Noninvasive, Systematic, and Sustained Modulation of Deep Brain Circuits in Awake Subjects

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ABSTRACT

Transcranial focused ultrasound has the potential to noninvasively and systematically modulate deep brain circuits and impart sustained, neuroplastic effects in awake subjects. The intersection of these key properties is critical for effective treatments of brain disorders, yet remains to be shown. Harnessing the full potential of transcranial ultrasound, we delivered 30-second stimuli to deep brain targets (left/right lateral geniculate nucleus) in non-human primates while they performed a visual discrimination task. This brief sonication induced a sustained bias in choice behavior that persisted up to 15 minutes following the ultrasound offset. This behavioral effect was accompanied by an increase in gamma activity with dynamics that matched the effects on behavior. Moreover, the ultrasound was delivered into the targets daily for a period of more than 6 months. There were no detrimental effects on the animals' discrimination accuracy over the course of this stimulation regimen, even though the stimuli exceeded the FDA 510(k) Track 3 intensity values. This study highlights ultrasound's capacity to modify deep brain activity in a safe and therapeutically relevant way in awake subjects, thus bringing the approach closer to therapeutic options for patients suffering from treatment-resistant disease.

Introduction

Mental and neurological disorders are frequently resistant to existing treatments.[1–8] Targeted neuromodulation has improved outcomes for many of these patients but existing clinical approaches—such as deep brain stimulation and transcranial magnetic stimulation—are either invasive or lack the capacity to directly modulate individual deep brain regions.

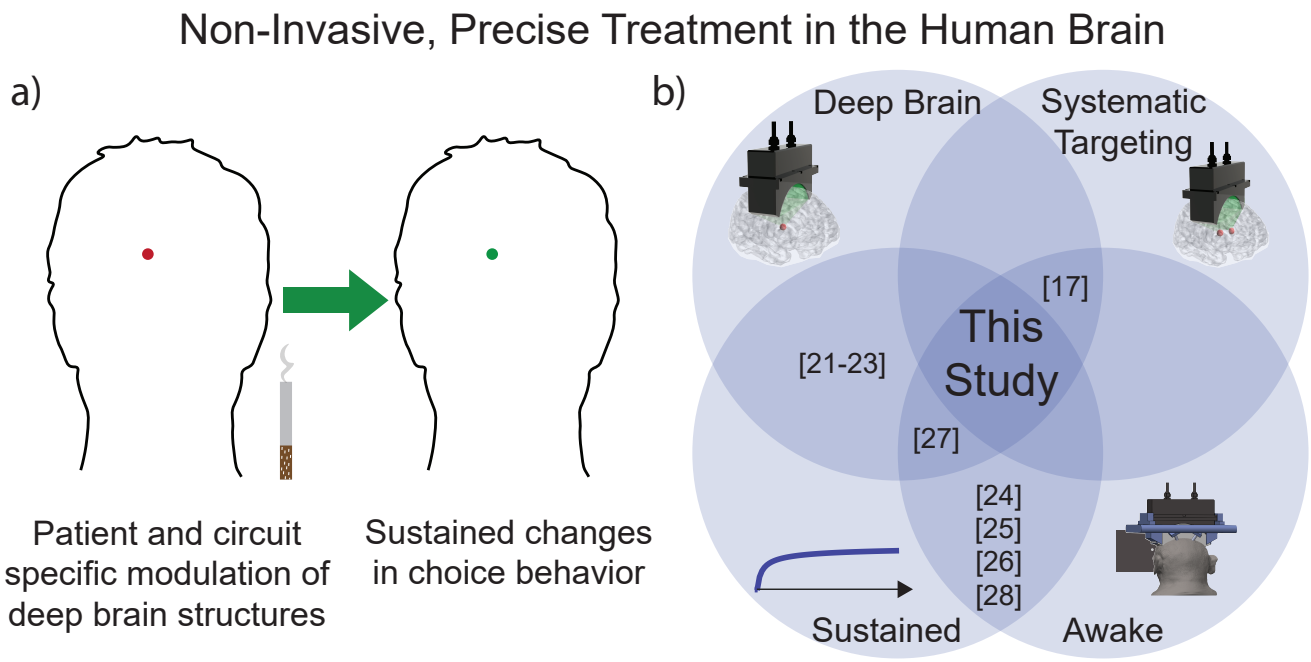

Figure 1. Non-Invasive Precision Medicine for the Brain
a) Durable Precision Therapies: Ultrasound uniquely combines the capacity to non-invasively target deep brain regions with high precision and flexibility. Its potential for inducing sustained changes in the targeted circuit is a key step towards ultrasound-based treatments of nervous sysstem disorders (e.g., addiction).
b) The Key Strengths of Ultrasound: Several studies (see inset) have shown ultrasound's capacity to modulate deep brain targets, produce sustained effects on the circuits, applying stimulation systematically to multiple regions, or evaluating effects on awake behavior. This study now combines these strengths. The study leverages Remus[17]—a custom phased array system—to systematically target multiple deep brain structures and induce sustained and region-specific changes in awake behavior.

Transcranial low-intensity focused ultrasound can noninvasively modulate deep brain circuits with millimeter precision[9]. Transient modulation of neuronal activity within targeted regions has been shown in several pre-clinical and clinical models using neuronal recordings[10–13] and behavioral metrics.[14–18] While transient perturbations are useful for diagnostic and guidance applications, therapeutic translation of ultrasound requires a robust demonstration of its capacity to induce sustained changes in awake behavior through the focal perturbation of deep brain circuits (Figure 1a). Additionally, the generation of effects that outlive the stimulation is critical to avoid auditory, tactile, or other artifacts.[19,20]

Proofs of concept of durable changes have been published.[21–28] However, the full strength of ultrasound—programmatic targeting of multiple deep brain regions to induce sustained and region-specific neuroplastic effects in awake subjects (Figure 1b)—has not yet been demonstrated. This demonstration is critical for effective and personalized treatments.

This study leverages Remus,[17] a custom phased array platform, to simultaneously demonstrate ultrasound's capacity to induce sustained changes in awake behavior through programmatic targeting of multiple deep brain regions (Figure 1b). The study targets the left and right lateral geniculate nucleus (LGN) during a well established visual discrimination task.[14] Inhibition/excitation of the LGN during this task results in an ipsilateral/contralateral bias in the subject's choice behavior.[29,30] The phased array system enables flexible and reproducible targeting of the left and right LGN without any changes to the experimental setup, which allows us to systematically evaluate lateralized effects. Using this approach, we evaluate the polarity, magnitude, and duration of the induced neuromodulatory effects.

Results

Noninvasive, Sustained, and Reversible Neuromodulation

Remus,[17] a 256-element phased array transducer system (Figure 2a), delivered ultrasound to the right (red) or left (blue) LGN while the subject performed a simple visual discrimination task (Figure 2b). We found that a single 30-second sonication induced a sustained but reversible contralateral bias in the subjects' visual choice behavior (Figure 2c). This effect was specific to the stimulated hemisphere; stimulation of the left/right LGN induced a rightward/leftward bias in the subjects' choices (Figure 2d). The behavioral effects outlived the stimulation by 15 minutes (final time point for which the effect in Figure 2d is significant; two-tailed t-test, $p < 0.05$).

We quantified the effects on choice behavior using a two-way ANOVA, with factors sonicated side and time. Notably, in this analysis, we only included times following the ultrasound offset. This way, the reported effects are free of artifacts that can be associated with transcranial ultrasound [19,20]. The effect of the sonicated side was highly significant ($F(1) = 17.87$, $p = 1.1e-4$). Time or its interaction with side were nonsignificant in this model.

These effects on choice behavior were accompanied by an increase in gamma activity recorded over visual cortex (Figure 2e). As in the behavioral analysis, we only assessed the activity following the ultrasound offset, to make sure the recordings are not affected by a potential artifact that could be associated with the ultrasound. A two-way ANOVA, with factors signal frequency and time, identified a significant effect of signal frequency ($F(2) = 4.12$, $p = 0.017$). Time or its interaction with frequency

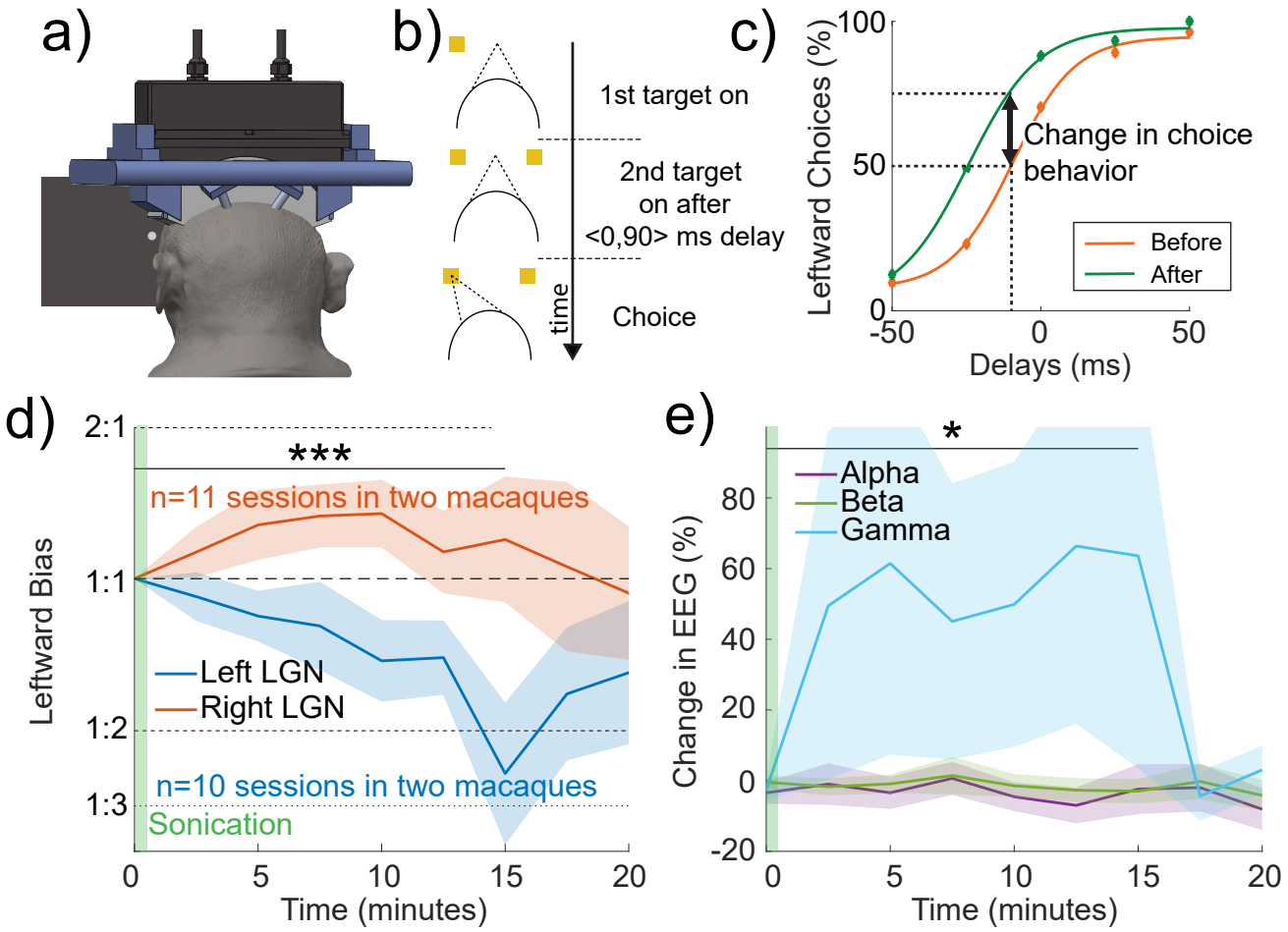

Figure 2. Noninvasive, Sustained, and Reversible Modulation of Deep Brain Circuits and Choice Behavior.
a) Apparatus: A system for reproducible delivery of ultrasound into deep brain targets[17] delivered 30-s of ultrasonic stimulation into to the left/right LGN while the subject performed a visual discrimination task.
b) Choice task: Following fixation of a central target, a target appears in the right or left hemifield, followed by a second target in the opposite hemifield. There is a random delay (range 0 and 90 ms) between the onset of the two targets. The subject is rewarded for selecting the target that appeared first.
c) Quantification of the effects on choice behavior: A baseline epoch prior to the ultrasound (orange) is used to establish the point of equal preference for each session. We quantify the proportion of leftward choices at this point of equal preference following the stimulation (green). The data represent an example right LGN stimulation session.
d) Sustained Modulation of Behavior: Sonication of the right (red) or left (blue) LGN induces a persistant contralateral bias in the animals' choices. The data are shown as mean$\pm$s.e.m. $***: p < 0.001$: two-way ANOVA detected a significant effect of the stimulated side on the choice behavior (see text for details).
e) Sustained Increase in Neural Activity: Neural activity was recorded from parieto-occipital leads (see panel a). Mean$\pm$s.e.m. gamma, beta, and alpha activity as a function of time. The modulation by the frequency band was assessed using two-way ANOVA (see text for detail). $*: p < 0.05$.

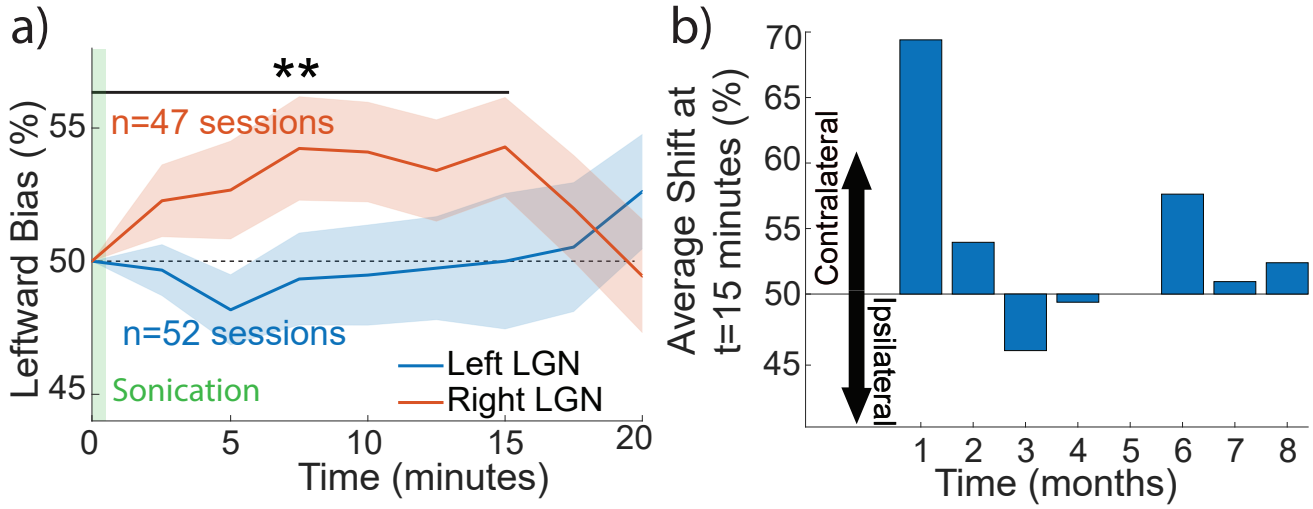

Figure 3. Behavioral Adaptation.
a) When all sessions are included the effect is smaller but still significant. Significance measured with a two way ANOVA with factors time and side sonicated. Side sonicated showed significant variation ($F(1) = 8.4, p = 0.0041$). $** : p < 0.01$
b) The strength of the effect diminishes over time, suggesting that the subject is able to adapt to the effect in order to maximize their reward. During month five, one subject was on vacation and the second subject was participating in a study with much lower ultrasound intensities.

were non-significant. Since gamma activity provides a tight correlate of multi-unit spiking[31–33], this effect suggests an excitation of the stimulated circuits.

Both the behavioral and neural effects showed a similar temporal profile (Figure 2d-e). Moreover, both effects are consistent with an excitatory effect of the ultrasound on the stimulated deep brain circuits[14].

Behavioral Adaptation

The stimulation was applied to the subjects over the course of many months. As a consequence, we found that the subjects learned to compensate for the effects of ultrasound on the LGN. When all sessions are included (Figure 3a) the contralateral bias is still significant but the effect is smaller. This compensation is expected because an ultrasound-induced bias decreases the discrimination accuracy and therefore the reward income for the animals. Figure 3b shows the average effect across months (30 day periods) measured during the 10-15 minutes following sonication. The subjects' bias shows a sudden decrease after the initial sessions. During the fifth month, one subject was on vacation and a second subject participated in a separate experiment with much lower ultrasound intensities. After this period the effect rebounded slightly but then decreased again. The data presented in Figure 2d show only the sessions acquired during

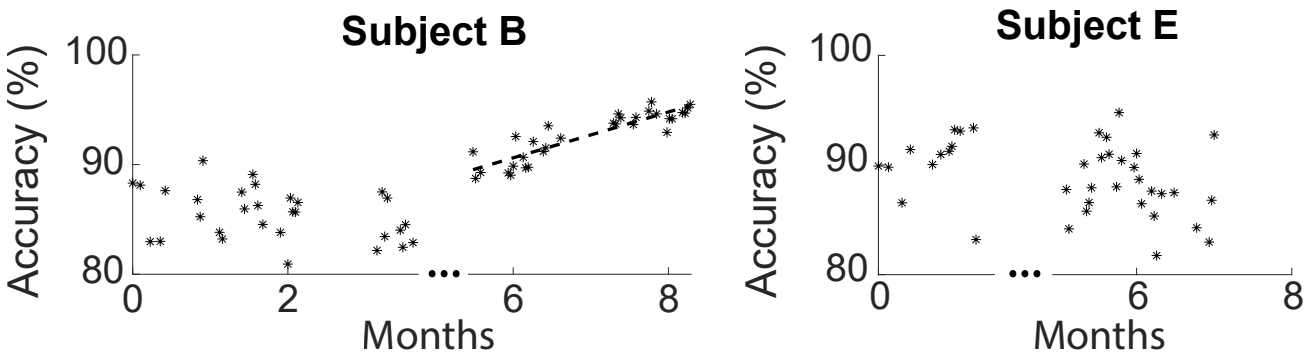

Figure 4. Chronic Modulation of Deep Brain Circuits Is Safe.
Repeated application of neuromodulatory ultrasound to deep brain circuits is safe. Significant damage to the LGN would cause a notable decline in the subject's visual discrimination performance. We observe no such decline, with both subjects showing consistent or improving performance across sessions. Both subjects took a break in the middle of data collection (indicated by the ellipsis). A linear fit to accuracy is only significant in the second block of sessions for subject B ($p < 0.001; r = 0.8$). This demonstrates that the repeated neuromodulation was safe at the functional level.

months 1 and 6.

Safety

The safety of these sonications was tested by measuring each subject's accuracy across sessions (Figure 4). Damage to the LGN would manifest in a decrease in the subject's accuracy but we see no such effect. After chronic sonication across multiple months, both subjects show stable or improving accuracy (the improvement in the second set of sessions for subject B is significant, $r = 0.80, p < 0.001$, all other linear fits are non-significant). Thus, the subject's behavior reveals no evidence of damage as a result of chronic neuromodulatory stimulus.

Parameters

A variety of pressures and duty cycles were used to acquire the data in Figures 2-4. Tables 1 and 2 give a summary of the spatial peak temporal average intensity (I_{SPTA}), the spatial peak temporal peak intensity (I_{SPPA}), the duty cycle (DC), the number of sessions recorded during sonication of each LGN, the number of sham sonications, and whether or not the beam was scanned to multiple locations during the sonication (see the following sections for details on sham controls and beam scanning). Given the subjects' adaptation to the ultrasound stimulus, we do not have sufficient data to examine the relationship between acoustic parameters and the behavioral effect. For details on the estimation of *in situ* pressure, see detailed methods.

Table 1. Sonication Parameters in Subject B. Intensities are given in (W/cm^2)

I_{SPTA}	I_{SPPA}	DC (%)	Left	Right	Sham	Scan
1	30	3.6	8	6	0	No
1	30	3.6	8	7	0	Yes
1	10	14.4	8	8	8	Yes
2	60	3.6	8	8	0	Yes

Table 2. Sonication Parameters in Subject E. Intensities are given in (W/cm^2)

I_{SPTA}	I_{SPPA}	DC (%)	Left	Right	Sham	Scan
1	60	1.8	9	8	0	Yes
2	15	14.4	4	5	0	Yes
2	60	3.6	7	5	5	No

Controls

In each subject, one parameter set was selected in which to deliver a sham stimulus. The sham sonication delivered the same amount of acoustic energy but the phases applied to each element of the transducer were randomized in order to create an unfocused beam. Figure 5 shows the measured changes in behavior resulting from the sonication parameters for which a control was also delivered. The subject's showed no change in behavior as a result of sham sonications.

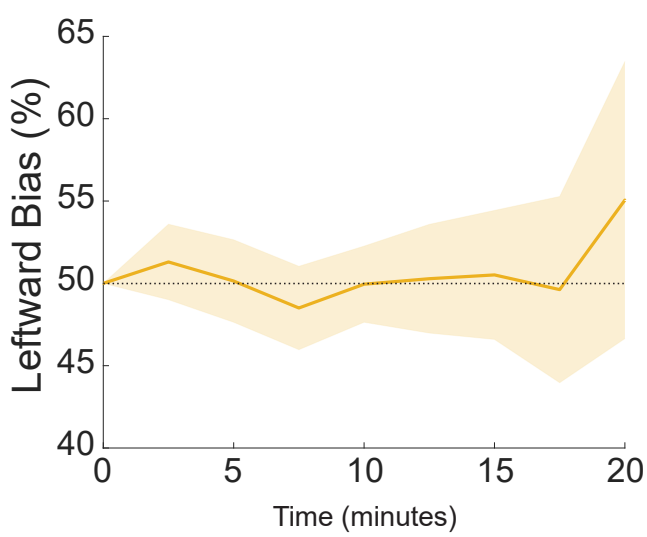

Figure 5. Sham Sonications
Sham sonications delivered the same amount of energy with random phases applied to each element. No behavioral changes were noted during sham sonications.

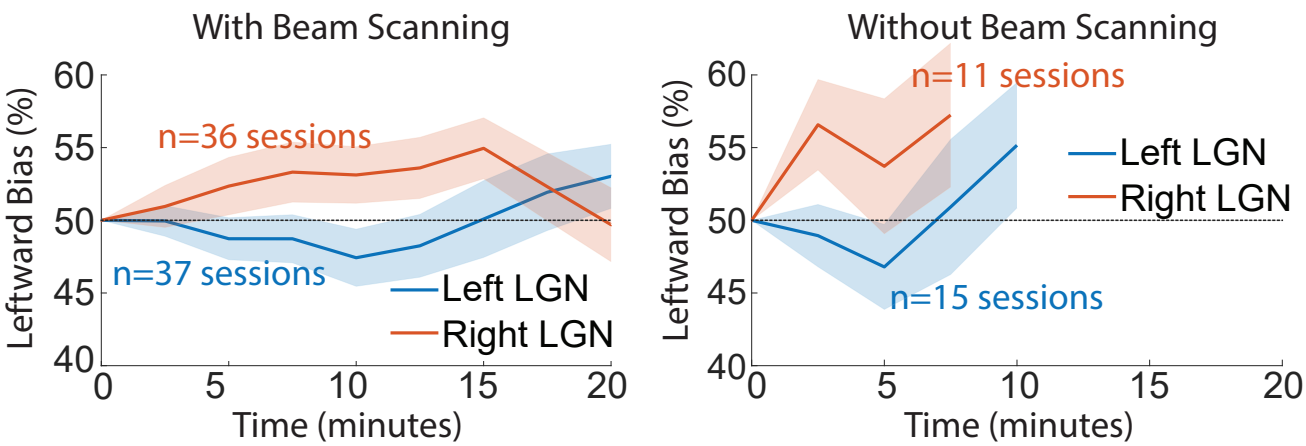

Figure 6. Beam Scanning
Changes in behavior measured with (left) and without (right) beam scanning.

Beam Scanning

In early sessions, we observed asymmetric effects when sonicating the left/right LGN. To address the possibility that this was due to poor targeting we began scanning the beam during sonication. The beam was steered to five locations (the central target was complemented by targets $\pm 1.5mm$ in the left/right dimension and $\pm 3mm$ in the inferior/superior dimension). Thus, when beam scanning was on, the duty cycle at the transducer was five times the duty cycle at each target location (the duty cycle values given in Tables 1 and 2 represent the duty cycle at target). Figure 6 compares the observed changes in behavior after we began beam scanning (left) to the results observed before we began beam scanning (right).

Discussion

We demonstrated the capacity of ultrasound to non-invasively induce durable and reversible changes in awake behavior and EEG rhythms. Our results show that a 30 second sonication can induce behavioral and circuit level changes lasting up to 15 minutes. These results provide further evidence of ultrasound's capacity to effectively rewire deep brain circuits in a targeted, noninvasive, and therapeutically relevant manner.

Our results extend and reinforce prior studies by demonstrating persistent, target specific changes in choice behavior in awake behaving primates. The 15 minute duration of the behavioral effects coincides well with another NHP visual behavior study that found changes in saccade latency which persisted

for 18-31 minutes after a 20 second sonication of the frontal eye field.[26] Other studies have similarly shown changes in NHP behavior[27], fMRI[21–23] or motor evoked potentials (MEP) in humans[28] that persist for minutes to hours following sonications with durations between 40 and 120 seconds. Thus, our measurement of lateralized behavioral changes adds considerable evidence to a growing consensus that ultrasound can induce durable and reversible changes in neuronal activity.

Similarly, the duration of ultrasound induced changes measured in this study compares favorably to the duration of changes induced by trains of TMS pulses with a similar duration.[34] This is significant because TMS has emerged as an effective alternative for patients suffering from treatment resistant depression[35] and it is gaining momentum as a potential treatment for many other neurological disorders.[36] Ultrasound improves on TMS by providing focused modulation of neural circuits at any depth - allowing the direct treatment of emotional circuits that TMS can only effect indirectly. Thus, ultrasound is likely to offer effective treatment options to patients suffering from treatment resistant disease.

The sustained behavioral effects also address lingering concerns that ultrasound neuromodulation may be mediated by an auditory or tactile artifact.[19,20] Most of the behavioral data presented in this study was acquired with the ultrasound off—thus, without the possibility of tactile or auditory confounds. Because of time averaging, the behavioral bias measured up to time $t = 5.5$ minutes does include trials that the subject performed while the ultrasound was active. However, all of the measurements after that time were acquired entirely while the ultrasound was off. Thus, these data demonstrate artifact free modulation of neural activity using transcranial ultrasound.

Methods

Animals

Two male macaque monkeys (*macaca mulatta*, age 7 and 5 years, weight 9.5 and 12 kg) participated in this study. The procedures were approved by the Institutional Animal Care and Use Committee of the University of Utah.

Acoustic Parameters

All ultrasound stimuli had a center frequency of 480 kHz. Intensity at the focus was estimated using MR thermometry[17] to estimate a conversion between voltage on the transducer and pressure at focus. To maintain consistency, the result was averaged across the two subjects. The resulting conversion assumed that the *in-situ* pressure was approximately 46% of the free field pressure. Each sonication lasted thirty seconds and consisted of several 30 ms pulses. Pulsing was done with a rectangular envelope.

Task

We trained two NHPs to perform a visual choice task. This task was used in many previous studies (e.g.,[14,37]). Briefly, the subject was seated in a comfortable primate chair and was presented with visual stimuli shown on a monitor. The subject's eye movements were tracked and recorded using an infrared eye tracker (Eyelink, SR Research, Ottowa, Canada).

Each trial in the behavioral task begins with the subject fixating on a central visual stimulus point. After a random delay a target appears in either the left or right visual hemifield. A second target then appears in the opposite hemifield after a delay between 0 and 90 ms. The subject was rewarded for looking at the target that appeared first. Subjects received a liquid reward with a probability $0.5 <= p <= 1$ if they looked at the target that appeared first within 2 s. In the condition in which both targets appear at the same time both subjects are rewarded for either choice.

Sonication of the right and left LGN was interleaved across sessions. The left LGN was sonicated in 52 sessions (32 in subject B and 20 in subject E) and the right LGN in 47 sessions (29 in subject B and 18 in subject E). Changes in behavior were quantified by fitting a sigmoid to a subject's average choice behavior in five minute blocks (Figure 2c, negative delays mean the target in the right hemifield appeared first). In each session, baseline behavior was measured in the five minutes before the sonication and the delay at which the subject had an equal preference for either target was recorded. Changes in the subject's behavior in future five minute blocks were then quantified by measuring the change in the subject's preference for the leftward target at the baseline delay.

The subjects complete a minimum of 600 trials to provide an adequate baseline before the 30 second sonication which begins synchronously with the beginning of a trial and the task continues throughout the

sonication. Both subjects occasionally paused at the beginning of the sonication but generally continued to perform trials while the stimulus was active. Trials continued without change or interruption after the sonication was completed. The subjects generally worked daily throughout the work week.

Both subjects were allowed to continue doing trials for as long as they were willing after the sonication. Subject B willingly performed the task for an hour or more while Subject E often quit shortly after the sonication. Thus, the number of sessions decreases with increased time after the sonication and the standard error of the mean, shown by the shaded regions in Figures 2d and 3a are continuously updated to include this decrease in the number of sessions. In addition to sessions being excluded because the subject stopped working, at each time point sessions were excluded if the subject was working at a rate of less than 1 trial every 10 seconds. A total of 61 sessions in subject B and 38 sessions in subject E were included in this study. At the end of the 20 minutes displayed in Figure 2d 51 sessions remained in subject B and 20 sessions remained in Subject E. Sessions in which the subject worked for less than five minutes following the sonication were excluded.

EEG

EEG signals were recorded by attaching electrodes to the surgically implanted pins used to secure the transducer to the subject's skull. A front pin was used as a reference electrode and the signal from the two rear pins was averaged to generate the EEG signal. The signal was filtered with a notch filter centered at 60, 120, and 180 Hz.

The power in the α, β, and γ bands was then measured using the Fourier transform in 500 ms windows. Windows in which the EEG signal exceeded 100 μV were assumed to be noise and were excluded. The α, β, and γ bands were defined as the frequencies between 7 and 12 Hz, 12 and 30 Hz, and 30 and 70 Hz, respectively. The 500 ms windows were then averaged in 5 minute increments every 30 seconds to produce the results given in Figure 2e. The baseline value was determined by averaging all the five minute windows prior to the sonication.

Statistical analyses

The two-way ANOVA, used to establish the difference in behavior between the two stimulation targets, was evaluated in time windows of [0.5,5.5], [5.5,10.5], and [10.5,15.5] minutes following ultrasound

the offset of the stimulation. The windows start at 0.5 in order to exclude trials performed during the sonication.

Acknowledgments

This work was funded by the Focused Ultrasound Foundation and the NIH grants F32MH123019 and R00NS100986.

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