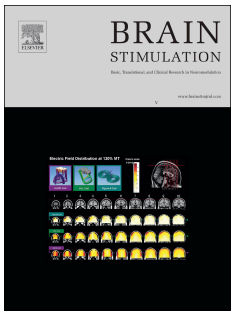

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Thalamic transcranial ultrasound stimulation in treatment resistant depression

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Major depressive disorder (MDD) is a leading cause of disability worldwide with one-third of cases being treatment resistant[1]. Symptom heterogeneity suggests variability across affected brain networks, prompting efforts to personalize circuit-based neuromodulatory interventions. For example, personalized deep brain stimulation (DBS) has been achieved by selecting different treatment targets based on phenotypes or mapping stimulation responses[1]. However, DBS is invasive, and the stability of optimal long-term treatment within a dynamic and adaptive brain remains unknown. Noninvasive approaches, such as transcranial magnetic stimulation (TMS), have shown promise in modulating putative mood networks but are unable to target deeper subcortical regions.

Transcranial ultrasound stimulation (TUS) or low intensity focused ultrasound is an emerging, non-invasive method with millimeter spatial specificity and a unique ability to achieve deep subcortical neuromodulation. TUS can reversibly modulate brain networks and confer durable behavioral effects[2,3]. Preliminary studies suggest that TUS applied to classical TMS and DBS targets can improve anxiety, worry, avoidance and mood[4–6]. To examine whether dynamically steered TUS (Fig. 1A) may identify personalized therapeutic subregions in MDD, we employed dual-phased array crossbeam focusing to stimulate subcortical mood-related circuitry.

A 46-year-old man with treatment-resistant depression underwent TUS interventions aimed to 1) assess the therapeutic potential of candidate brain regions based on self-report and 2) objectively investigate the effects of a top candidate target using neuroimaging. His major depression began ten years prior, characterized by anhedonia, lethargy, poor concentration, and hopelessness (baseline 6-item Hamilton Depression Rating Scale (HAMD-6) rating of 11). He had failed over 10 different oral agents and psychotherapy. He had transient positive effects from both electroconvulsive therapy and TMS, but discontinued treatment due to rapid relapses, cognitive decline, and other side effects, e.g. headache.

The subject underwent a three-phase assessment: an exploratory phase, candidate brain region testing phase, and top-candidate testing with neuroimaging phase. Following an exploratory phase (Supplementary Methods), three regions were targeted for serial testing: ventral capsule (VC), bed nucleus of stria terminalis (BNST), and anterior nucleus of the thalamus (ANT). The top candidate region was then compared to an unfocused control, and resting-state fMRI was collected post-stimulation. Behavioral outcomes were collected using visual-analog scales (VAS) of depression and the 6-item Hamilton Depression Rating Scale (HAMD-6). TUS was delivered using an ATTN201 wearable device, equipped with dynamic steering (Supplementary Methods; 128 transducer elements; Attune Neurosciences, Inc., San Francisco, CA). Stimulation parameters were consistent across all candidate regions: 500 kHz fundamental frequency, 25 Hz pulse repetition frequency, 13% duty cycle, and 300s (5 min) pulse train duration. Stimulation was bilateral, alternating between left and right lateralized regions every 15 minutes, i.e. 10 min inter pulse train interval. The unfocused control stimulation constituted the same acoustic energy at the array surface but without a deep brain focal pattern, to approximate the same acoustic and peripheral experience as focal stimulation. Eight total pulse trains (four left and four right) were performed to complete a full session (Supplementary Methods); each followed by a 24-hr washout period. Figure 1B shows the simulated crossbeam ultrasound intensities for right lateralized regions overlaid on T1-weighted MR images. Simulated spatial peak pulse average intensity (I_{SSPA}) ranged from 42.2 to 50.2 W/cm^2 at the target for active conditions and <2 W/cm^2 at any given target for the unfocused control. This study was approved by the Advarra Institutional Review Board, and the subject provided written informed consent to complete this study.

The intermittent TUS protocol was well tolerated by the participant without any adverse effects. A post-stimulation MRI scan did not reveal any structural changes, including edema or

hemorrhage. Over serial stimulations, a reduction in VAS-depression and HAMD-6 was observed across all stimulation conditions (Fig. 1C-F). When compared to the unfocused control condition, ANT stimulation further reduced VAS-D scores over time ($t(2)=-8.87$, $p=0.013$, one sample t-test; Fig. 1D), in contrast to VC/BNST stimulation ($t(2)=-2.6$, $p=0.152$). Similar trends were observed in the HAMD-6 scores but without significance. An example spontaneous verbal report following an exploratory ANT stimulation day included: “I think I'm having less obsessive-compulsive thoughts... when I start getting on myself for something it's just hard to get off, but I feel like I've been moving through my thoughts a little bit better," suggesting a reduction in ruminative thinking.

We subsequently evaluated the effects of stimulation on functional connectivity within the default mode network (DMN), a network of brain regions implicated in self-reflection and rumination[7]. At baseline, resting-state DMN connectivity was hyperconnected in this subject as compared to that of aged-matched healthy individuals (Fig. 2H; n = 84; age, mean = 43.96 y, SD = 18.3 y; sex, 41 F). Resting-state fMRI following double-blinded ANT stimulation showed a reduction in DMN connectivity when compared to the atypically high levels seen in the baseline condition; smaller reductions in DMN connectivity compared to baseline were also seen following the unfocused condition (Fig. 1G, H; see Figure 1S for additional axial cuts). Notably, subjective sleepiness was not affected by stimulation, rated as a 4 on the Stanford Sleepiness Scale across the ANT and unfocused conditions, and is therefore unlikely to explain the changes in DMN connectivity.

Here, we demonstrate that thalamic TUS has the potential to elicit a subjective reduction in depression symptoms and is associated with decreases in DMN connectivity. In contrast, the VC/BNST target did not statistically reduce symptom scores. Symptom trajectories suggested improvement over hours with intermittent stimulation, as compared to other non-invasive methods, e.g. TMS, which evolve over days to weeks. Prior studies applying TUS to depressed individuals have targeted the subgenual cingulate[4] and fronto-temporal cortex[5]. Here, we

investigated the effects of TUS on two subcortical targets: VC/BNST and ANT. In contrast to VC/BNST, ANT is not a common target for DBS in MDD but has been implicated in emotional regulation by way of its direct connectivity with anterior cingulate and prefrontal cortex[8]. While ANT DBS has been linked with increased rates of depressive adverse events[8], we find that ANT TUS led to an improvement in depressive symptoms, highlighting the distinct mechanisms of these two neuromodulation modalities. Notably, this participant later underwent a clinical trial involving intracranial DBS mapping (NCT04004169), for which VC/BNST yielded the strongest acute mood responses; stimulation mapping did not include thalamic implantation.

It is intriguing to consider that symptom improvement associated with thalamic TUS was causally related to decreases in DMN connectivity, shown to be hyperconnected in this individual and generally overactive in MDD[7]. Current depression treatments, ranging from medications (SSRIs, psychedelics) to mindfulness, have been associated with a reduction in DMN connectivity[9]. Indeed, nodes where neuromodulation alters DMN activity/connectivity have been proposed as defining potential interventional hubs in MDD[1]. Furthermore, the DMN connectivity has been implicated in a broad set of conditions such as OCD, anxiety, and ADHD highlighting the potential impact across mental health conditions. Prior lesion and DBS-based studies have suggested that ANT may modulate DMN activity[10]. Here, we confirm this finding using a novel, non-invasive method. Further studies are needed to confirm the generalizability of our findings in MDD and to understand whether our results are due to selective engagement of ANT or nearby thalamic structures, e.g. dorsal medial thalamus, which are also within the ultrasound field. Ongoing further studies are required to assess TUS parameterization to improve treatment efficacy, as well as effects of stimulation over longer durations of time.

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Conflicts of Interest: K.R.M, C.H.G., and T.D.I. have equity/stock options and have received salary and/or consulting fees from Attune Neurosciences, Inc. J.L.C. has equity/stock options and receives salary from Options MD.

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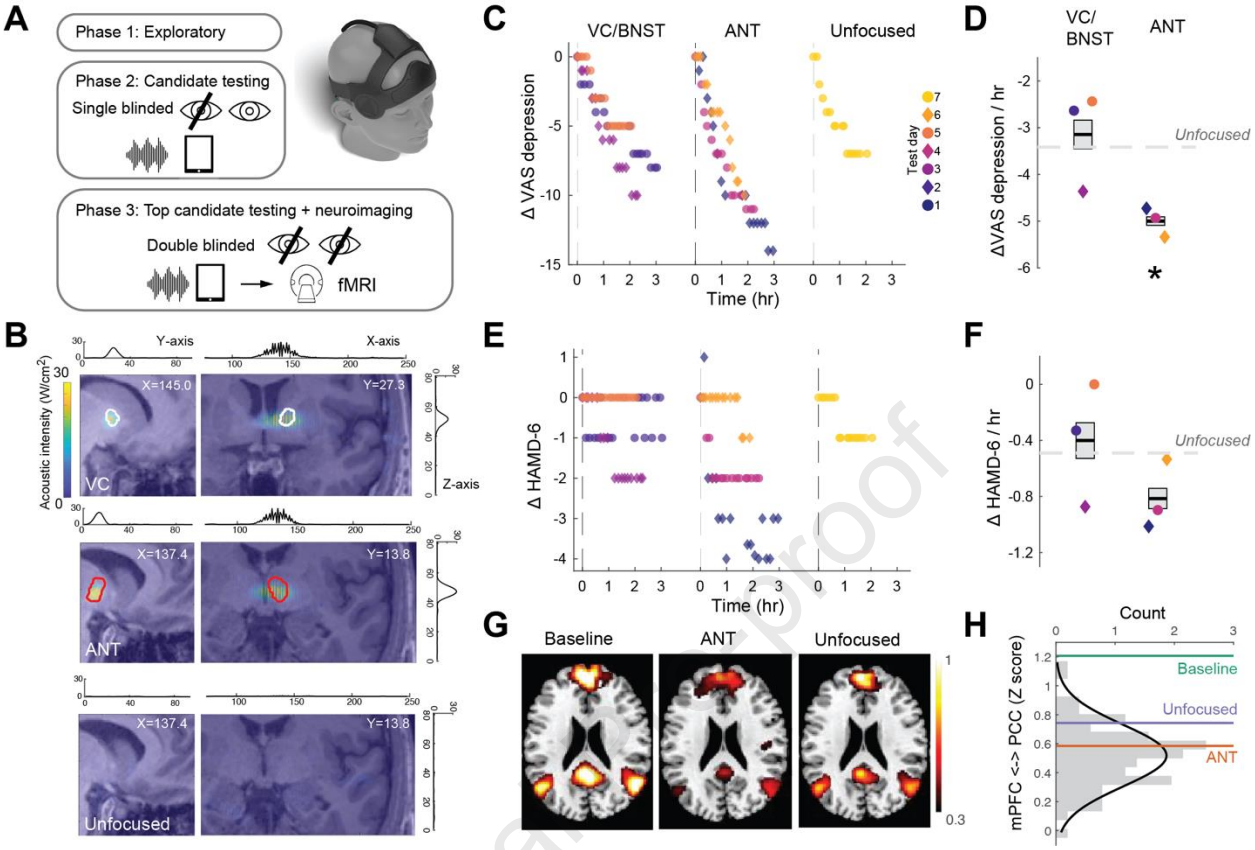

Figure 1. ANT stimulation reduces VAS depression and suppresses default mode network connectivity. A) Depiction of three phase experimental design. TUS study device illustrated in inset. B) Simulated field of TUS crossbeam intensities overlaid on a sagittal and coronal cross-section of T1-weighted MRI coronal for the right-lateralized VC (top row; outlined in white), ANT (middle row; outlined in red), and Unfocused (bottom row) conditions. Note that the VC and ANT masks are non-overlapping; the mask of each of the other active condition is not seen in the respective cross-section. C, E) Trajectories of VAS depression and HAMD-6 over time grouped according to each replicate stimulation condition: VC/BNST (left), ANT (middle), and unfocused (right). The color codes represent each day of testing an individual condition. The x-axis represents session time, where the start of each visit equates time 0. The y-axis represents the change in symptom scores over a stimulation session from the pre-stimulation survey for any given day. Each point represents a survey assessment taken during the span of the stimulation protocol. Survey assessments were taken immediately following each 5 min stimulation pulse train and after each 10 min inter pulse train interval. D, F) Averaged change in VAS depression and HAMD-6 score per hour for each condition: VC/BNST (left) and ANT (right). The unfocused stimulation condition is given by the dotted gray line. The ANT stimulation condition statistically reduced the averaged VAS depression per time, as compared to the unfocused control ($p = 0.0127$; one sample t-test). G) Visualization of DMN connectivity based on a medial prefrontal cortex seed; ANT stimulation reduces DMN connectivity as compared to the baseline and unfocused conditions (Fisher-transformed correlation coefficient units). H) Normalized probability density function of anterior-posterior DMN connectivity in a group of healthy controls (grey histogram bars) and overlaid black normal distribution curve. Colored bars indicate baseline/pre-stimulation (green), ANT (orange), and unfocused (purple). Note that unfocused condition occurred the following day, i.e. 24-hrs, after ANT stimulation; the extent to which wash-out of

stimulation had occurred remains unknown. *Abbreviations*: ventral capsule (VC); bed nucleus of stria terminalis (BNST); anterior nucleus of the thalamus (ANT); visual analog scale (VAS); Hamilton Depression Rating Scale (HAMD); medial prefrontal cortex (mPFC); posterior cingulate cortex (PCC)

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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