatment to 10 sessions over two weeks at the clinics' request, with comparable power levels but added individualized in-situ estimates. Most patients showed a ≥50% reduction on the Beck Anxiety Inventory, sustained at 1 month after the final session, with a responder rate of 86% and a mean change score of ~18. Given a typical placebo expectation effect of 30–50% in anxiety and no placebo control in this study, the effect could not be clearly distinguished from placebo. He noted that anxiety typically returns to baseline by one month under placebo conditions, and these patients had not. There were no safety issues during the trial.

Two new transducers are in development, one defocusing and one using a tACS-style ramp-up protocol to eliminate the audible click. He noted that showing patients a brain image on screen increases the placebo effect, to the extent that the team now turns the brain image away during sessions. Outside a trial context, this same effect may be clinically useful. In parallel meditation work, patients are deliberately given the click to practice with at home.

Retrospective analysis revealed that patients with larger effects received more energy on target. In patients with smaller effects, side lobes were frequently observed just outside the target, potentially modulating adjacent tissue. The angle of entry also appeared important, with near-orthogonal incidence preferable.

Session 1 discussion moderated by Rees Cosgrove, with panelists James Mahoney, Bomin Sun, Tommaso Di Ianni, Pierre Mourad, and Jay Sanguinetti.

Q. How do we measure progress since 2024?

- Conference attendance is up, addiction trials registered have grown from roughly 2 to at least 20, ARPA-H was willing to contemplate $100 million for a single device program, low-intensity neuromodulation has advanced markedly, and the field now has room for serendipitous therapeutic discovery by applying a familiar tool and finding it does something entirely unanticipated.
- Expansion continues across sites, devices, and targets internationally, with the prospect of extending to other behavioural addictions (e.g. gambling, food, sexual behaviours). This shift carries significant importance for a stigmatized and marginalized population.
- Historically, neurosurgeons have not always viewed psychiatric disease as disease warranting surgical intervention, but the suffering of severely ill psychiatric patients can be immense, and many such cases are effectively terminal.
- The broader shift is from location to circuits: understand the circuit, understand the nodes, and modulate one node.

Q. How specific is nucleus accumbens targeting?

- In the DBS experience, a 2 mm shift along the anterior-posterior axis produces different effects, particularly relative to the anterior commissure.
- The RNI approach uses the Insightec device with an approximately 5 × 5 × 7 mm treatment box, MR-guided and adjustable intra-procedurally, bilateral, anterior to the anterior commissure, effectively the VC/VS as understood in the DBS literature
- The same target does not mean the same effect. DBS, LIFU and lesioning at one target may do very different things.

Q. Are we inhibiting or exciting, does it behave differently in grey versus white matter, and does location matter?

- Dr. Di Ianni's data shows that the inhibition of blood flow appeared to reach a point of non-linearity and then hold, reminiscent of some but not all forms of DBS.
- The answer depends on pulsing, pulse sequence, and neuron type, invoking mechanical force across cell geometry.
- Sanguinetti notes that with their parameters, and similarly in Taylor Kuhn's work, perfusion increases in the amygdala target while BOLD decreases, suggesting supporting structures around the neuron are also changing. Large reductions in inflammatory markers and glial activation in target regions were observed their PD and AD trials.
- Some groups are moving away from the excitatory/inhibitory framework altogether toward network disruption. For instance, at the level of a symptom such as worry, an amygdala-centred loop can be disrupted by either an excitatory or inhibitory intervention, and what matters clinically is the loop, not its sign. This reframing is motivating efforts to pair FUS with psychotherapy or meditation training as a different vector into

the same network.

- The Insightec workflow allows the target can be refined progressively during the procedure using thermometry and behavioural readouts, in the manner of essential tremor ablation. With smaller devices, we consider a nominal target, but in reality, we are targeting a much larger region of the brain, and a closed-loop readout that permits progressive target refinement is what will increase therapeutic efficacy.

Q. How do we establish ground truth for energy delivery, and what is the right readout?

- One approach involves acquiring human skulls, obtaining CTs, and measuring in an Onda AIMS tank, with the caveat that rehydrating a dry skull brings another challenge. MR thermography in-scanner has not proven sensitive enough outside 7T or animal work.
- With adequate closed-loop adjustment, precise ground truth becomes somewhat secondary for targeting purposes. What remains critical is thermal modeling to avoid skull overheating, an area where models also diverge widely and no agreed measurement solution currently exists.
- Other ground-truth strategies include sonicating at or near the tips of implanted DBS or epilepsy monitoring electrodes, or the PD paradigm in which a transient LIFU effect is followed by a lesion at the same spot, so the anatomy is subsequently visible.
- These are precisely the questions that made phase one of the APRA-H program so expensive.

Q. What is underlying mechanism of symptom response in Dr. Sun's patients with Alzheimer's disease?

- Dr. Sun postulated that the effect is certainly not attributable to the PTT target, with cortical and subcortical exposure the more likely mechanism given the distribution of amyloid and tau.
- Dr. McDannold raised the possibility that high energies may be affecting skull bone marrow, given known links between skull marrow and the immune response[16,17], raising the possibility of an immune-mediated effect in AD.
- A parallel was drawn with transcranial pulse stimulation, another wide-field rather than focal ultrasonic technique. Short pulses moved widely across the cortex applied in AD on the hypothesis of disrupting amyloid plaque.[18,19]
- The evidence points away from a direct neuronal circuit effect and toward something at the level of skull, meninges, endothelium, astrocytes and microglia, which would be consistent with emerging preclinical findings that the majority of the effect of non-ablative LIFU is non-neuronal.
- It appears to be a diffuse, lower-intensity FUS to a larger part of the brain with no lesion. If the results are replicated, the real value of the phenomenon may be that it eventually reveals a novel biomarker and mechanism in AD beyond amyloid-based therapeutics.[20]

Q. Do we need to understand mechanism before proceeding?

- Anesthesia was used for decades without a mechanistic explanation. The operative question is whether real results are being obtained that help patients.
- Non-specific effects extend beyond placebo. Activation elsewhere in the brain not elicited by LIFU at the target itself may nonetheless be elicited by the procedure, and control conditions must be designed accordingly. The field would benefit from more dedicated reporting of null results.
- Dr. Mayberg introduced the notion of "purposeful plasticity". If an intervention opens a window, the patient must then use it, as in stroke rehabilitation, where the capacity must be restored and then trained.

Session 2: Mechanisms of FUS Neuromodulation

Discussion moderated by Noah Philip

Keith Murphy, PhD (co-founder and CTO, Attune Neurosciences) presented on *"Focused ultrasound wearables for rapid treatment exploration".*

Preclinical FUS neuromodulation. His work uses a system combining viral labelling of deep brain areas, implanted optical fibres for recording, and a simple focused transducer, now commercially available through Brainbox.

Using PET imaging, glucose uptake at the target decreased across hemispheres. Notably, he never observed an *increase* in glucose uptake, even when cell signalling indicated increased activity, suggesting the measured effect may not be a straightforward index of neural activity.

With sufficient stimulation, the group observed deep brain cooling, attributed to vascular-CSF interplay permitting slow fluid exchange, accompanied by measured vasoconstriction. This effect was blocked by ibuprofen, implying cyclo-oxygenase dependence, and could be abolished without abolishing the underlying neural activity, dissociating the two processes.

Analysis of the Allen Brain Atlas for genes plausibly relevant to ultrasound neuromodulation showed cortex and thalamus to be profoundly different, raising the possibility that what ultrasound does in one region has little to do with what it does in another.[21,22] The conclusion offered to the field: ask which mechanism, short-term or long-term, and in the interim anchor on a set of clinical treatment parameters the community can agrees upon.

Wearable devices for FUS neuromodulation. The design goal is rapid, reliable placement without heavy operator requirements, and comfort sufficient for long-duration use. The latter matters because the largest clinical effects may require dosing for hours or possibly days. The ATTN-201 uses two bilateral 64-element arrays creating a crossed focus deep in the brain, with a pressure distribution he described as peanut-shaped depending on steering.

Registration is performed using the LiDAR sensor built into an iPad or iPhone, which detects the participant's face and the device simultaneously. Carrying that coordinate system into MRI space yields thousands of fiducials rather than the usual three or four and the process can be completed by a patient remotely. Imaging through the same low-frequency elements produces a signal that shifts dramatically as the device moves relative to the skull. Moving the device across many LIDAR-known positions while capturing these crude signals builds a lookup table from which position can be derived retrospectively, or from which device movement can be detected and the system shuts off. In tank conditions, the method interpolated device position to approximately 0.4 mm, with near-maximal accuracy from about five pings, fast enough to run between pulses.

Simulations do not match reality uniformly across steering positions, and the mismatch varies by position. Rather than characterizing ~400 points per transducer, the space can be sub-sampled to about 20 points, with per-array calibration taking roughly 15 minutes using a robot, substantially faster than acoustic holography. The method was validated on a hemispheric array in collaboration with Charles Caskey.

His group mounted 10 temporal skull fragments with transducers and compared against participants' actual skull thicknesses and incidence angles. Optimizing the attenuation coefficient for accuracy yielded an alpha of approximately 15, after which steering across many points and skulls could be bounded such that exposures remain within FDA and ITRUSST safe zones with ≥97% confidence.[9,13]

Motivated by the long-standing question of why motor cortex outperforms adjacent sensory cortex for pain, the group compared CM versus VPL thalamus focused ultrasound neuromodulation and an unfocused sham. 30 participants received all three conditions with 7-day gaps between sessions. Near-field sensation did not differ across conditions. Within-session pain change did not differ significantly between the three conditions. The next day, however, the effects were substantial. CM was clearly superior to VPL. Appendicular nociceptive pain responded most strongly at day one. Within that subgroup, CM produced a 35–40% reduction lasting 3 days. In participants with pain duration under 25 years, pain levels did not return to baseline.

Precision functional mapping showed enhancement of the somato-cognitive action network tracking inversely with pain across multiple individuals, alongside a reduction in default mode network activity. A preliminary responder biomarker emerged as reduced delta power after CM stimulation relative to unfocused sham, which may relate to CSF dynamics or slow-wave sleep. ARPA-H awarded the group $8.3 million to examine deep biomarkers of these outcomes, using Bayesian optimization across seven brain areas.

Robert Chen, MD presented on *"Mechanisms of human ultrasound neuromodulation: neurophysiological insights."* Dr. Chen (University of Toronto, Krembil Research Institute) presented results from several clinical studies.

Theta-burst TUS induces plasticity. An 80-second train of theta-burst patterned TUS (tbTUS; 5 Hz bursts) applied to the motor cortex increases corticospinal excitability, measured by TMS, at 5 and 30 minutes. A duration- and duty-cycle-matched TUS protocol produced no effect, nor did sham stimulation. The effect was present in 14 of 15 subjects.[23]

Pharmacological dissection. 14 healthy subjects completed 5 sessions each, taking one drug per session in random order, double-blinded via a compounding pharmacy: carbamazepine (sodium channel blocker), nimodipine (calcium channel blocker), lorazepam (GABA-A positive modulator), dextromethorphan (NMDA receptor antagonist), and placebo. Under placebo, an expected increase in excitability at 5 and 30 minutes was observed. Lorazepam

produced a slight increase at 5 minutes that was not sustained by 30 minutes. Carbamazepine, nimodipine and dextromethorphan each abolished the plasticity effect.[24] The NMDA, calcium-channel and GABAergic results are consistent with an LTP-like mechanism. Sodium-channel and calcium-channel results are consistent with direct activation of mechanosensitive ion channels.

Metaplasticity and depotentiation. 15 healthy subjects completed four sessions, combining tbTUS with sub-threshold continuous theta-burst TMS (cTBS-150). tbTUS alone increased excitability at 5 and 30 minutes and cTBS-150 alone produced no effect as expected. When cTBS-150 was followed by tbTUS, the magnitude of plasticity was unchanged, but its duration was prolonged suggestive of a homeostatic metaplasticity effect. When the order was reversed, tbTUS followed by cTBS-150, the tbTUS effect was abolished, suggestive of depotentiation.

Intracranial recording of deep targets. In 10 patients with GPi DBS using a sensing-enabled device that allows wireless local field potential recording, tbTUS was compared to a 10 Hz protocol (previously shown to be inhibitory in the motor cortex), an active sham (occipital cortex) and a passive sham. tbTUS increased theta power in the GPi shortly after stimulation. The 10 Hz protocol increased beta power for up to 40 minutes. Neither sham condition produced a significant change. Another study recorded from STN in 17 patients while sonicating GPi, motor cortex or occipital cortex. GPi sonication increased beta power in STN. Motor cortex sonication increased theta power and reduced beta. Occipital sonication produced no significant change. UPDRS scores showed slight improvement in the motor cortex group, with a correlation between UPDRS change and beta power change. This work was recently published.[25,26]

Sonication demonstrably alters basal ganglia oscillations in humans in a protocol-dependent manner with plasticity effects consistent with LTP-like mechanisms and a plausible clinical correlate in beta power.

Elisa Konofagou, PhD (Columbia University) presented on *"Mapping mechanical, thermal and hemodynamic responses during FUS neuromodulation"*.

Mechanical and thermal mechanisms can operate simultaneously during LIFU, with cavitation a third possible mechanism, and all may engage tissue concurrently. Dr. Konofagou's group has spent a decade bringing ultrasound imaging to bear alongside MRI, exploiting its high temporal resolution and whole-brain coverage.

Using elasticity imaging in preclinical studies, micron-scale displacements were measured in milliseconds, capturing both the push of the ultrasound and the subsequent relaxation. The percentage increase in CBV correlated with brain displacement, and the EMG amplitude of the evoked motor response correlated with displacement as well. Both left and right hemispheres illuminate on CBV imaging, with the sonicated side showing a stronger response. A pattern also observed in non-human primates. At MI ~1.55, responses were localized to the retrosplenial and prefrontal cortex, whereas increasing to MI 2.2 (above the diagnostic limit) engaged the entire brain. The key point was not simply that a local effect gets stronger with increased pressure, but the whole brain becomes engaged at higher pressures.

Combining MRI, CT, MR angiography and ultrasound in non-human primate studies[14], CBV responses were mapped around a subcortical focus with cortical regions following suit. Duty cycle emerged as a critical variable: 2% versus 6% produced different effects, and increasing duty cycle increased connectivity, which is key to engaging thalamocortical coupling. Increasing MI from 1.9 to 2.5 engaged basal ganglia and diagonal septum, with more modest effects in ACC, lateral prefrontal cortex and hypothalamus, the deepest structure requiring the highest MI to engage. With longer duration, an entirely off-focus region, the posterior medial cortex was activated, suggesting a network-level rather than a purely local effect. Measurements were highly repeatable across sessions.

Using a thermocouple, temperature rise remained under 0.2°C at lower pressures but increased ~2°C when pressure was doubled. Comparing FUS against laser stimulation (which is purely thermal), the highest pressure tested 850 kPa and the laser both decreased heart rate, whereas lower pressures increased it, indicating that below half a degree of temperature change, the effect is primarily mechanical, while at higher pressures the thermal component dominates and converges with the effects of the laser. Breathing rate increased across the pressure range.

Her group also turned to the peripheral nerve modulation to test whether the same mechanisms applied outside the brain using concurrent stimulation and imaging. Cavitation showed no correlation with nerve activation at matched temperatures, whereas nerve displacement did correlate with EMG response. Off-nerve displacement produced no leg activation, suggesting that displacement not incidental thermal or cavitation effects drives the response.

Applied to pain models, neuropathic pain suppression approached, but did not reach the pain-free baseline, though it outperformed ibuprofen and gabapentin comparators. Nociceptive pain suppression came very close to the pain-free baseline. An anti-inflammatory component was also identified.

In carpal tunnel syndrome, at pressures comparable to those used in brain studies, on-nerve theta-burst sonication suppressed the somatosensory evoked potential on EEG and reduced pain sensation, while off-nerve sonication produced no suppression or occasionally increased pain sensation. Sham pulses were delivered simultaneously so that patients could not distinguish conditions.

Wynn Legon, PhD presented on *"Human FUS neuromodulation: toward targeted clinical therapies in psychiatry."* Dr. Legon (Fralin Biomedical Research Institute, Virginia Tech) presented two anxiety-relevant targets for FUS neuromodulation.

Target selection was grounded in meta-analytic convergence. A 2015 meta-analysis identified zones implicated across multiple psychiatric conditions converging on the aMCC and bilateral AI, later referenced as a possible convergence zone for neuromodulation, with a separate anxiety-specific meta-analysis converging on the same two regions.[27]

Healthy participants with characterized state and trait anxiety received LIFU to aMCC, AI, or sham, followed by the No–Predictable–Unpredictable threat task, in which threat of shock is delivered under no-threat, predictable and unpredictable conditions, with an auditory probe of system state.[28] Under no-threat and predictable-threat conditions, anxiety ratings did not differ across LIFU conditions. Differentiation emerged specifically under cued and unpredictable threat. Decomposed into an anxiety-potentiated response (APR) and a fear-potentiated response (FPR), LIFU to the anterior insula reduced both APR and FPR, while LIFU to aMCC reduced only FPR. This dissociation was predicted given that both regions are implicated in anxiety. Across 40 subjects, a 50% response rate was observed, with ongoing work to characterize responders versus non-responders. EMG startle, electrodermal response, heart rate, and EEG were measured to pair bodily responses with brain effects. Differential effects emerged depending on which metric was assessed. EMG correlated with EEG but not with electrodermal response, indicating that effects were selective to target and measure rather than reflecting a global effect.

12 auditory startle stimuli were delivered before and after intervention, with responses normalized to the first trial. Early slope was defined as trials 2–6 and late slope as trials 7–12. State and trait anxiety correlated positively with these slopes, consistent with the hypothesis that anxious individuals fail to habituate. LIFU to aMCC normalized the early slope (the immediate reaction to novel stimuli) accelerating habituation relative to sham, with no effect observed on the late slope.

Clinical trials are now underway. The group is also investigating dosing strategies inspired by the accelerated TMS literature, delivering substantial energy in a single sitting while spacing sessions to exploit plasticity mechanisms. In an ongoing chronic pain trial using a one-day accelerated protocol, no effect was observed on day one, but clinically meaningful differences versus sham emerged and persisted through 3 weeks across 21 subjects.[29,30] Resting-state changes in pain networks at 3 weeks correlated with the observed clinical effects. To address beam shaping cost-effectively, single-element handheld devices are paired with holographic lenses. Without a lens, the device effectively produces a broad sham and with a lens attached the beam can be shaped to target. This approach is used across the group's ongoing trials.

Jan Kubanek, PhD presented on *"Known mechanisms of ultrasonic neuromodulation."* Dr. Kubanek is from Washington University and is co-founder of SPIRE, which is currently running a multi-site trial for treatment-resistant depression.

Ultrasound targeting the thalamus in essential tremor suppresses tremor within seconds of low-intensity sonication, non-destructively. This has now been replicated by several groups.[31–33] Given early concerns about auditory artifacts and generic confounds, this body of work provides the convincing evidence that a deep target can genuinely be modulated, at times with durable effects.

Four biophysical mechanisms of ultrasonic neuromodulation were rendered in a space defined by two parameters: pulse-average intensity (I) and carrier frequency (f). This rendering separates cleanly and resolves an apparent paradox in the literature where one set of studies reports neuromodulatory effects increasing with frequency and another reports the opposite. Plotted in this space, the two camps fall into different mechanistic regimes, so both may be correct while harnessing entirely different mechanisms. At the frequencies that penetrate the human skull, mechanical effects predominate.

Cycle-by-cycle vibrations may expand the leaflets of the lipid bilayer, producing cycle-by-cycle capacitance changes, transmembrane currents, and integration to spiking threshold—a model with evidence both for and against it. Effects on mechanosensitive ion channels are better established,[34,35] including careful pharmacological work showing ultrasound mechanically pushing on channels to produce calcium influx, which in turn amplifies the responses of other channel populations.[36]

Effects increase with intensity, as expected, but also with burst duration (the length of the delivered tone) which is less obvious and implies a cumulative underlying process. The two variables appear to interact multiplicatively. Clinically, sonication of the subcallosal cingulate on day zero produces consequences that unfold over several days and potentially weeks, a finding his group has replicated in a crossover trial.[37]

Ultrasound can directly modulate synaptic plasticity and alter synaptic strength.[38] He proposed that thinking of neural networks as dynamical systems may better explain durability. A perturbation can move the system to a different stable state within an attractor landscape. It need not be a change in the hardware; a change in the software suffices, provided it is stable. This framing may help reconcile the observation that neuroplastic effects typically last tens of minutes to hours while clinical effects last days to weeks.

Dr. Kubanek argues that the overarching question 'what is the mechanism' is wrong. The right question is 'what are the *mechanisms*?' since they depend on the parameters used, which is an unsatisfying conclusion, because the hope had been to understand mechanism first and then optimize parameters from it. The relationship is circular and we must accept that as a field.

Session 2

Discussion moderated by Noah Philip with panelists Keith Murphy, Robert Chen, Elisa Konofagou, Wynn Legon, and Jan Kubanek.

Q. What advice would you give someone designing their next FUS trial, to embed mechanistic inquiry?

- Add regulatory and reimbursement constraints to the parameter space. Constrained by what the skull transmits and what will plausibly reach patients, the space collapses from roughly five dimensions to two, which is tractable. We need to think about attractor states in reimbursement.
- Start from a biomarker that can already be measured (e.g. tremor, beta oscillations), because that makes parameter adjustment toward a clinical target far easier.
- Plan it, monitor it, then assess it. Working closely technical personnel and understanding every step matters. The parametric space is vast but is narrowing and knowing it matters for safety as much as efficacy.
- Do not prioritize mechanism until there is a minimum viable product: a result compelling enough that observers say this technology will change the world, which was argued is what unlocks funding for mechanistic research.
- Historically, most LIFU work was mechanistic. As it moved into the clinical space and appeared to work, mechanism was left behind. No established dose-response curves exist for LIFU in humans. Nearly everyone in the field is using a particular energy, pulsed in a particular way, derived from early preclinical work, but whether that has actually translated is unclear.
- Team up with a group that knows the outcome measure extremely well, take parameters from the literature, and test whether a signal they know well changes.
- One lab is attempting to aggregate published parameters and effects across studies. The relationship is currently a flat line.
- Mechanism is the bridge between a beam and a behaviour, but that the field has a circular logic problem: an observed effect gets attributed to what was done, when it may reflect something else entirely.

Q. What do your mechanistic findings imply for FDA safety standards, specifically mechanical index?

- MI 1.9 is a diagnostic imaging limit. Below MI 3, there is broad agreement that it can be safe. Duty cycle and pulse duration matter as much as MI. It matters to know the parametric space for efficacy and safety. The field may be too conservative, and what's currently observed may only be the tip of the iceberg.
- Operating between 1.9 and 3 implies moving into a cavitation-based mechanism which raises the question: is cavitation safe? Clinical BBB opening is performed with cavitating bubbles routinely and safely. Cavitation within specific limits can be safe, and it occurs in diagnostic imaging as well.
- Rather than repeatedly relitigating the 1.9 boundary, the field could establish a safe range and find new ways to work within it. For instance, Ben Hayes' work showed that cortical FUS produced no effect on fMRI,[39] but the target lit up when paired with a small amount of cutaneous electrical stimulation. The alternative, simply dialing up intensity until something happens, is always available but not always wise.
- Effectiveness and safety are usually discussed separately, but the FDA takes a holistic benefit-risk view. A procedure that meaningfully reduces the risk of suicide may justify a small trade-off in safety.
- If the work can be made to function at NSR levels, the field has a technology that is extremely scalable, deliverable outside academic centres and potentially at home, which is what the field ultimately needs.

Q. Isn't what we call mechanism really a readout? Once you have a reliable readout you can test parameters, and a reliable readout can scale. Does a scalable readout need to be a brain readout?

- Dr. Legon described within-patient measurements tracking where the bolus of energy sits relative to meta-analytic ROIs of the aMCC, which can be inflated or deflated. The single strongest predictor of effect was whether the energy went where it was intended to go, independent of a dose-response relationship. He acknowledged the anatomical problem directly: the ventral AI is small and irregularly shaped, the dorsal AI and aMCC are considerably larger, making precise targeting difficult given the comparatively small volume of energy delivered. Some groups are now moving the focus within the target volume itself.
- Vascular anatomy remains an underappreciated determinant. Aligning with a large cerebral artery produces something completely different from targeting basal ganglia, thalamus, hypothalamus or amygdala directly. Because the effect is mechanical and thermal, and the thermal component redistributes perfusion, knowing the structures, networks and vessels involved is essential.
- There is a structural problem with biomarker-guided closed loops. When a biomarker appears coupled to the effect, the train of effect is already underway, so one cannot observe its absence and switch, having already delivered the exposure. A biomarker that is detached from the effect, or obtainable at very low dose, might exist, but might not.
- Essential tremor and PD have usable biomarkers, but not every patient has an electrode in the brain. EEG is a promising scalable option, though it still requires validation.
- Psychiatric questionnaires are noisy, but the intervention can be repeated several times and the noise averages out. Before converging on the subcallosal cingulate, Dr. Kubanek's group tiled the cingulate into subregions and probed individual tar-

gets double-blinded while collecting depression scores, obtaining a usable average readout with relatively small error bars, which pointed to the intersection of pathways predicted by prior anatomical work.

- Whatever the state of biomarkers across psychiatry, the field does have a very dependable state where people are very definitively ill, and we can look for change within that.

Q. Could personality and phenomenology be underused predictors?

- A simple, inexpensive five-factor personality measurement was proposed, noting that agreeableness correlates with placebo response, while neuroticism and extraversion predict responsiveness to treatment generally, with identifiable neurocircuitry behind both.
- No patient-level prediction emerges from the five-factor model without large samples.
- Positive hits in DBS, where high neuroticism, anhedonic fatigue and psychic pain load onto common circuits, allowing researchers to backwards from brain to personality.
- It is important to consider whether such selection constitutes cherry-picking. Trials should indeed select to avoid wasting patients' time, but a recurring psychiatric problem has been that that removing the layer a trial was designed for often reveals another.

Q. Do we need to know how much tissue is engaged, and when?

- Biomarker-guided parameter optimization is a road already travelled in clinical neuroscience with limited success, and that the field still needs to know what tissue is engaged, how much, and what parameters affect what, including whether engagement at 5 minutes differs from engagement at 30 minutes, given that published protocols range across that interval.
- The comparator is a drug that soaks the entire body with unknown bioavailability and receptor density, raising the question of whether MR-ARFI validation is really needed in every patient.
- With TMS you have a twitch, with electrical stimulation you can measure it superficially with EEG, with focused ultrasound there is nothing visible to believe in. Dose may be the Achilles heel. Clinicians want to know the dose, as they do with a drug, and something simpler than MR-ARFI that still reports how much energy reached the brain, coupled to a readout, would go a long way.

Session 3: FUS Clinical Results and Safety

Discussion moderated by Nir Lipsman and Benjamin Davidson

Ali Rezai, MD presented on *"Focused ultrasound neuromodulation for addiction."* Dr. Rezai is Executive Chair of the WVU Rockefeller Neuroscience Institute.

Substance use disorder affects 48 million people in the US, yet only 19% are treated annually. Despite over 15,000 treatment centres nationwide, there are over 80,000 overdose deaths annually with the annual cost exceeds $700,000 per patient. Between 40–60% of patients relapse after a 28-day residential program, and the average person relapses more than five times. Addiction is a chronic brain disorder and network dysfunction requiring management analogous to diabetes, hypertension or asthma, conditions with comparable relapse rates.

A NIH/NIDA-sponsored open-label DBS study (2018–2023) targeted bilateral nucleus accumbens and ventral anterior internal capsule in patients with end-stage opioid use disorder and multiple overdoses. Intraoperative stimulation produced acute reductions in craving and anxiety in all participants, and two achieved complete abstinence with increased frontal glucose metabolism on FDG-PET. Two participants were lost, however, not to non-response but to feasibility: protocol fatigue, non-compliance, and the psychosocial instability of the population. The conclusion was that DBS is not a feasible option for this group, and that the simplest possible solution was required.

The FUS trial enrolled 46 patients across 49 procedures, all with severe treatment-resistant substance use disorder (opioids, stimulants, cocaine, methamphetamine, alcohol and others), all having failed multiple inpatient, residential and outpatient programs and medications, most with multiple overdoses. 38 procedures used the Insightec ExAblate (2021–2026) across open-label dose escalation, open-label short- and long-term studies, and a sham-controlled RCT. 11 procedures used NaviFUS (2025–2026) in an open-label dose escalation study.

Treatment consists of a single session targeting the bilateral NAc lasting 20–30 minutes. The Insightec procedure is performed within the MRI using a stereotactic frame as a 1.5-hour outpatient procedure. NaviFUS uses image-guided navigation and does not require a headframe. Both incorporate live monitoring of vital signs alongside clinical, neurological, and behavioural status, including anxiety, fear, and craving.

The target was derived from the OCD DBS target developed with Benjamin Greenberg, Wayne Goodman and Steven Rasmussen, modified to account for the ultrasound volume of tissue activation and refined further with tractography.[40] Approximately half the treatment volume lies in the ventral anterior internal capsule and half in the accumbens core not shell, roughly 4–5 mm anterior to the anterior commissure, targeting GABAergic medium spiny neurons. Dr. Rezai emphasized this as a dual grey- and white-matter target.

The treatment involved selective, personalized activation of the pathological craving network through cue presentation before and during treatment, then neuromodulation. Intraprocedural craving and behavioural ratings after each five-minute sonication block inform dose and location, and dosing continues until craving reduction is observed. Dr. Rezai stated that without this activation step, the best outcome is unlikely to be achieved, and the effect appears to be cumulative across sonication blocks.

Parameters for the Insightec system include: 220 kHz, power 80–100 W, 100 ms pulse pattern, and 27% duty cycle distributed across 8 sub-targets (3.3% per spot), delivered up to 30 minutes in six 5-minute blocks, with real-time monitoring of acoustic activity at the focal spot. A single treatment was 20–30 minutes in total.

Published open-label results showed a 91% reduction in cue-induced opioid craving, both immediate and sustained, and 92% negative urine toxicology over 90 days. 5 of 8 participants achieved complete abstinence, with the remaining 3 reporting only a single use of an illicit substance.[41] Craving reductions were comparable for methamphetamine and cocaine. Resting-state fMRI showed decreased connectivity from NAc to reward and cognitive regions from baseline to 90 days.

Long-term craving data extend to 365 days with attrition (n=14 at baseline, n=3 at day 365). Dr. Rezai described being surprised that a 20-minute procedure produced sustained reduction in drug use over 90 days and, in some patients, one to two years. Additional fMRI and PET analyses show frontal executive network changes and dorsal anterior cingulate changes after a single 20-minute treatment.

In a small series, a single 20-minute treatment produced approximately 90% reduction in food craving and over 95% reduction in binge eating episodes. Dr. Rezai framed the effect as pan-addiction. Regardless of whether the addiction involves drugs, alcohol, gambling, or food, the same brain circuitry is implicated.[3,42]

Patients reported difficulty "connecting" to cues that would normally induce craving, reduced thoughts and dreams about drugs or alcohol, reduced anxiety, depression, anhedonia, shame and guilt, improved frustration tolerance, and greater involvement in family, work and education without change in natural pleasures such as food.

A representative case was drawn from the health-record data. A 40-year-old man with a 17-year history of severe opioid use disorder beginning after a knee injury, with two prior overdoses, a longest prior sobriety of 6–9 months, and 17 ED visits plus 12 rehabilitation encounters before treatment. After FUS in 2024, there were zero ED visits and zero rehabilitation encounters.

Dr Rezai described a recent unintended adverse event which occurred during a FUS-neuromodaultion treatment–a case that has since been published.[43] The event occurred on February 4, 2025, with the Insightec device, during the crossover phase of the RCT as a participant moved from sham to active treatment. The patient became unarousable following the third sonication and the procedure was aborted. MR thermometry showed no temperature increase at the target. MRI revealed microhemorrhages. The patient was hospitalized, recovered consciousness over 24–48 hours, and was discharged to a cognitive recovery centre. As of May 2026, the patient is ambulatory, independent for activities of daily living, with intermittent confusion and episodes of incontinence, engaged in group activities, denying drug cravings, and close to baseline behavioural status.

As a result of this event, the study was paused and a technical case review was conducted with Insightec, the FDA, and internal and external consultants which ran for approximately 9 months. The acoustic feedback signature in this patient was found to be unique compared with the previous 30 patients treated using identical parameters. The mechanism was presumed to relate to cavitation.

Learning from this case, Dr Rezai described that group and has introduced device-level mitigation strategies including exclusive use of Modulate Power mode in which the system d**e**livers the prescribed power but adaptively reduces it in real time based on live acoustic feedback so as not to exceed the cavitation safety threshold. New cavitation safety halt rules were also implemented.

Clinical procedure mitigations included a baseline venous blood gas on the morning of the procedure, real-time pCO_2 monitoring via nasal cannula, real-time respiratory rate monitoring, additional checks for potential sources of gas bubbles including IV and transducer lines, and T2*-GRE MRI monitoring between each sonication block.

Eligibility changes added requirements around serum bicarbonate, venous CO_2, respiratory rate and oxygen saturation, excluding HCO_3 > 28 mEq/L, with COPD, pulmonary fibrosis and uncontrolled asthma added to exclusions on the grounds that they affect CO_2 monitoring accuracy and patient safety.

The FDA subsequently cleared the trial to restart, and 23 patients have since been treated with no safety issues. Safety analyses across sites now cover 38 patients and 273 sonications at RNI, plus an additional Korean site operating under the new safety limits. Aggregate safety across the program include 37 of 38 Insightec procedures with no hemorrhage, swelling, or imaging findings and all 11 NaviFUS procedures with none. Sustained long-term safety show no neurological changes, improvements in anxiety and mood, no worsening on the Snaith-Hamilton Pleasure Scale, and improvements in Neuro-QoL subscales for satisfaction with and ability to participate in social roles and activities, along with gains in positive affect and well-being.

What comes after treatment. The plasticity window opened by FUS is insufficient on its own for individuals who have lived with addiction for decades, similar to teaching someone to walk again after a stroke. Concurrent behavioural therapy, medication, social support, employment, housing, food support, and childcare, along with reintegration into community, all are required, since these individuals have been disconnected from their families and lives for decades. Ultrasound is one part of a broader ecosystem of care.

Noah Philip, MD (Brown University, VA Providence) presented on *"Low-intensity FUS to the amygdala for depression and anxiety."*

The amygdala is not a traditional depression or DBS target.[44,45] It was chosen deliberately because it is implicated in essentially every psychiatric disorder, substance use, psychosis, depression, anxiety, PTSD, so that a demonstration of modulation would be broadly useful.

The BrainSonix system was chosen for MR compatibility. It is a single-element transducer with a fixed 65 mm focal length, focal width ~4 mm, and non-zero energy length of ~30 mm, within which the biological activity remains unknown. All procedures were performed inside the scanner and every participant received a CT. Acoustic modeling was not ready in 2019 when the trial was initiated and was therefore applied post-hoc. It will be prospective in the next study.

Participants were randomized to right amygdala (target) or contralateral somatosensory cortex (active control), with assessment immediately, 24 hours and 1 week post-sonication, before crossing to the second target. The active control design tested a precision hypothesis rather than an efficacy hypothesis. The main question was not whether ultrasound outperforms no ultrasound, but whether the intervention is precise.

The first 10 participants were presented, with a second 10 completed and not yet reported. The completion rate was 100%. One participant required extended follow-up under a pre-specified protocol after psychiatric worsening.

Amygdala perfusion changed by approximately 1.3–1.4 z-scores from baseline after amygdala sonication, with no change after control sonication. Perfusion in the adjacent head of the right hippocampus was also unchanged. Individually, 50% of participants showed increases and 50% decreases with the common feature being the magnitude of change rather than its direction. Perfusion in the control region was flat across the study.

Symptoms improved across all participants over the course of the study, a non-specific effect potentially attributed to placebo, study participation, or the small sample size. However, correlations between symptom change and perfusion change appeared only after target sonication, across scales and domains, and never after control sonication. Some degree of amygdala perturbation appeared therapeutic, while too much was associated with worsening, implying a narrow therapeutic window.

In 7 of 10 participants, unprompted, following amygdala sonication, participants described feeling "clear," "light," "calm." This occurred in 0 of 10 after control sonication. The finding independently replicated in the next 10 participants. Dr. Philip noted that these experiences are not captured on a MADRS or HAMD, but they matter enormously at small sample sizes, and the community should be querying and evaluating subjective experiences systematically. Interestingly, participants also reported feeling somewhat off immediately, sleeping poorly that same night, and returning the next morning feeling markedly better.

Group-level ASL showed changes not only at the target but in the contralateral amygdala and ipsilateral rostral anterior cingulate as well. Functional connectivity from the basolateral amygdala was reduced, largely within somatosensory and dorsal attention networks, only after target sonication, mirroring Taylor Kuhn's earlier findings of increased perfusion alongside reduced connectivity. Connectivity changes also correlated with symptom scores. During on-versus-off trials (30 seconds on, 30 seconds off), BOLD changes appeared in ventromedial prefrontal cortex, anterior cingulate, and left insula, indicating an integrated circuit response.

One participant worsened after sonication. No serious adverse events were observed, though substantially more side effects occurred after amygdala sonication than after control sonication. The participant experienced worsening at one week and entered a pre-defined protocol of weekly rating scales and neuroimaging for the following month. His amygdala perfusion showed an enormous spike, taking roughly two weeks to return toward a more normative level, incidentally providing useful test-retest information about the ASL signal itself. Post hoc modeling revealed that this participant's beam morphology was unusual and his skull attenuated less than others, meaning he received a higher dose than anyone else in the study. This finding was the reason his next study will not increase pressure or use an accelerated design.

Dr. Philip concluded that amygdala neuromodulation using focused ultrasound is safe with some degree of psychiatric risk. Adverse events are also evidence of target engagement and that is acceptable. His group's next study is planned as a spaced dose-escalation, sham-controlled design with participants receiving one, two or three sessions per week, or sham, over the course of a month, with extensive imaging to characterize the dose-response relationship.

Greg Fonzo, PhD presented on *"Daily repetitive left amygdala FUS in mood, anxiety and trauma-related disorders."* Dr. Fonzo (Dell Medical School, University of Texas at Austin) presented the published trial in this population.[46]

Mood, anxiety and trauma-related disorders share exaggerated negative emotional reactivity with the amygdala at its centre. A meta-analysis from Amit Etkin's laboratory found abnormal bilateral amygdala activity across psychiatric conditions.[47] The supplementary analyses showed that for non-psychotic disorders with hyperactivation, the abnormality is left-lateralized, which is the rationale for targeting the left amygdala in his study.

Targeting used T1 MRI loaded into the neuronavigation system. The transducer was secured to the left temporal window. Localizer images are then acquired, capturing the transducer's T1-weighted bullseye pattern. The notional hit location was computed assuming a straight line at focal depth with no correction for beam deformation. Displacement from the center of the left amygdala was measured and the transducer adjusted and re-imaged accordingly. The final location was marked on an individualized head model using neuronavigation for treatment sessions conducted outside the scanner.

52 participants were recruited (29 patients, 23 healthy controls). 47 completed both concurrent FUS/fMRI visits (25 patients, 22 controls). 24 of 25 patients initiated daily treatment and 21 completed the 5-days-a-week, 3-week protocol supporting the feasibility of daily delivery where required. Double-blind sonication used visually identical transducer pads, one active and one containing a thin layer of porous foam that blocked transmission. Investigators were blinded to condition. Parameters were 10 Hz PRF, 5% duty cycle, derated I_{SPTA} kept below 720 mW/cm^2 within FDA diagnostic guidelines. The primary outcome was the general distress subscale of the Mood and Anxiety Symptom Questionnaire selected as a transdiagnostic measure of negative affect.

Attenuation was observed across all clinical measures, with moderate-to-large effect sizes and a significant reduction on the primary outcome. Sonication resulted in acute inhibition of left amygdala BOLD signal during stimulation in both patients and controls, using a 30-second-on/30-second-off design. Following a single administration, active versus sham showed attenuated BOLD activation to faces bilaterally in the amygdala, with similar attenuation observed in the anterior cingulate cortex, pointing to a circuit-wide effect rather than purely focal effect. The protocol was well tolerated with no serious adverse events. The most common side effects were decreased concentration, tinnitus, dizziness, lightheadedness, and unusual sensations in the head, face, and body, all mild to moderate in severity and all resolved within or before the following session. Important study limitations include that the treatment phase was open-label, single-arm, and BOLD remains an imperfect index of underlying neuronal function.

Dr. Fonzo discussed next steps as refining the parameter set further before proceeding to a randomized trial, which is where the work is ultimately headed. Priorities include optimizing energy delivery to the target, defining optimal parameters, verifying delivery accuracy, and establishing what the ground truth for that verification should be.

Salvador Guinjoan, MD, PhD presented on the topic *"Low-intensity focused ultrasound modulation of human deep white matter tracts."* Dr. Guinjoan (Texas A&M) presented a neuromodulation approach distinct from work presented thus far by targeting white matter tracts rather than grey matter.

Empirically, every efficacious surgical target for depression targets white matter tracts, connections, not regions. This holds for capsulotomy, ALIC DBS, anterior cingulotomy and subcaudate tractotomy. It also holds for subcallosal cingulate DBS, where Helen Mayberg's group initially targeted Brodmann area 25, but efficacy was subsequently attributed to the underlying white matter and regional connectivity.[44,45]

Substantial in vitro work documents distinctive effects of ultrasound on myelinated axons, and two of the most mechanosensitive ion channels in the CNS, TRAAK and TREK, are concentrated at the nodes of Ranvier.[35] In contrast to grey matter, which is extremely heterogeneous, white matter is close to a crystalloid structure of axons, nodes, and myelin, which he argued offers a simpler substrate for neuromodulation.

Parameters were drawn from the only published human LIFU protocol available at the time of FDA submission, originally developed for motor cortex. The study was crossover, sham-controlled, and conducted in patients with depression, targeting the ALIC. Probabilistic tractography[73] was used on a per-participant basis to connect thalamus with orbitofrontal and anterior cingulate cortices, with the region of highest streamline density between them selected as the target, a location that varies considerably between individuals.

Target engagement was demonstrated by reduced functional connectivity in regions reached by the sonicated tracts and blunting of the autonomic response to the testing condition in the active versus sham condition in the same individuals. Rumination did not change contrary to his hypothesis. On the PANAS, the only change was an increase of one dimension of positive affect.

In a dose-finding study involving 30 healthy participants, the group varied dose by delivering the same parameters either once or three times, separated by a defined interval. Acute effects showed a dose relationship that appeared non-linear. The most consistent effect at the higher dose was decreased connectivity between right frontal and dorsolateral prefrontal cortex and thalamus. There was preliminary evidence of a relationship between individual streamline count and the magnitude of functional disconnection. Over the 30-minute post-stimulation window, the difference between 1 and 3 doses recovered, a time course that parallel Dr. Chen's observations at the motor cortex despite the entirely different target. Simultaneous EEG-fMRI showed a dose relationship in the alpha range, greater for 3 doses than 1, strongest at anterior leads, and significant only during the initial 6 minutes.

In supraventricular tachycardia, cardiologists do not ablate near the atrioventricular node hoping to hit the right spot. They position the electrode, test reversibly, and ablate only once they have documented that they are on the correct spot, achieving success rates above 90%. The same logic was proposed for psychiatry: use LIFU to probe circuits reversibly in individual patients before proceeding to definitive intervention. Dr. Guinjoan proposed the same logic for psychiatry: use LIFU to probe circuits reversibly in individual patients before definitive intervention.

However, an important caveat is that nothing after psychiatric surgery is acute, and since long-term plastic change is what ultimately predicts response, 1-2 sonications are unlikely to predict much on their own. He argued that repeated, chronic LIFU exposure, producing neuroplastic changes more analogous to surgery, is a more realistic path forward. His group is planning to test this directly, comparing two doses in treatment-resistant depression versus healthy controls.

Session 3

Discussion moderated by Nir Lipsman and Benjamin Davidson with panelists Ali Rezai, Noah Philip, Greg Fonzo and Salvador Guinjoan.

Q. What was the experience of the adverse event, and what did the field learn?

- Dr. Lipsman opened by noting that there is no such thing as a procedure with zero risk, thanking Dr. Rezai for speaking candidly and observing how connected the community had been in discussing the case. The question remains on how such experiences should be incorporated into trial design, patient selection, outcome definition, and the management of unexpected events.
- Dr. Rezai was clear that the study was never a non-significant-risk study. The 1.9 MI threshold is used generically by the FDA and IRBs as an NSR marker, but the goal of the study was dose titration, and at lower doses benefit was not seen acutely in these patients. This was framed as a risk-benefit calculation. For cocaine and methamphetamine use disorder, no approved medication exists at all, leaving these patients with few options. Dose escalation whether from medications or devices inevitably will produce greater risk. Dose-finding often requires escalating to a high threshold to identify the upper limit of safety, before subsequently titrating downward.
- Dr. Rezai described the acute event as very challenging for everyone involved. The immediate response was to stop and care for the patient, followed by a systematic comparison of every patient, device and setting variable against the previous case. He characterized the 9 months that followed as making the field far better informed.
- Eyal Zadicario (Insightec) noted there is a category difference between the parameters we transmit (power, duty cycle, frequency), all tightly controlled and known and the parameters at the focal spot through the skull, which are not measured but assumed from a model of skull transmission and tissue behaviour. Drawing on Insightec's lesioning experience across many thousands of patients, very consistent input parameters were shown to produce up to a five-fold difference in tissue response. Rather than assuming a simulated MI or pressure that does not reflect the individual patient, the field should measure the tissue's actual acoustic response directly. In lesioning, that surrogate is thermometry. For neuromodulation in this study, it is acoustic feedback measured in real time at the focal spot, used to modulate power so that transmitted power always aligns with a maximum acoustic feedback setting. He also noted that the acoustic signature in this patient was distinctly different from the others, and that patient selection criteria were subsequently modified as a result.
- Dr. Rezai closed the discussion by noting that the case has been published so that the community can learn from it and that this is not something to hide.

Q. Should acoustic monitoring and adaptive power be used with other devices?

- The answer depends heavily on system configuration. Insightec 220 kHz systems differ from 500 kHz systems. Frequency, duty cycle, timing and pulse intensity all interact with one another.
- Most studies at this meeting used different parameters. The wide variation is not inherently problematic, but there is a clear need for further standardization across the field.

Q. Why do the two amygdala studies differ, and what does that tell us?

- The findings are not, in fact, very different. Both studies showed modulation of insula and anterior cingulate. Both studies saw modulation of the target after sonicating it, local effects, distributed effects, and distributed effects related to symptom outcomes.
- Differences may reflect statistical power (approximately 25 versus 10 participants), patient populations and comorbidity profiles.
- Beyond laterality, Dr. Philip's protocol delivered double the exposure (two 10-minute applications of the same parameter set), so differences may reflect dose or exposure duration rather than side treated.
- On the theme of adverse-event monitoring, it is important to build into protocol design a mechanism to retain and continue studying participants when something unanticipated occurs, where it remains safe to do so, rather than simply excluding or withdrawing them. As dose and intensity continue to be pushed, further unexpected findings should be anticipated and when it occurs, it should be leveraged rather than discarded.

Q. Is the amygdala too heterogeneous a target?

- Dr. Fonzo's answer was no though it remains an unknown. Using his system, the focal width spans several centimetres in the axial dimension. Individual amygdalae differ in shape and size, and the group effect appeared localized to the basolateral portion which he attributed to skull-related beam deformation pulling the focus laterally.
- What the field needs is a tool capable of imaging an individual's amygdala at sufficient resolution to map its subnuclei, allowing the operator to specify which subnucleus to sonicate and then confirm where the beam actually went. This capability does not exist yet.
- A tractography study mapping amygdala subnuclei by connectivity patterns was noted as a potential path forward, one that could allow the target to be reverse-engineered rather than located by trial and error within the amygdala.

Q. Why are the accumbens results so robust, and what do non-responders look like?

- Dr. Rezai reported that craving reduction is robust both immediately and afterward and attributed most failures to psychosocial and environmental factors. For instance, patients returning to homes where drugs remain readily available. He described patients who relapsed reporting that they had not been craving: "I was just sitting at a table, they brought the drugs, and I did it because it was there."
- Dr. Mahoney added that when these patients did use, the episode was isolated, with less reinforcing effect, and rather than following the trajectory of escalating use end-

ing in overdose or emergency care, patients rapidly contacted a peer recovery coach, therapist or the research team. The habit persisted in the absence of the craving that drives it.

- Dr. Rezai noted the driver is removed but the habit remains. PET imaging shows frontal lobe activation similar to effects seen with DBS. He also reports that a small number of patients had personality disorders identified later, which also contributed to non-response.

Q. Which part of the nucleus accumbens was targeted, and can results be obtained below MI 2?

- No lesion is generated. This is neuromodulation so the explicit intent is not to knock out the NAc. The target box is approximately half situated in the ventral ALIC and half in the NAc core.
- Achieving results at lower intensities is under active investigation. Lower levels may be achievable, though this depends on frequency, duration, system and each system differs.

Q. What is the timing and durability of the ASL signal after amygdala neuromodulation?

- Dr. Philip noted in his study, ASL acquisition occurs roughly 25 minutes after the system is turned off, given the sequence of procedures, so it is not an immediate measure of response. Directionality in the ASL literature, particularly where nearby vasculature is engaged, requires careful interpretation. In the participant who worsened, weekly ASL scans showed return toward baseline at approximately two weeks post-treatment. The next study will acquire ASL far more regularly. ASL is promising and underutilized, and likely functions as an acute, subacute and secondary marker of response.

Q. Can subjective reports separate active treatment from placebo?

- Dr. Sanguinetti reported obtaining the same subjective reports across amygdala anxiety studies, consistent enough that his group has built an LLM-based daily diary to capture them and apply micro-phenomenology and offered to share the tool. He asked what the placebo participants say, noting some of his placebo participants specifically report calmness.
- In Dr. Philip's active-control design, the reports occurred in 7/10 participants after target sonication versus 0/10 after control. This result replicated independently in the next 10 participants. There is clear value in including narrative outcome measures from the beginning of studies and to analyze them either qualitatively or with language models.
- Dr. Sanguinetti added that patients with the biggest effects had the most sleep disruption, and the two patients in his series who worsened had the beam falling just outside the amygdala at the highest power in the study, independently replicating Dr. Philip's dose-and-targeting observation.

Session 4: Other Uses of Focused Ultrasound

Discussion moderated by Ali Rezai

The session explored the broader versatility of ultrasound including emerging mechanisms, applications and indications.

Clement Hamani, MD, PhD presented on *"FUS nanodroplet neuromodulation in preclinical models."* Dr. Hamani is the preclinical lead at the Harquail Centre for Neuromodulation at Sunnybrook Research Institute.

Nanodroplets are sub-micron, liquid-filled particles that vaporize into microbubbles on sonication. When loaded with a therapeutic agent, they release it at the sonicated site, enabling focal pharmacology without systemic side effects. His lab studies phenobarbital-loaded nanodroplets in preclinical models. Despite being an older drug, phenobarbital reliably reduces metabolic activity, has a long half-life so the effect persists for hours rather than seconds, offers neuroprotection, and has established precedent in human use for stroke and traumatic brain injury. He described three studies of FUS-triggered phenobarbital release, targeting the motor cortex, amygdala and hippocampus in various preclinical models.

i. Motor cortex. Pentobarbital was released at the motor cortex and locomotion measured as the behavioural readout.48,49 The treatment was safe. No BBB permeability was visible on MRI, no off-target effects, and no systemic organ damage were observed. In all animals, the contralateral paw angle opened, a reliable gait signature of unilateral weakness, and animals shifted to preferring the ipsilateral paw. This proof-of-principle study showed that a behaviour can be modulated with FUS-triggered, focal drug release.

i. Amygdala. This study was motivated by agitation and aggression behaviour observed in AD, for which the amygdala is a key structure.50 Using a resident-intruder paradigm, mice were sonicated with pentobarbital-loaded or empty nanodroplets after aggressive behaviour was established. Female mice showed no aggressive under any condition. Among males, mice receiving pentobarbital showed clear reductions in both the proportion of animals attacking and the number of attacks relative to sham. The sonicated volume was somewhat larger than the amygdala itself.

i. Hippocampus. In a preclinical model of TBI, the fluid percussion injury model, animals were sonicated at the hippocampus underlying the cortical contusion immediately after trauma under three conditions: pentobarbital-loaded nanodroplets, empty nanodroplets, and FUS neuromodulation alone. Cognition was assessed using the novel object recognition, novel object location and the Barnes maze.

Unexpectedly**,** animals receiving empty nanodroplets performed better than those

receiving phenobarbital, suggesting that empty nanodroplets modulate brain tissue independent of any drug release. A further control compared sonication alone against non-sonicated controls and found that sonication alone worsened memory performance. Dr. Hamani interprets these results as suggesting that neuromodulation is doing *something*—a single session produces a measurable behavioural effect nearly 2 weeks later, accompanied by corresponding changes in plasticity measures.[38,51] He offered this as independent, preclinical support for the durable single-session neuromodulation effects reported by the West Virginia group in the clinical trial in addictions.

Dr. Hamani argued for the value of starting with behaviour rather than mechanism in the field. Once the behavioural effect is established, the search of mechanism can follow as he has designed his preclinical studies.

Raag Airan, MD, PhD presented on *"Ultrasound targeted drug delivery and glymphatic modulation."*

Ultrasonic drug uncaging. Ketamine functions simultaneously as an antidepressant, a dissociative anesthetic, an analgesic and a drug of abuse, with each action being a side effect relative to the others, alongside cardiovascular and genitourinary effects. Strong preclinical and clinical evidence attribute these functions to spatially distinct brain regions. If a bolus dose could be delivered to only the region tied to the desired effect, one could have the therapeutic action without the rest.

The approach involves IV infusion of ultrasound-sensitive, drug-loaded particles, followed by an image-guided transcranial FUS procedure that induces drug release from particles circulating in the blood volume of the target tissue without BBB opening.[52] The group began with nanodroplets similar to Dr. Hamani's, then shifted to acoustically activatable liposomes because they are stable under refrigerated storage and require neither fresh preparation and freeze-thaw cycles.

With free ketamine, ultrasound does not change distribution or clearance. Comparable drug reaches medial prefrontal and retrosplenial cortex regardless of the sonication site. With the ultrasound-sensitive vehicle, delivery is confined to the sonicated site while clearance remains unchanged, only the amount delivered to the target differs.

Electrocorticography revealed distinct regional signatures. Sonicating the medial prefrontal cortex produced high-beta to gamma activity, while sonicating the retrosplenial cortex produced potent slow-wave activity shifting to beta.

Interestingly, targeted delivery produced a larger functional effect than dose-matched free ketamine, despite achieving a similar concentration at the target (roughly 1.2X drug at the target while strong suppression elsewhere). The same pattern appeared behaviourally: in the open field test, only animals receiving targeted mPFC delivery spent more time in the centre with no locomotor change, as well as neurochemically: a surge of serotonin in prefrontal cortex only when uncaging occurred there, not with retrosplenial uncaging and not to a similar degree with free ketamine.

In another study, ropivacaine (a sodium channel blocker) loaded into the same vehicle enables a non-invasive, needleless nerve block. Applied to the brain, it produces regional anesthesia. Targeting V1 knocks out visual evoked activity, which does not occur if the target is moved to frontal cortex. Targeting S1 renders the contralateral limb unresponsive to mechanical and thermal stimuli. Dr. Airan described this as a pseudo-lesion, effectively suppressing activity within the ultrasound focus for approximately an hour, long enough to run an assay.

The group has secured funding for a first-in-human trial of targeted ketamine delivery to the dorsal anterior cingulate for chronic pain. He framed a broader vision for targeted neuropharmacology: pharmacologic functional brain mapping as a diagnostic tool, bolus local infusion as a therapeutic one, and a scientific tool to finally understand how ketamine actually works.

Ultrasonic debris clearance. Dr. Airan described this application as arising serendipitously. During a drug delivery experiment, the transducer was accidently left on, revealing a smear of drug distribution around the brain that he had not seen before.

A protocol was subsequently optimized for glymphatic and neuroimmune effects, applied to two preclinical models of hemorrhagic stroke, subarachnoid and intraparenchymal.[53] Three 10-minute applications delivered over 5 days cleared blood cells from the CSF and interstitium to the deep cervical lymph nodes via meningeal lymphatics, shifted microglia from a disease-associated to a homeostatic state, and shifted aquaporin polarization in astrocytes toward the vascular endfeet.[16,17] The protocol produced improved functional recovery and a survival benefit.

The effect was abolished by blocking mechanosensitive channels with a broad-spectrum inhibitor. He noted these channels, while present on neurons, are more consistently and highly expressed across astrocytes, microglia and endothelial cells. Spatial transcriptomic analysis revealed that the principal component was microglial phenotypic change, followed by astrocyte change, rather than synaptic proteins or immediate early genes. Dr. Airan proposed that what appears to be neuromodulation, in his studies and others, may in fact be glial modulation.

IRB approval was recently obtained for a first-in-human trial in mild cognitive impairment and biomarker-positive AD, framed as a tool to control the glymphatic system and neuroinflammation.

Renana Eitan, MD presented on *"FUS in psychiatry: toward personalized, circuit-based interventions."* Dr. Eitan (Jerusalem Mental Health Center, Hebrew University, co-founder and CMO of Nuri Braintech) described her vision for an entirely different application of FUS: prevention in PTSD.

When considering a new technology in psychiatry, the field typically starts with need, then works backward to circuits. Several key questions in the field remain unresolved.

i. Can a single session change behaviour? In PTSD, psychiatry already accepts that a single traumatic event can durably alter the brain for the worse.

ii. Are repeated courses required as with TMS and ECT?

iii. Is continuation treatment necessary? For instance, as with ECT and DBS where symptoms recur once treatment stops.

Preventive medicine could reach vastly more people with both biological and economic impact. Adult psychiatrists receive patients whose disorders began in youth, at the most severe stage.

Most people are resilient after a traumatic event. Some develop symptoms and recover, and a minority develop chronic symptoms. There is a short window for intervention immediately after the traumatic event, but no effective preventive treatment currently exists.[54,55] Psychological first aid and grounding help patients in the moment, but do not alter prognosis. Dr. Eitan's own experience as chair of psychiatry at a large Tel Aviv hospital during a period of mass casualties was that nothing available made a difference to eventual PTSD incidence. A virtual reality program trialled over a decade earlier was acceptable to patients but failed to prevent PTSD.

Not everyone should be treated. Epidemiological data increasingly define high-risk groups, and imaging work can support identification of high-risk patients within the acute window.

Dr. Eitan discussed an upcoming clinical trial from her group. The design recruits high-risk patients after acute trauma in the emergency department, randomized to active treatment or sham, using the Insightec helmet for FUS neuromodulation coupled with intensive neuroimaging. Unlike the ten-versus-ten studies typical of the field, this design requires substantially larger numbers of participants.

Ideally, the research helmet will give way to something closer to routine emergency care. She envisions a small, hand-held device labelled "emergency medicine" rather than psychiatry or neurosurgery. Her analogy was the tetanus shot – administered in the emergency department to everyone at risk, before infection sets in.

She proposed several other possible prevention windows in psychiatry: postpartum depression, substance use disorder and depression after remission given the known recurrence risk, and the prodromal phase of schizophrenia, where clinicians recognize the syndrome in adolescents and young adults but currently have nothing to offer before psychosis emerges. She also pointed to a population close at hand – first responders and medical staff, in whom she has repeatedly seen severe PTSD, and for whom interventions have proven difficult to deliver as a group.

Dr. Eitan closed on a note of her skepticism about the durability of neuromodulation in chronic illness. Reviewing outcomes of historical ablative procedures, she noted that many patients were out of hospital for a period but relapsed years later. It is hard to believe that 20 minutes could cure a disorder whose pathophysiology begins in utero and manifests decades before the patient is seen. That skepticism, she said, is precisely why she is pursuing both the preventive window on one side and HIFU capsulotomy for severe OCD on the other in her research program.

Kullervo Hynynen, PhD presented on *"Expanding the treatment envelope for focused ultrasound ablation."*

Because of the acoustic impedance of the skull, waves arriving at large angles are reflected. Shifting the focus toward the skull reflects most of the energy and overheats the bone where transmission does occur. Ablation using focused ultrasound is therefore confined to the central brain, and the size of this treatable envelope varies with individual skull shape and structure, and in some patients the treatable envelope is zero.

There are four approaches to enlarging the treatment envelope:

i. Optimize frequency (650 kHz is close to optimal, with perhaps 20% available from local tuning)

ii. Improve focusing algorithms

iii. Increase tissue absorption

iv. Reduce the threshold for brain damage

Microbubbles injected into the bloodstream act as reflectors for each transducer element[56], allowing the signals to be tuned so that all waves arrive at the focus optimally. This yields roughly a 20% increase in focusing, potentially enough to make some currently untreatable patients treatable.

Simulations using two-photon microscopy data of rat brain vasculature, with gas microbubbles inserted computationally, show hot spots around bubbles that then diffuse. Early experiments using conventional sonications with injected microbubbles achieved a four-fold increase in temperature elevation at one third of the power, and, importantly, the threshold for tissue damage was also lowered.[57] Damage was sometimes seen in front of the focus

with a single-focus transducer and 1.5MHz frequency used is impractical transcranially. Moving to 550–600 kHz with 10 ms pulses at a 1% duty cycle (rather than 500 ms pulses at 50% duty cycle) achieved ablation at 0.015 W, several orders of magnitude below conventional requirements and low enough to permit treatment anywhere in the brain.

The necessary tools have been developed to achieve control as well. Passive acoustic mapping with multiple receivers reconstructs bubble location from constructive interference at the focus.[56,58] Spectral analysis of the received signals reveals a sharp threshold at which a subharmonic appears at half the driving frequency, serving as a calibration point (i.e. detecting the subharmonic reveals the pressure amplitude in the brain). His team has developed a purpose-built array with separate transmit and receive elements that enables electronic beam scanning with three-dimensional bubble imaging at 100,000 volumes per second in the living rabbit brain.

Using the subharmonic signal for calibration, dropping power by 50% after detection produced BBB opening with no tissue damage.[59–61] At 100% of the calibration level, histological and MRI damage appeared, and the damage threshold derived from bubble imaging agreed well with observed outcomes. Some damage is still observed slightly outside the intended volume, and further optimization is needed before clinical use. These cavitation activities must be controlled very precisely, and the necessary tools now exist to achieve this goal.

On the future, asked whether one device could ever perform lesioning, neuromodulation and BBB opening: technically possible, but commercially unlikely. Expect multiple devices from multiple companies. Asked where he expects the field will be in five years: *"Five years from now it will be ten times bigger, and five years from that, it'll be in every home."*

Session 4

Discussion moderated by Ali Rezai with panelists Clement Hamani, Raag Airan, Renana Eitan, and Kullervo Hynynen.

Q. What is the cavitation risk with nanodroplets and liposomes, and can we use and acoustic feedback to monitor them?

- Liposomes are liquid-phase with no gas element, meaning they should not cavitate more than tissue itself does, so there is no inherent acoustic feedback mechanism to monitor and equally no cavitation risk beyond that of the ultrasound exposure alone.
- On kinetics, the technique restricts the volume of distribution by converting bound drug to free drug only at the sonicated site, rather than by altering blood flow or systemic clearance.

Q. Are there natural analogues such as vagal, carotid, or breathing interventions that could be potentiated with focused ultrasound?

- Dr. Airan pointed to Dr. Konofagou's peripheral nerve work as the closest analogue which suggests that ultrasound alone did not change neurotransmitter levels. When ketamine was given with ultrasound, prefrontal cortex GABA signalling was modulated. Ultrasound therefore appears able to modulate the effects of other modalities, raising the possibility of combining it with vagal nerve stimulation or similar approaches.

Q. Was the mechanosensitive channel blockade neuronal or glial?

- Dr. Airan clarified that a broad-spectrum blocker was used without cell-type specificity, and it blocked both the clearance effect and the microglial effects, supporting the non-neuronal hypothesis.
- Dr. Hamani notes that preclinical transcriptional changes are more consistently structural extracellular matrix and vascular genes, not neuronal or plasticity genes.

Q. Do oligodendrocytes changes accompany astroglial and glymphatic effects?

- Oligodendroglial changes would be highly relevant to durability effects.
- Dr. Airan reported that oligodendroglial emerged above neuronal markers in his analyses.
- Dr. Hamani noted limited oligodendrocyte change in his own preclinical studies though sampling tissue without separating grey from white matter.

Q. Why is microbubble-based mapping not widely used to localize the neuromodulation beam?

- The field has spent more effort on acoustic radiation force imaging instead of microbubble-based mapping shows where the beam goes.
- Dr. Hynynen replied that his group uses it routinely in their trials, but that it requires a purpose-built array which is non-trivial to construct.

- Arthur Lung (NaviFUS) described their approach as combining received signals from dedicated receivers with a forward model informed by neuronavigation geometry, and the accuracy is bounded by the accuracy and resolution of the neuronavigation system itself.

Q. What happens when patients relapse and is retreatment durable?

- Dr. Mayberg notes that in major depressive disorder, patients treated with medications or ECT do well and then relapse in a way that frequently cannot be re-treated the same way, because the patient has moved on and acquired new adaptations to the remission they achieved. In DBS, by contrast, patients can regain the capacity to respond to a drug that previously stopped working. This raises the question of whether FUS shows evidence of successful retreatment, and whether the effect should be conceived as intermittent but returning to a new homeostatic state.
- In the NAc neuromodulation trial, Dr. Rezai reports ~10% of patients require retreatment, characteristically at ~9 months, when craving profiles rise again. He postulates the brain as constantly seeking equilibrium with neuromodulation nudging it toward a better one.
- Dr. Mahoney adds that these patients do not necessarily relapse immediately, it may take a week or two, but the duration of use is shorter, they do not typically reach the emergency department or overdose, and they contact the research team, in part because having sustained abstinence longer than ever before. They see retreatment as an opportunity.
- Dr. Eitan drew on her DBS experience, suggesting it will not be a simple answer for psychiatric indications. In PD, turning the device off produces intolerable symptoms within 30 minutes. In OCD, the device can be off for a week with no effect. Symptoms take time to return and time to wear off. This is the same device at an adjacent target with entirely different temporal dynamics. She described a patient whose stimulator was off without their knowledge and saw his OCD acutely worsened, then normalize to YBOCS 0 on restart, remained well for three years until the generator failed, when symptoms again rose acutely. The variability between patients is very large including vulnerability to relapse that does not disappear, and a neuroplastic account will be insufficient. In depression, most patients recover naturally over months, so a durable post-treatment remission is partly consistent with natural history. In OCD, where symptoms persist for a decade in treatment-resistant cases, a durable remission and a retreatment that can restore it carries different meaning.
- Dr. Greenberg reported that the longest interval one of his OCD patients went after stimulation was turned off was about 6 months, which is notably long for OCD.
- Dr. Mayberg described a contrasting DBS observation. A patient who remained well for five years whose battery eventually wore out, who never returned for replacement and stayed well. This is evidence that some people in some disorders do remodel. The lesson for ultrasound is that the underlying reason for relapse needs to be reconciled.
- The concept of “medium-intensity” FUS was raised as distinct from low- and high-intensity approaches. Mechanical disruption of synaptic connectivity resulting in long-term remodeling may be fundamentally different from the electrical stimulation from DBS where networks that took decades to build are being disrupted.
- A question from the floor on whether retreatment should be built into trial protocols as a standard feature was met with agreement. An ethical parallel from the psychedelic literature was drawn, where relapse after a protocol may be particularly severe.

Session 5: Bringing the Field Together

Discussion moderated by Benjamin Davidson

Alik Widge, MD, PhD presented on *"Engineering cognition, from DBS to FUS."*

The field still cannot place a transducer on a patient's head and know it has engaged the target circuit. This gap is different from much of the rest of neuromodulation. In motor circuits you see the hand move. In DBS or lesioning for movement disorders, you see the tremor and then you don't. The question is: *"What's our tremor?",* a marker visible in seconds, obtainable efficiently and without requiring an MRI scanner so it can scale.

Market research on why DBS reaches under 10% of eligible movement disorder patients points to complexity. It is hard to use for clinicians. Adoption fails because programming is difficult, and randomized trials fail for the same reason. A contrast was drawn between open-label VC/VS DBS depression data showing ~50% improvement and a multicentre RCT in which the effect size halved, versus a European single-centre study using a blinded discontinuation design that succeeded[62] with the deciding factor being clinicians who already knew the target, the programming, and the patient selection.[63,64]

The symptom improvement curves for depression and OCD at this target are nearly identical, and the response rate in open-label addiction DBS is the same (~50–60%). Different DSM criteria, same target, same efficacy implies a shared underlying mechanism. Dr. Widge's proposed candidate is "stuckness": rigidity, the inability to disengage, what RDoC calls cognitive control.[65,66] The experience of knowing one doesn't want to keep doing something, yet being unable to stop.

With DBS on versus off, patients perform the Multi-Source Interference Task 5–10% faster with no increase in errors that is not a motor effect and not attributable to the hyperdirect pathway. The finding replicates in a separate cohort of epilepsy monitoring unit patients and in a different VC/VS patient group at Baylor using a different task.[67–69] Critically, the effect is sensitive to which part of the capsule is stimulated. The effect was also replicated in rats, enabling repeated-measures studies with tens of thousands of trials and computational modeling. Drift diffusion modeling identified specific parameters describing the capacity to shift and deploy new behavioural patterns. Applying that parameter back to patients from the Medtronic DBS trial showed that change in that parameter predicts who improved, and thus a strong candidate for "our tremor," though a prospective trial is still required.

Two practical applications follow. First, an algorithmic co-pilot that administers the task, monitors reaction time against settings, and recommends the next setting to try, not necessarily better than an expert programmer, but scalable in a way individual expertise is not. Second, mapping which tracts to target. The answer is mid-to-dorsal capsule, possibly more right-sided,[70] capturing lateral PFC and ACC, the cortical structures implementing cognitive control.

In a focused ultrasound trial with two patients thus far, his group sonicated the tractography-identified spot which produced the same effect as DBS, improved reaction time without increased errors on the same task. The effect is relatively sensitive, occurring only while sonication is on and fading within seconds of it being turned off. Patients notice the effect, describing it as being less forced to engage with whatever emotional experience would normally pull at them, less of the "I just can't" or "I have to" pattern of thinking. Unexpectedly, patients reported the effect lasting for days after a single sonication.

While the DBS work identified where to start, in practice the beam must be steered. In both patients tested, a "hot spot" exists, but its location varies from person to person, and because a measure of engagement exists, it can be located. Plans are underway to expand to a larger cohort.

Jennifer Rabin, PhD, CPsych presented on *"Measuring outcomes in psychiatric neuromodulation trials."* Dr. Rabin is the neuropsychology lead, at the Harquail Centre for Neuromodulation at Sunnybrook Research Institute.

Dr. Rabin presented the case of "Jane", a 21-year-old woman with treatment-resistant depression. Persistent low mood, worthlessness and hopelessness for as long as she could remember; long history of self-harm and chronic suicidal ideation with multiple attempts, unable to work for years and on disability support, and minimal benefit from antidepressants, TMS and ECT. She was referred for FUS capsulotomy, scoring in the severe range on both HAMD and MADRS at baseline. At 12 months post-treatment, her mood and concentration substantially improved, with no suicidal ideation or urges to self-harm. She had renewed interest in activities, re-engaged with hobbies and returned to part-time employment. Her concentration improved so much that she applied to, and was accepted into, a PhD program. She described feeling hopeful about the future for the first time in a long while, while acknowledging residual depressive symptoms. Asked whether, knowing what she now knows, she would undergo the treatment again, she said absolutely. On the MADRS and HAMD, Jane was a non-responder.

Her case highlights four limitations of current outcome measures:

1. Depression rating scales do not capture what patients find most disabling such as severe mental anguish and feeling trapped inside oneself rather than symptom checklists. Cognitive difficulties and anhedonia are also incompletely captured.
2. The 50% response definition disadvantages the most severely ill. Patients starting with extremely high scores have much further to fall to reach the threshold than patients with milder symptoms.
3. The scales offer very limited insight into functional recovery, whether patients return to work or school, re-engage with family and friends, or participate more fully in daily life.

4. They assume the same outcomes matter to everyone. In a condition as heterogeneous as depression, meaningful improvement looks very different between patients.

Dr. Rabin proposed a practical alternative: ask patients what success would look like. Dr. Rabin described applying this approach in FUS thalamotomy for tremor, where in addition to tremor severity scales patients were asked which activities they hoped to do again. A word cloud of the most commonly reported activities was dominated by cooking, drinking from a cup, writing, eating, and dining out without embarrassment. Treatment success was not determined by tremor reduction alone. Patients were most satisfied when treatment let them achieve the activities they had specified at baseline. She acknowledged that translating this into depression will be substantially harder because recovery is more heterogeneous and goals shift over time. For instance, a patient may begin wanting to get out of bed and later want to return to school.

She also discussed studies related to three objective behavioural markers from her group: cognitive control, speech and reward valuation.

Cognitive control, measured with an eye-tracking interleaved pro- and anti-saccade task, chosen as the most direct available measure of the brain. Pro-saccade trials capture processing and motor speed, while anti-saccade trials, which require suppression of the urge to look at the target, capture cognitive control. In 30 patients with depression and 30 controls tested before and after four weeks of dorsolateral prefrontal TMS, healthy controls remained stable over yoked intervals with a slight practice effect, non-responders showed a similar pattern, and responders showed significant improvement in anti-saccade reaction time. Crucially, no equivalent change appeared on the pro-saccade processing-speed task, supporting specificity to cognitive control.

Depression is associated with more negatively valenced and emotionally intense language, reduced expressed agency, lower and less variable pitch, more frequent pauses and slower speech. In collaboration with Winterlight Labs, participants responded to the single prompt "please tell me how you are doing today," largely remotely on their own devices, with NLP extraction of linguistic and acoustic features.[71] In 59 patients and 66 controls, a composite speech measure distinguished patients from controls, with the strongest effects for speech rate, then pauses and valence, and more modest effects for pitch, emotional intensity and agency. Pitch variance was the only feature that did not discriminate between groups. The correlation with HAMD scores was in the expected direction, but weak and non-significant. The more notable finding was a strong relationship between speech and the eye-tracking measure of cognitive control. Patients with more depression-like speech performed worse on the cognitive control task, suggesting that speech captures underlying cognitive difficulty that standard outcome measures miss. After TMS, patients with greater symptom improvement showed speech that became less depression-like, driven by emotional intensity, agency, valence and speech rate.

Reward valuation was assessed by delay discounting, where choices are made between smaller immediate rewards and larger delayed ones, summarized as area under the curve, with steeper discounting indicating a preference for immediate reward, a pattern typical of depression and supported by activity in the ventral striatum and anterior cingulate.[72,73] In a small sample of 15 patients treated with DBS or FUS and tested at baseline and 12 months, greater symptom improvement was associated with greater shift toward future-oriented decision-making, with a large effect size.

Returning to Jane: by the standard outcome measures that determine FDA and Health Canada approval, she was a non-responder, yet she is back at work, spending time with friends and making plans for the future. Symptom scales remain necessary and must be included, but they do not capture what matters most to patients and they miss meaningful signals. Outcome evaluation requires composite measures that combine symptom scales, patient-centred outcomes and behavioural biomarkers.

Rees Cosgrove, MD, FRCSC presented his talk, titled "*Surgery for psychiatric disease: past, present and future.*" Dr. Cosgrove delivered the meeting's closing talk, sharing personal experience and reflections of the field.

The past: seven decades of psychiatric neurosurgery. Neurosurgery for psychiatric indications spans nearly 75 years. Less widely appreciated is that the entire field of stereotactic surgery, introduced in the 1950s, was created specifically to make psychiatric surgery more precise and repeatable across centres, a response to an era with no treatments for psychiatric disease and enormous unmet demand. Four ablative procedures followed and were performed worldwide: anterior cingulotomy, subcaudate tractotomy, anterior capsulotomy, and limbic leucotomy. Dr. Cosgrove has personally performed approximately 175 of these procedures.[74,75]

In the 1990s, as DBS supplanted ablative surgery for movement disorders, the transition to DBS for psychiatric conditions seemed like a natural next step. The two large trials failing to reach statistical significance dampened enthusiasm across the field; for a period, DBS research proposals were rarely considered. Everyone doing the work knew there was signal there, but the outside world saw the trials alone. He noted the Abbott TRANSCEND trial is ongoing, with many centres in the room participating, and that this is the last large medical-industrial company still involved in this space.

The present: an opportunity for focused ultrasound. Neurosurgeons have championed this field, and that needs to change. Psychiatrists must lead. Dr. Cosgrove estimated there are roughly 70,000–80,000 psychiatrists in North America and calculated that the psychiatrists in the room represent approximately 0.02% of the profession. Psychiatrists trust other psychiatric leaders, as neurosurgeons trust neurosurgeons and neurologists trust neurologists.

Overcoming professional and cultural resistance is very difficult, because deep-seated professional or cultural bias tends to persist even with fairly convincing data. Colleagues may

agree in a conference room yet still decline to refer patients in practice. Despite 20–30 years of excellent results in movement disorder surgery, only a fraction of eligible patients are still being reached. He predicts that even an extremely successful TRANSCEND result will not meaningfully shift psychiatrist perception, because the core impediment is the idea of an electrode in the brain.

There is a real psychological difference in how patients perceive DBS versus focused ultrasound. Among well-informed individuals, willingness to accept an implanted electrode is far lower than willingness to accept a non-invasive procedure, a gap that widens further when the indication is psychiatric rather than neurological. He framed this as the field's key opportunity: one to be taken up and managed carefully.

In the early 1990s at MGH, while performing cingulotomies, he witnessed a demonstration of roughly 125 protesters outside his office window carrying banners protesting his work. This has not recurred with DBS. He attributed the stigma to the prefrontal lobotomy era and its cultural representations, but judged this no longer the field's primary obstacle, particularly with focused ultrasound which does not really look like surgery. Whatever resistance persists among physicians, he noted, patients who are truly suffering, along with their families, accept these treatments.

Nothing in medicine moves forward if it does not get paid for. Roughly half the procedures he performed during his career were not reimbursed. The hospital absorbed the cost. Most hospitals remain unwilling to engage in this kind of surgery outside research funding. The opportunity is that psychiatrists now have a revenue-generating procedure in TMS and that TMS is the door through which other interventions may eventually enter.

A proposal for the future. Dr. Cosgrove proposed specialized psychiatric neurointerventional centres offering the full range of treatments. A referral centre for treatment-refractory patients, staffed by an expert multidisciplinary group led by psychiatrists, assisted by neurologists, complemented by neurosurgeons, with behavioural therapists, pharmacists and imaging expertise. The structure is deliberately staged and financially self-sustaining. Patients enter for lower-risk non-invasive treatment such as tDCS or TMS. If that fails, LIFU neuromodulation, then minimally invasive HIFU, and only then invasive DBS or radiofrequency procedures. The referral relationship is designed so the community psychiatrist does not lose the patient, treat and return for ongoing psychiatric care.

His argument for the model was as much about discovery as service. Without a steady stream of patients, great ideas will not materialize, because you do not have the clinical material to work on them. He described learning more from the psychiatrists at MGH about psychiatric disease, disability and medications than from any other source, and the resulting exchange over imaging characteristics as a uniquely fertile learning ground.

Session 5 panel discussion moderated by Benjamin Davidson with panelists Alik Widge, Jennifer Rabin, and Rees Cosgrove.

Q. What talk do you hope to give, and what talk do you hope you don't have to give in two years?

- For neuromodulation, the hope is new data: what worked, the exact pulse parameters used, important outcomes achieved, and pivotal trials underway. The feared talk is not primarily that someone was made permanently worse because that seems unlikely with ultrasound devices calibrated never to reach lesioning energies. The real fear is that the field's early ambitions simply stalled out amid a broader downturn in research funding.
- On lesioning, the hoped-for talk would be that the SONIC FUS capsulotomy trial is progressing well, capsulotomies performed successfully, promising initial results, and the sham-controlled portion underway. The feared talk describes a trial where recruitment and retention proved incredibly difficult, and the procedure far harder than expected. Even so, failure only makes the field stronger.
- On biomarkers, the aspiration is to move from measurement at 12 months to very early markers. Knowing early that a treatment isn't working would spare patients weeks of unnecessary visits. An early signal that a patient is on the right trajectory could itself build hope and speed recovery.

Q. Who is driving referrals for FUS treatments?

- The model in which a community psychiatrist refers to an interventionalist and later receives the patient back is available now with TMS and ketamine, yet the dominant pattern is that patients refer themselves, seeking out treatment directly. Regulatory approval is only the first step; building direct patient awareness matter just as much for implementation.
- Dr. Cosgrove echoed from personal clinical experience offering focused ultrasound for movement disorders. In the first five years, approximately 85% of movement disorder FUS patients arrived of their own accord.

Q. What would make a psychiatrist refer?

- Dr. Richter identified three challenges from the perspective of a community-facing OCD specialist that, if addressed, would increase referrals: (i) Better ability to predict in advance who will benefit; (ii) Better ability to demonstrate change. She described patients in her intensive OCD program whom her team and the patients themselves consider clear successes, whose YBOCS has fallen only from 30 to 23 or 24, but move from being unable to leave the house to functioning normally outside it, a major shift that even WHODAS and quality-of-life measures fail to fully capture; and (iii) Access, which remains a significant barrier even for TMS, and where ultrasound may offer a path forward.

Q. Does effective focused ultrasound care require a multidisciplinary team, or can a single clinician deliver it?

- The panel converged on multidisciplinary teams.
- No individual clinician can achieve what a team achieves, with the Sunnybrook model cited as an example.
- A case for team-based care was also made from essential tremor. The condition is itself heterogeneous, complicated further by ET-plus and rest tremor, and while surgery works for both, the target differs. The correct target is determined with careful evaluation.
- Essential tremor is closer to a pure diagnostic entity, while treatment-refractory psychiatric disease is not, making multidisciplinary evaluation in psychiatric surgery absolutely necessary.

Q. What does the evidence tell us about how to define outcomes?

- From a historical perspective, Dr. Cosgrove described how the MGH group handled reporting of cingulotomy and limbic leucotomy outcomes. Τηεψ wanted to rate outcomes in terms psychiatrists would accept. They benchmarked against pharmacological trials, where an add-on drug producing ≥35% YBOCS improvement in 30% of patients would be considered successful.[118,119] Under a strict definition, both ≥35% YBOCS improvement and a CGI score of 1 ("very much improved"), approximately one third of refractory patients were clear responders after cingulotomy. However, patients showing real improvement were being classified as non-responders, so partial responders were defined as meeting either criterion. On that definition, response rates were 60–70% with a single intervention.
- The MADRS, HAMD and YBOCS have real limitations, but the reality is that regulators and payers will expect to see these scales, so the path forward is to use them alongside other outcome measures, not choose one over the other. Practically speaking, the field requires standardized measures for the world to see that a treatment is working, even when patients are already reporting that they feel better.
- Subjective improvement as a metric carries its own limitations. In pain neurosurgery, subjective experience remains the primary endpoint and patients sometimes report no benefit despite improved scale scores.

Q. What role does rehabilitation play in durability, and does the brain require training to use what treatment restores?

- Dr. Mayberg noted that data presented over the two days ultimately concerned how the ventral striatum learns to change its response to the environment, a learning phenomenon, not simply a switch being flipped. She argued that this retraining capacity in the ventral striatum may be exactly what's needed after changing the underlying pathology in the cingulate for MDD, since the two are different systems with non-overlapping white matter projections. A patient cannot learn to see their future and improve using their cognitive control system while a pervasive negativity is dragging them down. Once the negativity is switched off, the rest of the system still has to be retrained.

- Moving forward, it will be important to tell us how the patients did. What persisted? Was retreatment required? In psychiatry, often a treatment works, the patient does well for two years, then relapses, and the original treatment no longer helps because the brain has settled into a different, less accessible state of illness. Dr. Mayberg offered concrete benchmark to achieve in the focused ultrasound field: a meta-analysis of ~200 DBS patients show about half well at two years and many well at five years. Meeting that bar and understanding how to meet it was framed as the threshold for building a durable, credible field.
- Every neuromodulation technology in current use is effectively rehabilitative or rehabilitation-assisting. OCD patients still need to do exposure exercises; MDD patients still need behavioural activation. All of these therapies fundamentally give the patient new capacities that they then need to learn and sometimes need active encouragement to use. There is a familiar parallel in movement disorders, where deconditioned patients require physiotherapy and speech-language pathology afterward treatment.
- The phenomenon extends to all ablative psychiatric neurosurgery. Patients are impacted by chronic, recurrent, relapsing diseases, and surgery as changing the direction of a long walk into a dark woods. It remains a long walk back out, and there is no immediate cure. Most OCD patients cannot tolerate the thought of behavioural therapy before surgery, let alone participate in it meaningfully. The intervention changes enough that participation becomes possible afterward. This is offered as the explanation for why Gamma Knife results and radiofrequency results show improvement over time,[40,76,77] with patients sometimes moving from non-responder at two years to partial responder at three and complete responder at four.
- Another common clinical scene is that a patient insists they are no better, while their partner points out, they are now going out every day and doing shopping. Patients who do not perceive their own improvement are nonetheless often doing more in daily life. For instance, increased time outside the home and prompting them about their activities would likely reveal far greater engagement in life activities.
- Making better use of smartphones nearly everyone already carries may another way to demonstrate real-world improvement more concretely.
- The digital phenotyping field is growing quickly, and this kind of measurement may become available by the next FUS-PULSE.

Q. What does industry need to see to translate into commercial support?

- Short durability is not inconceivable as a business model. The TMS business reached several hundred million dollars in revenue after years of scepticism and non-payment, but longer-lasting therapies reach billion-dollar revenues. It's a big difference.
- Push durability much higher. If twenty sessions lead to a month of benefit, compliance drops and payers may decline to cover it. An ideal target would be durability of at least six months with yearly follow-up.
- An immediate biomarker is valuable not only for reprogramming but for patient selection, to screen out acute non-responders. An immediate biomarker correlated 80-90% with eventual response would match other neurosurgical modalities that have a very robust way of selecting patients in the OR.
- Appropriately placed lesions in psychiatric disease are durable and tend to improve

over time. DBS is durable too, in properly selected patients, but selection remains the hard part.

Q. Which biomarkers should the field prioritize?

- In programming DBS for PD, clinicians chase tremor because it is easy to see and measure, but there is a large discrepancy between objective and subjective tremor and improving quality of life means chasing the subjective measure.
- Chasing objective tremor means missing what actually drives quality of life. The spot that helps tremor is probably the worst spot for axial symptoms and depression.
- The lesson for FUS psychiatry is that an easily measured biomarker is not automatically the right one.

CLOSING REMARKS

Dr. Lipsman closed the meeting with an account of the Toronto reimbursement experience of focused ultrasound capsulotomy for OCD, offered as grounds for hope on the implementation question that had dominated the final session.

Sunnybrook has performed focused ultrasound capsulotomy for seven years, treating approximately 60 patients. In a single-payer system, the government must be convinced that a procedure is economically viable, safe, and effective. The team presented the safety and efficacy data, alongside the broader international experience of thousands of patients treated worldwide with capsulotomy, including close to a thousand in Canada, and made the case that a safer approach to therapeutic lesioning for OCD now exists with focused ultrasound. The initial response was that the data looked strong, but the procedure would not be funded.

The funding decision was a draft decision, open for public comment for two weeks. The team engaged patients, disease organizations, and international experts. A news story about a patient who had done exceptionally well was published around the same time. Historically, these decisions are typically not revisited, yet months later the decision was reversed. Funding was approved for a limited number of patients per year with the program remaining open to continued study. Dr. Lipsman highlighted power of patient testimony, and of families and caregivers speaking to the real impact of the condition and its treatment on their lives.

On referral pathways, Dr. Lipsman described Sunnybrook's approach as removing the complexity of the decision from the community psychiatrist's plate entirely. There are too many devices, procedures and parameters for a psychiatrist in a community setting to weigh independently. Once a patient has reached the limit of what conventional treatment can offer, they can be referred to a multidisciplinary centre to take care of the rest. He reported that taking the burden off the referring physician has significantly moved the dial.

He closed with thanks to the speakers, moderators and participants, his co-chair Dr. Davidson, the Focused Ultrasound Foundation, the Midas Touch Foundation, the steering committee, Leila Harwood and the conference event staff.

When asked what excites him most about the field, his answer was unequivocal: the people and the community. He noted the growing number of postdoctoral fellows, graduate students, medical students and residents now reaching out to work in focused ultrasound. He described the field as becoming a beacon for talent and offering that as the strongest reason to believe the field will continue to make a difference.

Participants were asked to hold June 2028 for the third FUS-PULSE symposium.

FROM THE 2024 ROADMAP TO 2026: WHAT CHANGED

The 2024 proceedings set out a roadmap organized around patient selection, device development, biological mechanisms and outcome measurement.[1] This section tracks progress on each in light of what was presented at FUS-PULSE 2026 and key gaps for the field related to each topic.

1. **Standardized reporting of sonication parameters.** ITRUSST consensus and practical guidelines now exist and are being embedded in device software. Presenters systematically reported frequency, power, pulse pattern, duty cycle and duration.[9,10] Even so, studies diverge substantially on parameters, systems and frequencies. Reporting of modeled in-situ exposure remains inconsistent and simulation tools vary with no agreed-upon ground truth.

2. **Safety.** Real-time acoustic feedback with adaptive power modulation, explicit cavitation halt rules, and physiological monitoring is now standard. A transparent publication detailed a serious adverse event with full root-cause analysis, with 23 subsequent patients treated safely.[43] It is clear that low intensity does not eliminate structural or psychiatric risk. The transmitted-versus-in-situ gap remains unmeasured in most systems. Cross-device safety frameworks do not yet exist.

3. **Narrowing the parameter space for neuromodulation.** Bayesian closed-loop optimization is now converging in approximately 23 evaluations.[78] Mechanistic work has separated frequency-dependent effects into distinct biophysical regimes. Proposals now aim to constrain the parameter space using skull transmission, regulatory and reimbursement limits.[13,25] At present, there is no established human dose-response curve for LIFU. Aggregated published relationships between delivered energy and effect show minimal correlation. Non-linear, target-, patient-, and time-dependent responses continue to complicate optimization at the group level.

4. **Target engagement metrics.** Emerging clinical biomarkers were presented, including ASL, BOLD, CBV, EEG, intracranial LFP from GPi and STN, heart-rate variability, startle habituation, eye tracking, speech, delay discounting and cognitive control reaction time. Existing biomarkers are not yet rapid, scalable and validated. Biomarkers may be coupled to rather than predictive of effect. Individual response direction is frequently bidirectional.

5. **Understanding bioeffects for neuromodulation.** Pharmacological dissection in humans supporting LTP-like mechanisms and mechanosensitive channel involvement,[23,24] evidence for substantial and possibly predominant non-neuronal effects,[20] and a dynamical-systems framing of durability.[34,38,79] However, mechanisms remain parameter- and tissue-dependent and cannot be generalized between protocols. The relationship between mechanism and parameter selection remains circular.

6. **Active sham and blinding.** Defocusing lenses are now available across at least three platforms with participants unable to distinguish conditions. Additional advances included foam-blocked transducer pads, ramp-up protocols that eliminate the audible click and active anatomical control designs. Yet placebo effects remain substantial and are modifiable by trivial factors. For instance, showing the patient a brain image increases them. Nocebo and expectancy effects in neuromodulation and ablation trials remain unaddressed.

7. **Clinical evidence for neuromodulation.** Published open-label outcomes have expanded to include severe SUD,[41] sham-controlled target engagement and single-arm treatment in mood, anxiety and trauma-related disorders,[46] NAc crossover trial in cocaine use disorder, an SCC crossover trial in depression,[37] pilot data in AD, binge eating, chronic pain, white matter tracts and cognitive control.[18,30,42,80] Current series remain small, open-label or single-arm. Adequately powered multi-centre sham-controlled evidence is still absent across psychiatric indications.

8. **Clinical evidence for lesioning.** FUS capsulotomy has now been performed in ~60 patients at one Canadian centre.[81,82] The SONIC randomized sham-controlled trial is preparing to begin (NCT06131502). New phase I capsulotomy trials in bipolar depression and anorexia nervosa have been registered (NCT07108257, NCT07113665). Randomized data is still pending, and patient selection criteria for lesioning versus other modalities remain poor.[75,77,83]

9. **Outcome measurements.** Patient-defined goals have been piloted in FUS thalamotomy. Objective behavioural markers including eye tracking, speech, and delay discounting have been validated against treatment response.[69,71] Composite frameworks have been proposed for outcome assessment. Regulators and payers will continue to require conventional scales. No agreed composite framework exists, and functional measures have their own limitations.

10. **Implementation and access.** Wearable and outpatient platforms have emerged. Approved, time-limited provincial funding decision for FUS capsulotomy in Canada. A staged referral-centre model has been proposed and implemented at various centres. Referral culture, reimbursement, workforce training and health-economic evidence may become the dominant bottleneck. Psychiatry remains a predominantly non-interventional field.

A ROADMAP TO 2028, TEN QUESTIONS FOR 2028

Synthesizing the closing session and the moderated discussion, the group identified ten questions the field should be positioned to answer when it reconvenes in 2028.

Ten questions for 2028

1. **What is our tremor?** For at least one lead indication, can we demonstrate a target-engagement readout that changes within seconds to minutes, does not require an MRI scanner, and predicts clinical outcome at the individual level? Groups working on candidate biomarkers agreed to share qualitative and micro-phenomenological instruments for capturing subjective response, so that promising readouts can be cross-validated across sites.

2. **What is the dose?** Can we report, for every patient treated, both the transmitted parameters and a measured or validated surrogate of what actually was delivered at the target, and relate that quantity to outcome? Multiple groups agreed that building a shared repository of delivered energy and outcome data would enable the kind of aggregate analysis of the parameter-effect relationship that no single centre can resolve alone.

3. **How durable is the effect and what happens on relapse?** Can the field report 6- and ideally 12-month follow-up, the interval at which symptoms return, the proportion of patients requiring retreatment, and, critically, whether retreatment works? Sites treating the same disorder agreed to harmonize follow-up timing protocols and outcome windows.

4. **Have the most mature applications moved beyond open-label?** Specifically, has the SONIC capsulotomy trial begun its randomized phase, has the sham-controlled RCT in severe substance use disorder been completed, and has a sham-controlled amygdala dose-finding study been reported? Participants called for a dedicated session on null and negative results at a future symposium to strengthen the evidence base in the field and reduce duplication of unsuccessful approaches.

5. **Can the field agree on a minimum reporting dataset?** Identical reporting of device, transducer, frequency, aperture, focal length, coupling, skull characteristics, modeled in-situ exposure, pulse timing, targeting method, monitoring, concomitant treatment, adverse events and outcomes across groups. Groups using the same device committed to harmonizing their reporting first as the most tractable starting point, and to open sharing calibration methods for phased-array systems so that modeled exposure becomes comparable across centres. Multi-site harmonization was also proposed more broadly, targeting the same anatomical structure or treating the same psychiatric disorder.

6. **Have we tested the non-neuronal hypothesis?** Do the glial, glymphatic, neuroimmune and extracellular matrix effects observed preclinically account for the clinical effects, and can they be measured in patients?

7. **Can we predict who will benefit before treating?** This includes phenotypic, personality, connectomic, skull-acoustic and early-response predictors. Equally important, can we identify patients at risk of worsening prior to treatment?

8. **What is the composite outcome framework?** Can the community agree on a package of outcome measures that pairs regulatory scales with patient-defined goals, functional and quality-of-life measures, objective behavioural biomarkers and, potentially, passively collected real-world data?

9. **How is adjunctive care built into the design?** Across indications, participants viewed focused ultrasound as rehabilitative rather than curative, so can trials standardize the behavioural, pharmacological and psychosocial treatments delivered alongside it, and test whether timing of intervention matters?

10. **What does implementation look like?** Referral pathways, multidisciplinary centre models, training, reimbursement evidence and health-economic analysis require further development. Can the Toronto funding experience for FUS capsulotomy be reproduced elsewhere?

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ABBREVIATIONS

ACC anterior cingulate cortex · **AD** Alzheimer's disease · **ADCS-ADL** Alzheimer's Disease Cooperative Study Activities of Daily Living · **AI** anterior insula · **ALIC** anterior limb of the internal capsule · **aMCC** anterior mid-cingulate cortex · **APR** anxiety-potentiated response · **ARFI** acoustic radiation force imaging · **ARPA-H** Advanced Research Projects Agency for Health · **ASL** arterial spin labeling · **BBB** blood-brain barrier · **BEACUN** Bayesian-Enhanced Adaptive Control of Ultrasound Neuromodulation · **BOLD** blood oxygenation level dependent · **CBV** cerebral blood volume · **CGI** Clinical Global Impression · **CM** centromedian nucleus of the thalamus · **COAT** Comprehensive Opioid Addiction Treatment · **CSF** cerebrospinal fluid · **cTBS** continuous theta-burst stimulation · **DBS** deep brain stimulation · **ECT** electroconvulsive therapy · **EEG** electroencephalography · **EMG** electromyography · **ET** essential tremor · **FPR** fear-potentiated response · **FUS** focused ultrasound · **GPi** globus pallidus internus · **HAMD** Hamilton Depression Rating Scale · **HIFU** high-intensity focused ultrasound · **I_{SPTA}** spatial-peak time-average intensity · **ITRUSST** International Transcranial Ultrasonic Stimulation Safety and Standards · **LFP** local field potential · **LIFU** low-intensity focused ultrasound · **LTP** long-term potentiation · **MADRS** Montgomery-Åsberg Depression Rating Scale · **MDD** major depressive disorder · **MI** mechanical index · **MMSE** Mini-Mental State Examination · **MoCA** Montreal Cognitive Assessment · **mPFC** medial prefrontal cortex · **NAc** nucleus accumbens · **NSR** non-significant risk · **OCD** obsessive-compulsive disorder · **PANAS** Positive and Negative Affect Schedule · **PD** Parkinson's disease · **PET** positron emission tomography · **PRF** pulse repetition frequency · **PTSD** post-traumatic stress disorder · **PTT** pallidothalamic tractotomy · **QoL** quality of life · **RCT** randomized controlled trial · **RDoC** Research Domain Criteria · **STN** subthalamic nucleus · **SUD** substance use disorder · **tACS** transcranial alternating current stimulation · **tbTUS** theta-burst transcranial ultrasound stimulation · **tDCS** transcranial direct current stimulation · **TMS** transcranial magnetic stimulation · **UPDRS** Unified Parkinson's Disease Rating Scale · **VC/VS** ventral capsule / ventral striatum · **VNS** vagus nerve stimulation · **VPL** ventral posterolateral nucleus of the thalamus · **VR** virtual reality · **WHODAS** WHO Disability Assessment Schedule · **YBOCS** Yale-Brown Obsessive Compulsive Scale

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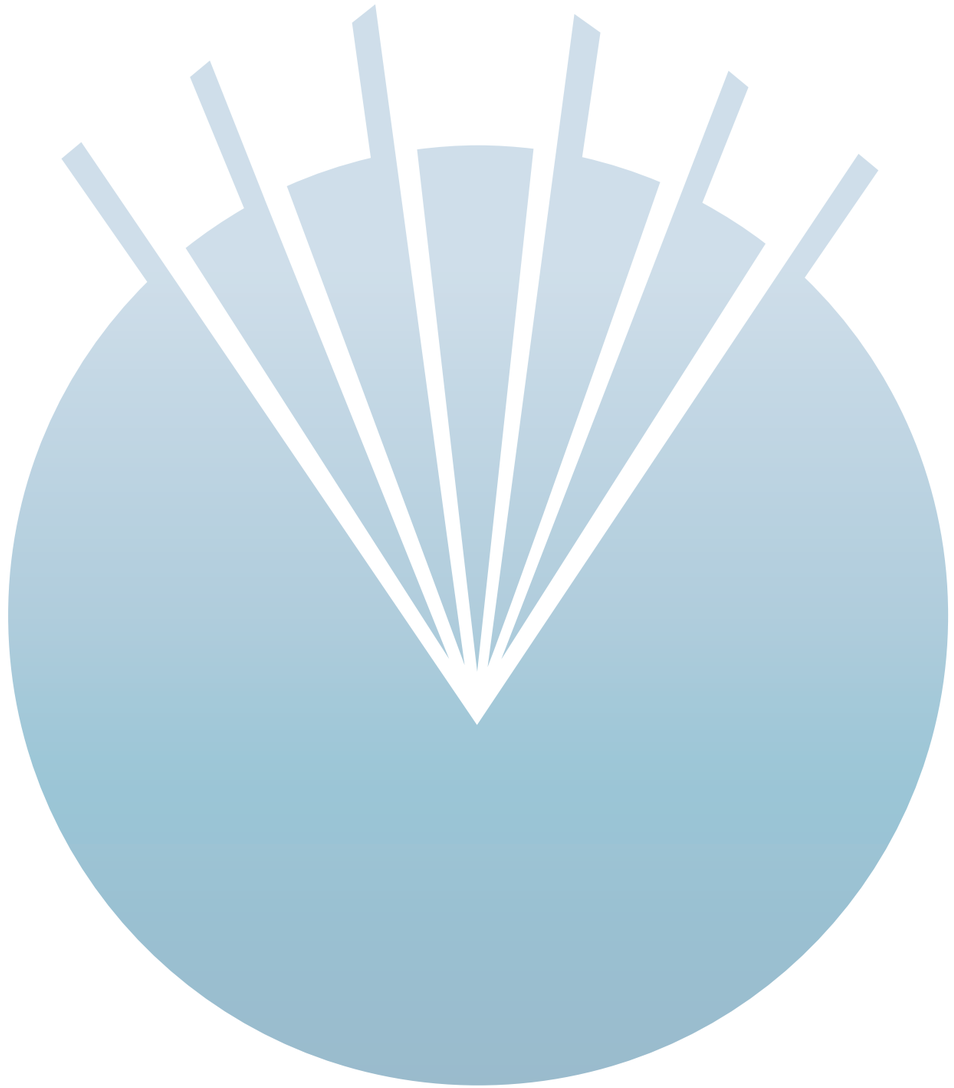

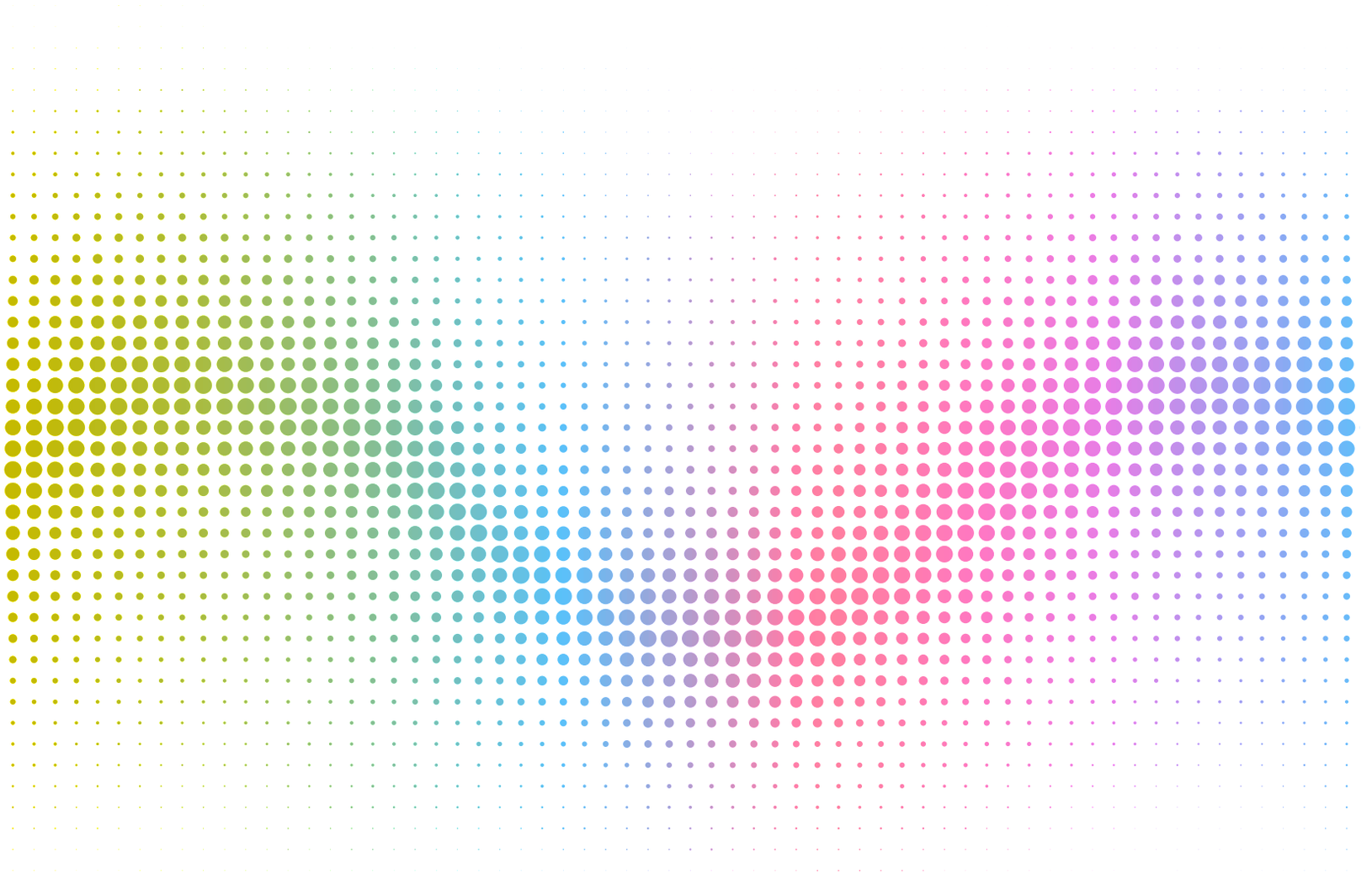

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