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Noninvasive targeted modulation of pain circuits with focused ultrasonic waves

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Abstract

Direct interventions into deep brain circuits constitute promising treatment modalities for chronic pain. Cingulotomy and deep brain stimulation targeting the anterior cingulate cortex have shown notable improvements in the unpleasantness of pain, but these interventions require brain surgeries. In this study, we have developed an approach that can modulate this deep brain affective hub entirely noninvasively, using low-intensity transcranial-focused ultrasound. Twenty patients with chronic pain received two 40-minute active or sham stimulation protocols and were monitored for one week in a randomized crossover trial. Sixty percent of subjects experienced a clinically meaningful reduction of pain on day 1 and on day 7 following the active stimulation, while sham stimulation provided such benefits only to 15% and 20% of subjects, respectively. On average, active stimulation reduced pain by 60.0% immediately following the intervention and by 43.0% and 33.0% on days 1 and 7 following the intervention. The corresponding sham levels were 14.4%, 12.3%, and 6.6%. The stimulation was well tolerated, and no adverse events were detected. Side effects were generally mild and resolved within 24 hours. Together, the direct, ultrasonic stimulation of the anterior cingulate cortex offers rapid, clinically meaningful, and durable improvements in pain severity.

Keywords: Ultrasound, Deep brain, Neuromodulation, Central chronic pain

1. Introduction

An estimated 20% to 30% of people suffer from chronic pain, a type of pain that does not resolve following healing of the initial injury.[13,61,68] Chronic pain is often recalcitrant, greatly diminishes the quality of life, and frequently results in psychiatric disorders[3,66] and, in some cases, suicide.[48] Imaging[12,22,29,44] and interventional[5,32,56] studies provide compelling evidence for the involvement of a deep brain neural hub in the limbic system, the anterior cingulate cortex (ACC), in the unpleasant, aversive component of pain.

The ACC is heterogeneous in structure and function. Three ACC subregions—anterior midcingulate cortex (aMCC), pregenual ACC (pACC), and subgenual ACC—have been implicated in emotional regulation associated with chronic pain.[43] Anatomically, the pACC is tightly linked to the prefrontal cortex, whereas sACC is connected with the amygdala.[57] These regions show a functional dissociation with respect to emotional valence: The sACC and pACC are modulated by negative and positive emotions, respectively.[64] The aMCC has been shown to play a role in the cognitive/evaluative aspect of chronic pain.[38] The aMCC is activated by actual pain experience, as well as by pain-related contextual cues.[42] Furthermore, activity in this area is modulated by attention toward or away from painful stimuli.[29,44]

Thus, the ACC serves a distinctive function of integrating the affective-cognitive parameters of pain perception. Indeed, preclinical models of neuropathic pain show a significant role of ACC in linking pain and depressive behaviors.[4,7] Moreover, ACC hyperactivity accentuates the aversive component of chronic pain.[55] The ACC also appears to integrate situational affective valence into the subjective experience of pain. For example, individuals who receive noxious stimulation while exposed to sad faces exhibit significantly greater activation of the ACC compared with individuals presented with happy faces.[70] Reduced ACC activity following lesions can cause deficits in response selection to noxious stimuli, kinetic mutism, motor neglect and impaired motor ignition, and aberrant social behavior.[15]

Surgical interventions into the ACC using cingulotomy are known to improve pain symptoms, which supports a causal role of this brain region in the processing of pain. Specifically, a systematic review that evaluated 244 patients across 11 studies showed that this well-tolerated procedure provides pain relief in over 60% of cases.[56] Deep brain stimulation (DBS) implants targeting the ACC provide an average of 35% to 48% reduction in pain intensity.[5,32] Despite the effectiveness of these treatment options, both cingulotomy and DBS require surgeries, which limit their scalability to benefit larger patient populations.

To address this issue, we have developed an approach and a device that can modulate the ACC and associated circuits

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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entirely noninvasively. The approach focuses ultrasonic waves into deep brain targets through the intact skull and scalp.[50,52,53] Critically, the device measures and compensates for the severe aberrations of ultrasound by the human head, thus delivering into each target controlled, deterministic ultrasound intensity.[51]

In this study, we have applied the approach and device to modulate the ACC in 23 patients with chronic pain. The primary aim of this study was to assess the effects on pain using a randomized crossover sham-controlled study design. In addition to the clinical outcomes, in a subset of patients, we validated target engagement using functional MRI (fMRI).

2. Methods

2.1. Trial design

This study was a pilot double-blind, randomized, controlled crossover trial assessing the efficacy and safety of focused ultrasound (FUS) stimulation of the ACC for patients with generalized chronic pain (ClinicalTrials.gov NCT05674903).

Subjects who met the study criteria (see below) completed baseline measures of chronic pain including the Brief Pain Inventory,[59] Patient-Reported Outcomes Measurement Information System (PROMIS) pain intensity,[25] PROMIS depression, and PROMIS anxiety metrics.[45] Following baseline, subjects were randomly assigned to active or sham groups. Both groups started with an MRI session (approximately 1 hour) which was primarily used to register the device to the patient's brain anatomy. Secondarily, that session also measured fMRI activation in response to ultrasound stimulation. Next, subjects participated in a treatment session outside of the MRI (40 minutes of stimulation; approximately 1 hour in total) using either completely active or sham stimulation. Subjects were monitored after treatment for 7 days and then crossed over to the opposite group if they continued to meet inclusion criteria. Subjects were required to have at least an average 24-hour numerical rating scale (NRS) pain score of 3 to crossover to the second treatment and delayed treatment after active or sham until this threshold was met. At the crossover, the subjects repeated the treatment procedure in the opposite group and were again monitored for 7 days postintervention.

2.2. Participants

This study was approved by the Institutional Review Board of the University of Utah. All subjects provided informed consent. This study recruited subjects with a primary diagnosis of chronic pain between the ages of 18 and 65. Pain had to be present for at least 3 months with moderate-to-severe levels of pain.

Exclusion criteria included any patient with a lifetime history of a serious suicide attempt; history of serious brain injury or other neurological disorder; brain stimulation in the past month (eg, electroconvulsive therapy, transcranial magnetic stimulation [TMS], vagal nerve stimulation); MRI intolerance or contraindication; or implanted device in the head or neck.

Table 1 summarizes the participant sample characteristics. The study population was 60% women and, on average, 46.6 years of age. The Brief Pain Inventory (BPI) 24-Hour Average Pain score ranged from 3 to 8 with an average of 5.35 for active and 5.21 for sham. Patient-Reported Outcomes Measurement Information System pain intensity score ranged from 54.2 to 74.4 with an average of 65.0 for active and 63.6 for sham. The study cohort corresponded to subjects with moderate-to-severe pain. Subjects had single or multiple sources of chronic pain that ranged broadly including fibromyalgia (10), myofascial pain syndrome (4), generalized pain syndrome (4), migraines (3), back pain (3), neuropathy (3), arthritis (3), chronic fatigue syndrome (2), complex pain syndrome, piriformis syndrome, atypical trigeminal neuralgia, cervical myelopathy, shoulder pain, foot pain, joint pain, endometriosis, scleroderma, dysautonomia, common variable immunodeficiency, temporomandibular joint dysfunction, Guillain–Barré syndrome, Crohn disease, and postcancer pain. Individual chronic pain etiologies, demographics, and pain scores are shown in Table S1 (available at http://links.lww.com/PAIN/C85).

Table 1

Demographic information.

	Real	Sham
Female (male) subjects	12 (8)	11 (9)
Age (SD)	46.5 (10.36)	46.7 (10.37)
Average NRS (SD)	5.35 (1.39)	5.21 (1.47)
PROMIS pain intensity 3a	65.02 (4.75)	63.60 (4.97)
PROMIS depression 8b	59.19 (6.97)	58.64 (8.48)
PROMIS anxiety 7a	57.8 (9.86)	58.39 (8.61)

Individual rows provide, separately for real (left) and sham (right) stimulation groups, the number of female (male) subjects, mean ± SD age, mean ± SD baseline numerical rating score of pain, and mean ± SD baseline scores of PROMIS pain intensity, depression, and anxiety.
PROMIS, Patient-Reported Outcomes Measurement Information System; NRS, numerical rating scale.

2.3. Interventions

This study evaluated FUS stimulation of the ACC over a single 1-hour session containing 40 minutes of active sonication. Ultrasound was focused on a target using 2 phased array transducers placed over the left and right parietal bones.[50] All treatments took place outside the MRI (**Fig. 1A**).

2.3.1. Registration

Before treatment, subjects underwent a standard anatomical (T1-weighted) MRI for treatment guidance. These scans enable the coregistration of the device's position to subject-specific brain anatomy, as described previously.[50] Treatments were performed outside the scanner. The head was locked in the same radiological mask and position as during the MRI scans, thus ensuring targeting reproducibility[50] (**Fig. 1B**).

2.3.2. Targeting

Following registration, 8 targets within the ACC were selected: 2 targets within the subgenual ACC (Brodmann Area 25[65]) and 6 targets from within the pACC to aMCC (Brodmann Areas s24, p24, a24, 33[65]). The arrays produce a −6 dB intensity field with lateral × elevational × axial dimensions of 2.4 × 3.6 × 20.4 mm (y, z, and x dimensions of the Montreal Neurological Institute [MNI] coordinate system) (**Fig. 1C**).[50] Each of the 8 targets was centered on the subject's midline in the x-dimension and white matter tracks from both hemispheres in the y-z dimension.[35] Each target was separated from the adjacent target by 4 mm in the sagittal plane (y-z dimension) to provide a continuum but avoid an overlap of the stimulated subregions (**Fig. 1**). In this plane, the target was also placed at least 4 mm from the outer edge of the corpus callosum to minimize direct stimulation of this highly connected area. The shape of the focus allowed for bilateral stimulation of the ACC. Average target location and distribution are shown in **Figure 1**.

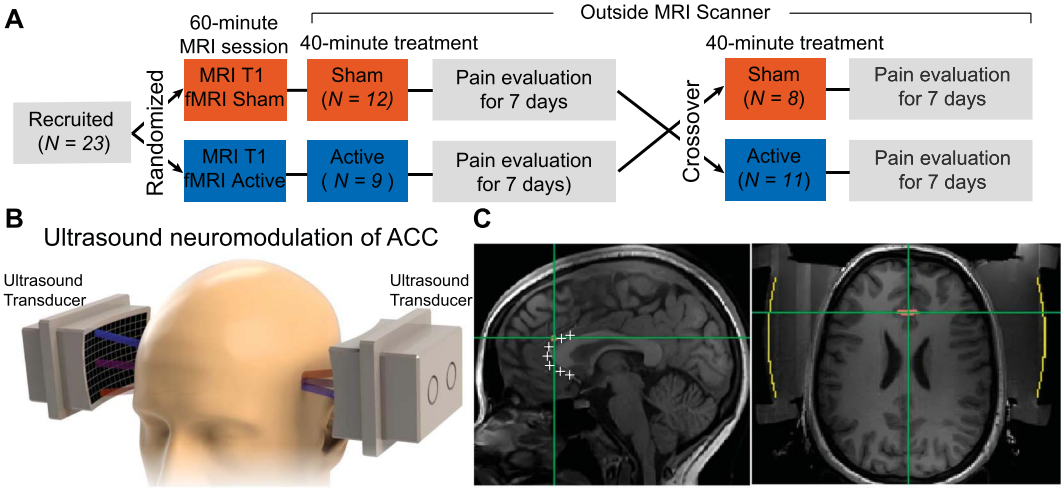

Figure 1. Experimental setup for noninvasive deep brain modulation of chronic pain. (A) The trial design showing randomization to MRI T1 and 10-minute fMRI measure of either active or sham stimulation followed by the first 40-minute ultrasound treatment session outside the MRI scanner, 7-day monitoring, washout, second treatment session outside the MRI scanner, and 7-day monitoring. There were 20 (20) data points available for the active (sham) conditions. See the CONSORT diagram in Supplemental Figure 1 (available at http://links.lww.com/PAIN/C85) for details. (B) Transcranial low-intensity focused ultrasound was delivered into the ACC target using a device described previously.[50–53] (C) The ACC targeting was validated using MRI.[50,52,53] Since the ACC is a large structure with respect to the ultrasound focus (2.4 mm × 3.6 mm × 20.4 mm[50]), we targeted 8 ACC subregions, indicated by the white crosses. The green crosshair exemplifies the targeting of one of the subregions. The pink regions outline the corresponding >50% peak intensity focal volume of the ultrasound.[50] ACC, anterior cingulate cortex; fMRI, functional MRI.

2.3.3. Treatment

The treatment session, performed outside the scanner, consisted of 2 stimulation blocks. Block A contained sixteen 30-second stimulations to test for immediate symptom reduction. Symptoms were assessed verbally after each sonication with subjects reporting any positive or negative changes to their pain. The targets were ordered randomly without replacement such that each target was stimulated twice. Verbal reports typically took 15 to 60 seconds between each sonication. We selected the 4 targets that yielded the strongest reduction in the pain symptoms. Block B delivered to these 4 targets twelve 3-minute sonications, randomly interleaved. The individual stimulations were again spaced by 15 to 60 seconds as the operator selected the next target and the subject reported any positive or negative changes from the previous stimulation. Sham stimulation used the same protocol but only provided auditory masking to the subjects; zero voltage to the transducers.

2.3.4. Stimulation parameters

Ultrasound was delivered to each target with amplitude of 1 MPa (estimated using the relative through-transmit skull correction,[51] spatial peak pulse average intensity (I_{SPPA}) 31.0 W/cm^2, mechanical index (MI) = 1.2, thermal index (TI) = 0.64), 30 milliseconds burst duration containing pulses of 5 milliseconds on and 5 milliseconds off (duty cycle = 50%), separated by 0.7-second burst interval (pulse repetition frequency (PRF) = 1.42 Hz, spatial peak temporal average intensity (I_{SPTA}) 0.66 W/cm^2). Thermal index at target was calculated using W/W_{deg}, with W = 310,000 W/m^2 and $W_{deg} = \Delta T\, \rho C/(2\alpha f)$ = 480,000 W/m^2, where ΔT is 1 degree of temperature change, ρ is density of brain tissue, 1030 kg/m^3, C is specific heat of brain tissue, 3630 J/(kg K), α is the absorption of brain tissue, 6 MHz^{-1} m^{-1}, and f is frequency, 0.65 MHz. Potential skull heating was assessed with both simulations and measurements inside ex vivo human skulls in previous work,[51] finding a maximum 0.047°C temperature increase for 30-millisecond pulses.

2.3.5. Relative through-transmit skull correction

The hardware provides the ability to directly measure and compensate for the attenuation of ultrasound by the head and hair. This functionality and the associated details have been described previously.[50,51] In brief, in this method, the transducers sequentially emitted a 10-cycle, low-intensity, 650 kHz pulse from each individual element while recording responses from all the other, nontransmitting elements. This through-transmit procedure enables a direct measurement of the ultrasound attenuation and phase shift by the skull and other obstacles in the transmission path, including the hair and the acoustic coupling. The through-transmit method is relativistic, performed in comparison to reference measurements taken in water for the same fixed geometry of the transducers. The relative differences in the received ultrasound waveforms between the 2 conditions enable the computation of the attenuation and phase shift the ultrasound experiences from each element to the target. The values are then used to scale the amplitude of each beam by the inverse of the estimated attenuation and to delay the emission time by the estimated phase shift. This approach restores the amplitude and field at the target.[50,51]

2.3.6. Sham stimulation

Sham stimulation used auditory masking as in previous studies.[6,71] Both the sham and active groups of subjects wore headphones during the intervention. The headphones delivered white noise combined with the sound of prerecorded ultrasound transmission pulses. These auditory stimuli were time-locked to the ultrasound stimuli during active stimulation to mask any sound associated with the ultrasound delivery. No ultrasound was delivered with the auditory masking during the sham stimulation.

2.4. MRI acquisition

MRI acquisition was conducted at the University of Utah Imaging and Neuroscience Center with a Siemens VIDA 3T system. Data collected included fMRI BOLD, high-resolution anatomical

magnetization-prepared rapid gradient-echo (MPRAGE), and 2 opposite phase-encoded spin-echo field maps. Data acquisition included the following sequences: fMRI BOLD (T2*-weighted): interleaved series, posterior-anterior (P-A) phase encoding, repetition time (TR) 2.0 seconds, time to echo (TE) 33 milliseconds, flip angle (FA) 80°, field of view (FOV) 207 mm, 52 slices, slice thickness 2.4 mm, bandwidth 2004 Hz/pixel, echo spacing 0.62 milliseconds, and 300 volumes per 10 minutes; MPRAGE anatomical: ascending series, A-P phase encoding, TR 2.4 seconds, TE 2.26 milliseconds, FA 8°, 192 slices, slice thickness 1.3 mm, bandwidth 200 Hz/pixel, and echo spacing 6.84 milliseconds; spin-echo field maps: interleaved series, A-P and P-A phase encoding, TR 9.5 seconds, TE 66 milliseconds, FOV 207 mm, 52 slices, slice thickness 2.4 mm, bandwidth 1162 Hz/pixel, echo spacing 0.96, and echo-planar imaging (EPI) factor 86.

The MRI visit served primarily to acquire an anatomical MRI of the subject for device-to-subject registration. The secondary objective of the session was to explore fMRI BOLD activity during simultaneous ultrasound stimulation of the ACC.

2.5. MRI processing

We implemented a minimal fMRI processing pipeline to enable individualized analyses in patient-specific, native MRI space. Functional MRI processing was performed using analysis of functional neuroimages (AFNI 24.0.04), ANIMA (3.0), and statistical parametric mapping 12 (SPM12 r7219) software packages. Processing was completed in 5 steps: reduction in BOLD outlier voxel signals (despiking) (AFNI), EPI BOLD distortion correction utilizing opposing phase-encoded spin-echo field maps (ANIMA), BOLD time-series spatial realignment to 10th volume (SPM12), BOLD time-series slice-time correction (SPM12), and spatial smoothing of time-series BOLD with 8-mm Gaussian Kernel (SPM12).

Special preprocessing consideration was given due to potential artifacts and MRI distortions that may be caused by the presence of ultrasonic transducers and water-based hydrogel coupling (PVA Hydrogel, UltrasoundCoupling.com) inside the MRI. These considerations led to the construction of our multipackage, study-specific processing pipeline. In particular, AFNI despiking was found to most accurately and consistently identify and remove gel coupling outlier signals from the EPI BOLD images. After despiking, all data were visually quality checked for removal of gel coupling signal before further preprocessing (Supplemental Fig. 5, available at http://links.lww.com/PAIN/C85).

2.6. Functional MRI analysis

Functional MRI BOLD activation individual analyses were conducted in SPM12 using a whole-brain general linear model (GLM). The design contrasted 5 interleaved 1-minute epochs of stimulation with five 1-minute epochs of rest throughout a 10-minute BOLD scan time. Stimulation blocks followed parameters used in the treatment session outside the scanner but used a 1-minute total sonication block duration. The data, for both active and sham stimulation, were analyzed using 2 directional t tests contrasting stimulation and nonstimulation blocks. BOLD significance was determined with the inclusion of uncorrected signal values of $P < 0.001$ and subsequent cluster analysis of $P < 0.05$. Head movement was minimized by the device itself, which uses a stereotactic radiotherapy thermoplastic mask (Aquaplast RT Open Eye and Mouth Slimline U-Frame; QFix[50]). This mask is used during gamma knife procedures requiring robust head fixation. We have also taken steps to maximize sensitivity in the fMRI data processing. First, we analyzed individuals in their native-subject space to decrease spatial distortions due to normalization to standard MNI space. Second, movement parameters were not included in first-level subject-space GLMs. This is because, in block-design fMRI experiments, the inclusion of movement parameters in subject-level GLM analyses decreases the sensitivity of the GLM to detect BOLD modulation.[24]

2.7. Functional MRI whole-brain group analysis

We performed a whole-brain, voxel-wise analysis to define brain activity changes associated with ultrasonic neuromodulation. To enable group-level activation analysis, in addition to the steps for first-level individual analyses, we performed the following fMRI processing steps following the slice-time correction: coregistration of high-resolution T1 to mean of realigned time series (SPM12), normalization of coregistered T1 to MNI space (using Advanced Normalization Tools ANTS), normalization of time-series BOLD by application of T1 normalization deformation fields (ANTS), and spatial smoothing of time-series BOLD with 8-mm Gaussian Kernel (SPM12). We performed 2 whole-brain directional t tests comparing rest blocks to sonication blocks (Off > On and On > Off t tests) to reveal decreases and increases in brain activation corresponding to active sonication.

2.8. Clinical assessments

The primary treatment efficacy outcome was the difference between active and sham FUS using the BPI average 24-hour pain intensity scores pre- and post-intervention. Brief Pain Inventory scores were completed daily for 7 days following the intervention. Secondary outcome measures were the PROMIS pain intensity, PROMIS depression, and PROMIS anxiety. Verbally reported average NRS pain score was also recorded throughout the treatment session to assess the immediate effects of stimulation.

The safety of FUS was assessed using a collection of spontaneously reported adverse events and General Assessment of Side Effects[49] that were recorded at baseline and 24 hours after both the active and sham treatment sessions.

2.9. Statistical analysis

The primary outcome of BPI average 24-hour pain intensity over the 7-day monitoring period between the sham and active group was compared using a repeated measures analysis of variance, with Greenhouse–Geisser-adjusted P value for multiple comparisons. Individual posttreatment days were compared between groups using a 2-sample t test with Bonferroni–Holm correction for multiple comparisons. Secondary outcomes of difference between groups in immediate pain reduction, PROMIS pain intensity, PROMIS depression, and PROMIS anxiety are all compared using the Wilcoxon signed-rank test to account for a nonnormal distribution of scores.

2.10. Randomization

Randomization was conducted by a volunteer not involved with the data collection who prepared envelopes before the trial with notes designating “active” or “sham” sealed inside. Before the start of each treatment, an envelope containing the random designation was given to the person operating the stimulation device and shared with no one else who interacted with the patient. Participants were not informed of their group allocation. Clinicians, study coordinators, and researchers applying the device to the subject during the MRI and treatment sessions were all blinded.

2.11. Ethical statement

Participants provided informed consent before participation. The University of Utah Institutional Review Board approved this study, which was developed in accordance with the ethical standards of Good Clinical Practice and the Declaration of Helsinki. This study was preregistered on ClinicalTrials.gov (NCT05674903).

3. Results

3.1. Study design

This study involved a randomized sham-controlled crossover design, in which patients were randomly assigned into active or sham treatment and crossed into the opposite arm 1 week later (**Fig. 1A**). Twenty-three patients with chronic pain were recruited for this study (**Table 1**). Two patients who started in the sham arm both completed the sham arm, then declined efforts to be contacted and did not cross over to the second arm. Neither subject experienced side effects related to the sham treatment. Their results and safety data are included in the analyses.

There was no dropout for patients who started in the active arm, although 1 patient who went into pain remission did not complete the crossover into sham (Supplemental Fig. 1, available at http://links.lww.com/PAIN/C85). Overall, 20 active and 20 sham data points were available for analysis of clinical effects (Table S1, Supplemental Fig. 4, available at http://links.lww.com/PAIN/C85).

3.2. Targeting

The ultrasound targeting was performed outside the MRI using the registered T1 MRI scan of the patient's brain and transducers, as in our previous studies[50–53] (see Methods).

3.3. Modulation of pain

The ultrasound was delivered into the individual ACC subregions over a period of 40 minutes. Standard NRS scores and PROMIS scores were measured for up to 7 days following the single intervention. Immediately following active stimulation, patients reported reduced NRS pain scores by 60.0 ± 33.1% (mean ± SD; **Fig. 2**). This corresponds to an absolute NRS change of −2.7 ± 1.4. By contrast, the sham stimulation, which only delivered auditory masking sounds (Methods) and no ultrasound, resulted in a 14.39 ± 32.15% reduction. The difference was highly significant ($P = 0.00013$, $z = 3.83$, Wilcoxon signed-rank test). Following the active treatment, 75% (15 of 20) of subjects reported a clinically meaningful (33%[41]) reduction in pain, with 60% (12 of 20) of subjects reporting a reduction greater than 50%. By contrast, following the sham treatment, 15% of subjects experienced a clinically meaningful reduction in pain and 10% (2 of 20) experienced a reduction greater than 50%. Together, these data suggest that the ultrasonic ACC treatments resulted in a substantial reduction of pain levels following a single-session intervention.

We further evaluated the durability of pain relief following the single-session treatments (**Fig. 3**). Pain reduction following active stimulation, but not sham stimulation, was particularly pronounced in the days following the intervention and remained statistically and clinically significant through the 7-day follow-up period (**Fig. 3**). A repeated measures analysis of variance confirmed a significant effect of the active treatment arm over the sham treatment arm (group effect—active or sham; $F_7 = 3.21$, $P = 0.0086$, Greenhouse–Geisser adjusted). The NRS levels associated with these effects are provided in Supplemental Figure 2 (available at http://links.lww.com/PAIN/C85). Following

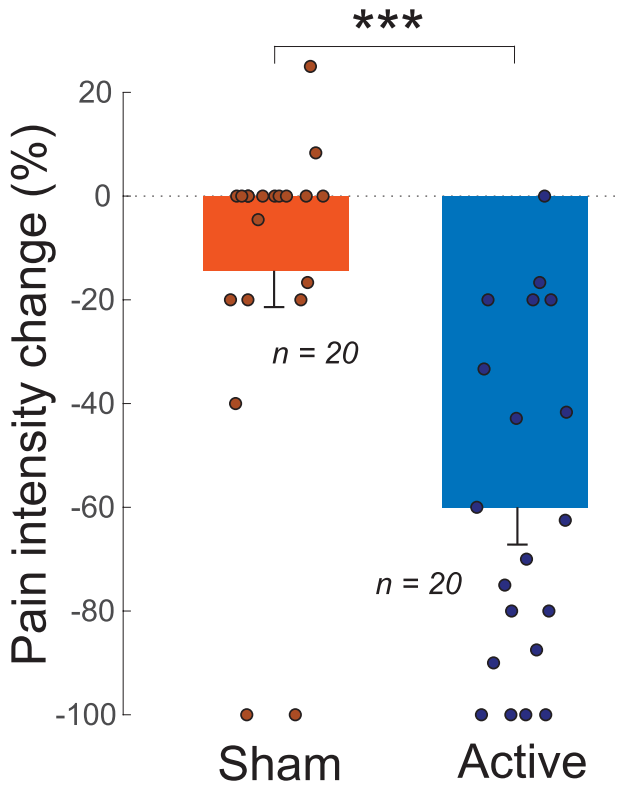

Figure 2. Rapid changes in pain intensity following ultrasonic modulation of the ACC. Mean ± SEM change in NRS scores in response to sham (orange) and active (blue) stimulation of the ACC, relative to the NRS scores before intervention. The individual data points are provided as colored circles. ***$P = 0.00013$, Wilcoxon signed-rank test. ACC, anterior cingulate cortex; NRS, numerical rating scale.

active treatment, 60% (12 of 20) of subjects reported a clinically meaningful reduction in pain at 24 hours and 7 days post, with 55% and 30% of subjects reporting a reduction greater than 50% at these timepoints, respectively. By contrast, following the sham

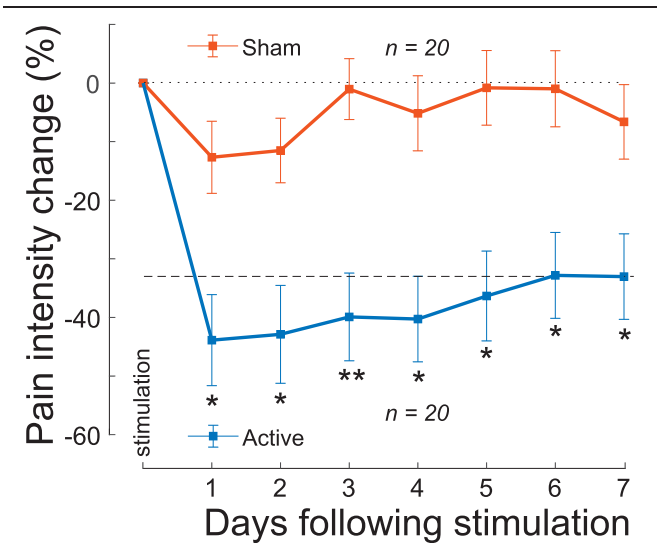

Figure 3. Durable changes in pain intensity following ultrasonic modulation of the ACC. Mean ± SEM change in NRS scores relative to baseline NRS scores taken before each intervention. The effects were measured for up to 7 days (abscissa). Data are provided separately for the active (blue) and sham (orange) stimulation. The dashed line represents a pain reduction level that is considered clinically meaningful.[41] The stars denote significant differences between the active and sham effects (*$P < 0.05$, **$P < 0.01$; Bonferroni–Holm-corrected for multiple comparisons). ACC, anterior cingulate cortex; NRS, numerical rating scale.

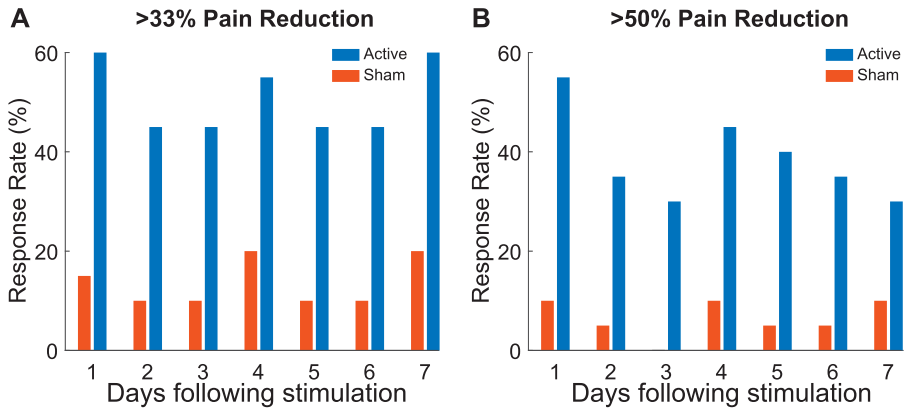

Figure 4. Response rates. Same format as in Figure 3, now showing the proportion of subjects who attained greater than 33% (A) and greater than 50% (B) reduction in pain intensity.

treatment, 15% (3 of 20) and 20% experienced a clinically meaningful reduction in pain and 10% experienced a reduction greater than 50% at 24 hours and 7 days post (**Fig. 4**).

The beneficial effects of ACC neuromodulation were also observed in the PROMIS pain intensity scores (**Fig. 5**). Active stimulation resulted in a mean ± SD decrease of 5.68 ± 7.2 points in the PROMIS pain intensity scores, and this effect was significant relative to the sham stimulation ($P = 0.0014$, $z = 3.20$, Wilcoxon signed-rank test). In the active FUS group, 55% (11 of 20) of subjects' pain scores improved by at least the clinically significant change of 2.5,[8] compared with 17% (3 of 19) for sham. The PROMIS depression score decreased by 2.27 ± 3.75 for active and 0.23 ± 6.16 for sham ($P = 0.14$, $z = 1.48$, Wilcoxon signed-rank test). The PROMIS anxiety score decreased by 2.87 ± 6.21 for active, and 0.65 ± 5.36 for sham stimulation ($P = 0.20$, $z = 1.29$, Wilcoxon signed-rank test).

3.4. Safety

The stimulation was well tolerated with no adverse events detected. There were no significant differences between active and sham stimulation for any of the measured symptoms (**Table 2**). All side effects related to treatment were resolved by the end of this study. There was no significant difference in the dropout rates between the active and sham conditions ($P = 0.49$, Fisher exact test). No significant worsening of pain, measured with the Brief Pain Inventory, was observed in either the sham or active treatment groups.

3.5. Functional MRI target engagement

Before the treatment session outside the MRI, sham and real stimulation were delivered inside the MRI to validate the ultrasound focus, using a target engagement procedure used and described previously.[51] We have specifically validated that the device can target both the ventral (subgenual) and dorsal parts of the ACC.

Significant effects were observed at target in 3 of 4 subjects in whom we tested the engagement of the subgenual ACC and 3 of 5 subjects in whom we tested the engagement of the dorsal ACC (**Fig. 6**). Within the subjects who showed significant effects, all subgenual ACC subjects showed deactivation at target, while 2 aMCC subjects showed target activation and 1 aMCC subject showed target deactivation. Second-level group analyses showed no significant clusters for the 4 subjects who received subgenual ACC, the 5 subjects who received aMCC, or the 10 subjects who received sham (Supplemental Fig. 3, available at http://links.lww.com/PAIN/C85).

4. Discussion

This study provides preliminary support for an exciting new treatment approach for chronic pain, using noninvasive FUS to modulate the deep brain targets known to reflect pain experience. The results demonstrate that it is possible to modulate deep brain structures in humans precisely, noninvasively, and in a controlled

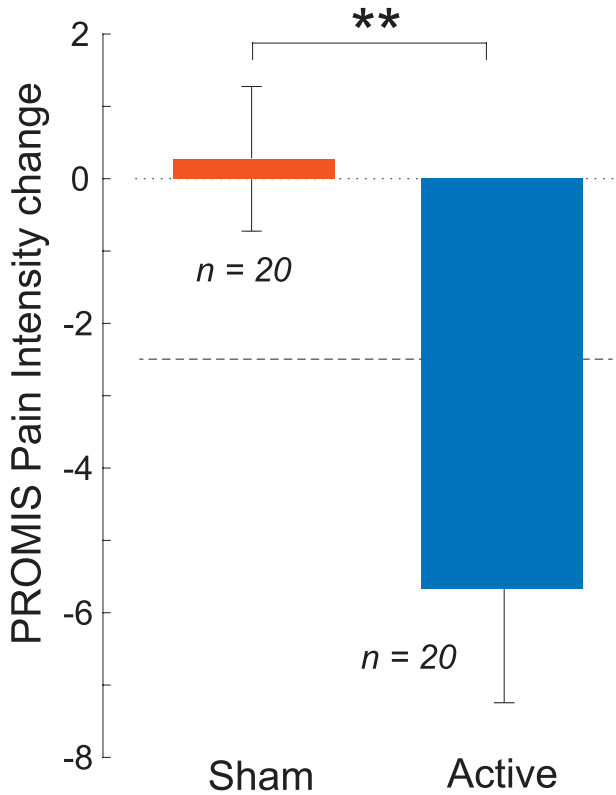

Figure 5. Change in PROMIS pain intensity scores at day 7 following ultrasonic modulation of the ACC. Mean ± SEM changes in the PROMIS scores at day 7 following the stimulation, relative to PROMIS scores before the stimulation. The dashed line provides the level of clinically meaningful reduction in pain.[8] $^{**}P = 0.0014$, Wilcoxon signed-rank test. ACC, anterior cingulate cortex; PROMIS, Patient-Reported Outcomes Measurement Information System.

Table 2

The stimulation was well tolerated by patients.

	Real (N = 20)					Sham (N = 20)				
No. of adverse events	**0**					**0**				
Study dropouts	**0**					**2**				
GASE rating	**Not present**	**Mild**	**Moderate**	**Severe**	**Related to treatment (%)**	**Not present**	**Mild**	**Moderate**	**Severe**	**Related to treatment (%)**
Headache	5	10	3	2	4 (20)	6	7	5	2	5 (25)
Hair loss	19	0	1	0	0 (0)	18	2	0	0	1 (5)
Dry mouth	6	11	1	2	1 (5)	5	10	2	3	0 (0)
Dizziness	13	6	1	0	1 (5)	12	3	4	1	0 (0)
Chest pain	20	0	0	0	0 (0)	18	1	1	0	0 (0)
Palpitations	18	2	0	0	0 (0)	17	3	0	0	0 (0)
Breathing problems	17	3	0	0	0 (0)	19	0	1	0	0 (0)
Subjective blood circulation-associated problems	19	1	0	0	0 (0)	17	2	1	0	0 (0)
Abdominal pain	16	2	2	0	0 (0)	13	6	1	0	0 (0)
Nausea	15	5	0	0	0 (0)	11	9	0	0	0 (0)
Vomiting	20	0	0	0	0 (0)	19	1	0	0	0 (0)
Constipation	15	4	1	0	0 (0)	15	3	2	0	0 (0)
Diarrhea	17	1	2	0	0 (0)	14	3	2	1	0 (0)
Reduced appetite	15	3	2	0	1 (5)	15	4	1	0	0 (0)
Increased appetite	16	2	2	0	0 (0)	15	4	0	1	0 (0)
Difficulty urinating	17	3	0	0	0 (0)	18	2	0	0	0 (0)
Problems with sexual performance or sex organs	16	4	0	0	0 (0)	14	4	1	1	0 (0)
Painful or irregular menstruation	18	0	2	0	0 (0)	18	1	1	0	0 (0)
Skin rash or itching	19	1	0	0	0 (0)	15	2	3	0	0 (0)
Tendency to develop bruises	17	2	1	0	0 (0)	14	4	2	0	0 (0)
Fever, increased temperature	19	1	0	0	0 (0)	19	0	1	0	0 (0)
Abnormal sweating	17	2	1	0	0 (0)	13	5	1	1	1 (5)
Hot flashes	17	2	1	0	0 (0)	10	6	2	2	0 (0)
Convulsions or seizures	20	0	0	0	0 (0)	19	1	0	0	0 (0)
Fatigue, loss of energy	8	7	5	0	0 (0)	5	5	8	2	0 (0)
Tremor	18	2	0	0	0 (0)	18	1	1	0	0 (0)
Insomnia, sleeping problems	7	7	5	1	0 (0)	9	3	4	4	1 (5)
Nightmares or abnormal dreams	18	0	2	0	0 (0)	16	2	1	1	1 (5)
Back pain	7	7	5	1	1 (5)	5	4	8	3	1 (5)
Muscle pain	8	3	6	3	0 (0)	3	4	10	3	2 (10)
Joint pain	7	5	6	2	1 (5)	2	6	10	2	2 (10)
Agitation	12	8	0	0	0 (0)	10	8	2	0	0 (0)
Irritability, nervousness	11	6	3	0	0 (0)	11	6	3	0	1 (5)
Depressed mood	13	6	1	0	0 (0)	10	6	4	0	1 (5)
Thoughts about suicide	18	2	0	0	0 (0)	18	1	1	0	1 (5)
Anxiety, fearfulness	13	3	4	0	0 (0)	10	6	4	0	2 (10)

Following the stimulation, the patients were asked to complete a standard clinical questionnaire[49] that assessed potential side effects. The data are shown separately for the active (left column) and sham (right column) stimulation.

manner. In this approach, a phased array device delivers ultrasound into specified deep brain targets, while measuring and compensating for the aberrations of ultrasound by the head.[51] Using this approach, we administered low-intensity ultrasound to the ACC of patients with chronic pain. A randomized crossover sham-controlled evaluation revealed that the intervention could provide a rapid, clinically meaningful, and durable reduction in chronic pain.

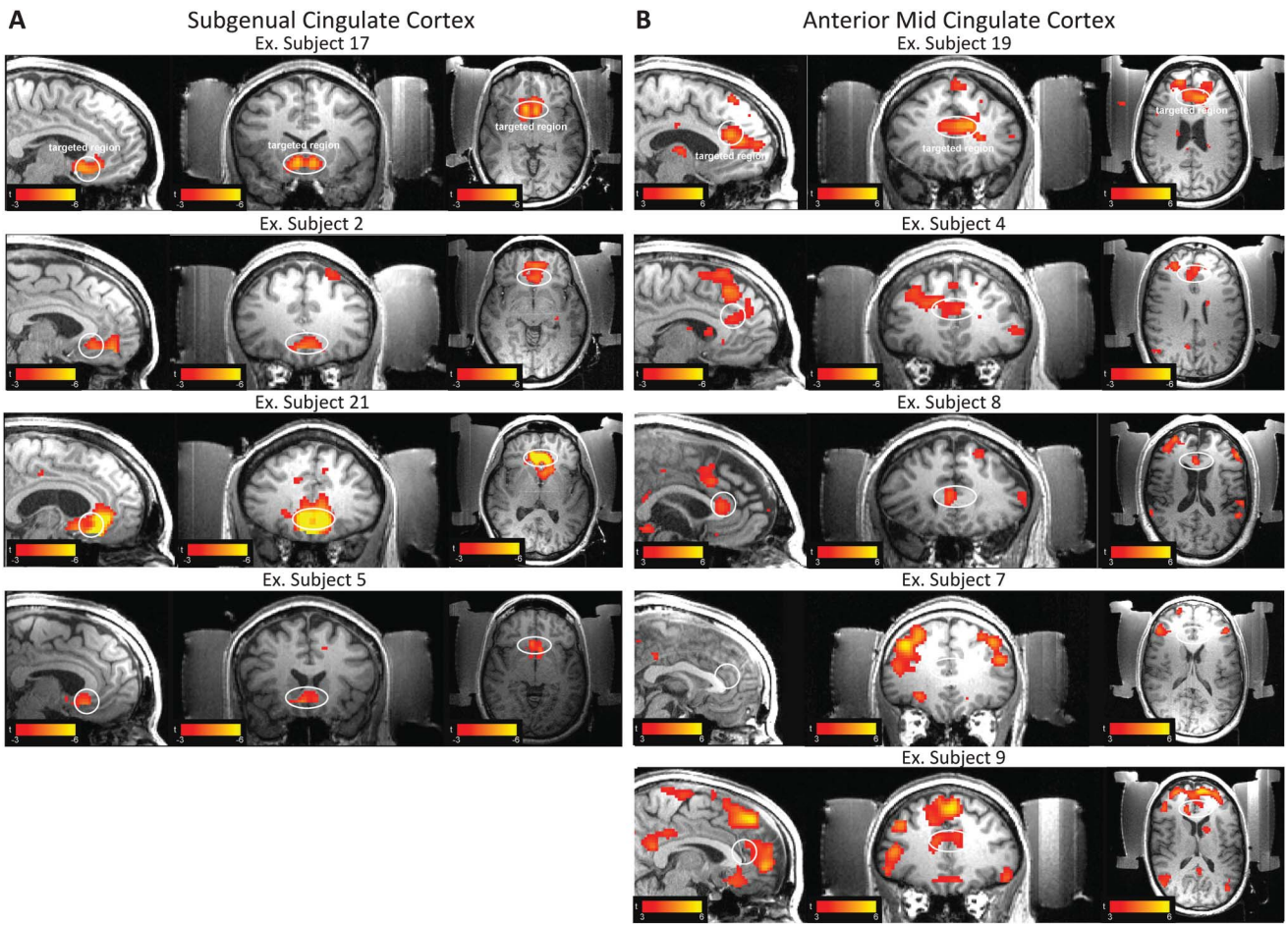

Figure 6. Target engagement. Data for all subjects that received active stimulation subgenual ACC (left panel): subject 17 (cluster-level $P < 0.0001$; false discovery rate corrected, $k_E = 369$ voxels), subject 2 (cluster-level $P < 0001$; false discover rate corrected, $k_E = 414$), subject 21 (cluster-level $P < 0.0001$; false discovery rate corrected, $k_E = 5791$ voxels), subject 5 (signal inclusion $P < 0.005$; cluster-level $P = 0.016$; false discovery rate corrected, $k_E = 183$ voxels). aMCC (right panel): subject 19 (cluster-level $P < 0.0001$; false discovery rate corrected, $k_E = 1344$ voxels), subject 4 (cluster-level $P < 0.0001$; false discovery rate corrected, $k_E = 1992$ voxels), subject 8 (cluster-level $P = 0.034$; uncorrected, $k_E = 47$ voxels). Subjects 7 and 9 did not show significant activation at the target region. Group analysis was nonsignificant for both targets. ACC, anterior cingulate cortex; aMCC, anterior midcingulate cortex.

Rapid improvements in chronic pain can be obtained using medication treatments[23] or surgical interventions, including cingulotomy[56] and DBS.[5,32] Nonetheless, medication treatments require frequent readministration, often carry significant side effects,[34] and can be addictive.[21,36] On the other hand, the surgical options carry significant risks, including brain hemorrhage and infection.[16] The ultrasound waves used here provide an alternative, drug-free and incisionless treatment option for chronic pain.

Targeted noninvasive modulation of deep brain circuits has long been a dream of neural sciences. Ultrasonic energy has been a prime candidate for attaining this goal. Ultrasonic waves combine a unique triad of properties—noninvasiveness, depth penetration, and sharp focus. Since sound waves have a much lower speed of propagation than electromagnetic waves, sound waves have a relatively small wavelength. Thanks to diffraction,[11] the short wavelength enables relatively sharp focus at depth. Nonetheless, the technology has been impeded by formidable barriers—the skull and hair, which attenuate and distort ultrasonic waves severely and unpredictably.[51,54] The approach presented in this study directly measures and compensates for these barriers in each individual, thus delivering into specified targets a controlled, deterministic amount of ultrasound intensity.[51] This way, low-intensity ultrasound can provide targeted noninvasive neuromodulation in an effective and safe manner.[50–53]

Three previous studies[2,31,58] applied low-intensity ultrasound to various brain regions of healthy individuals who rated the intensity levels of thermal stimuli. It was found that the stimulation could change thresholds of thermal perception or decrease the perception of thermal pain. The ultrasonic study performed here differs in 3 fundamental ways. First, we applied the intervention to patients—as opposed to healthy individuals, and measured changes in clinical metrics of pain inherent to the patients, not induced externally. Second, we have measured and corrected for the ultrasound aberrations by the head.[51] Third, we have focused the ultrasound on the target using phased arrays, which provide focal, precise, and flexible ultrasound delivery.[50,52,53]

At the mechanistic level, we and others have found that ultrasound mechanically activates ion channels[27,28,40,47,69] and directly elicits action potentials.[37,60] When ultrasound is delivered into neural tissues for dozens of seconds or longer, it also induces neuroplastic effects.[14,17,26,40,62,63,67] These effects are, at least in part, due to activation of glial cells.[39,40] In addition, these effects are a function of the ultrasound parameters used in these studies.

Careful modeling work has suggested[46] that low-energy insonations produce aggregate neuroinhibitory effects, whereas higher-energy insonations tend to produce neuroexcitatory effects. Ultrasound-induced neuroplastic effects provide a unique opportunity for noninvasive reset of the malfunctioning circuits. A durable reset based on induced neuroplastic effects is the primary hypothesized mechanism underlying the sustained effects reported in this study.

As a validation of target engagement, this study replicated the results of our previous studies,[51,53] which used the same device and showed modulation of fMRI BOLD signals at the ultrasound focus. Our previous studies targeted the subgenual ACC with low-energy insonation parameters and found a decrease of BOLD signals at the ultrasound target. Focused ultrasound modulation of BOLD signal has been demonstrated by other groups in previous human studies[1,10,30] and in nonhuman primates.[33] The validation of target engagement using this or other devices is critical for next-generation ultrasound-based neuromodulation.

In this study, we observe bi-directional polarity of modulated fMRI BOLD signals. This bi-directionality between activation and deactivation at the target may be due to biological differences between the subgenual ACC and the aMCC. For the statistically significant subjects, ultrasound applied to the subgenual ACC resulted in deactivation at the target, as reported in our previous studies. Similarly, this deactivation was largely restricted to the ultrasound target region. By contrast, 2 of 3 subjects with significant modulation at the aMCC showed an *activation* in the target region. Moreover, this aMCC modulation was consistently paired with changes in activity superior to the target in the dorsal medial prefrontal cortex, regardless of activation or deactivation at the target. Taken together, our data suggest that neuromodulatory effects of ultrasound may be not only parameter- but also brain-region-dependent. Indeed, the subgenual ACC and aMCC have unique cellular architectures, with the aMCC containing both larger cell bodies and higher glia-to-neuron ratios.[20] As noted, ultrasonic-induced neuroplastic effects are, in part, due to activation of glial cells.[39,40] As such, the neurobiological composition of the stimulated circuit may constitute a key factor to control for in future studies.

Three lines of evidence support the notion that the ACC modulation effects were due to the stimulation and not due to a generic artifact. First, there was a substantial and significant contrast in the reduction of the pain intensity levels between active and sham stimulation. This is even though the sham stimulation was controlled for a placebo using an active auditory protocol applied in previous studies.[6,71] Second, the active stimulation elicited localized effects and did not elicit a consistent activation of the auditory or somatosensory cortex (**Fig. 6**). Finally, the lack of MRI BOLD activation at target in some of the subjects provides negative control data, implying the observed modulation in other subjects was not due to a pervasive generic artifact.

This study has certain caveats. One is the limited number of participants. Nonetheless, these initial effectiveness and safety data encourage a large-scale, pivotal study to determine the effectiveness and safety of ultrasonic treatments for chronic pain. A second, important caveat is the relatively heterogeneous population of patients. The goal of this study was to provide initial proof of the concept of modulation of the aversive component of pain, potentially applicable to diverse etiologies and subgroups of pain. This diversity may nonetheless limit the treatment effectiveness. Future studies should either gather data from a large number of patients with the goal of determining which etiologies and groups are most responsive or focus on a defined subgroup. Third, we used MRI to ensure the precise targeting of the ultrasound in the ACC. Although this may be a strength with respect to scientific rigor, the use of MRI poses practical limitations. Future work should develop registration approaches that are both accurate and do not require MRI.[9] Fourth, we did not quantify subjects' ability to distinguish active from sham or expectations of pain relief. Subjects were informed during recruitment and at consent that this was an exploratory trial and would not lead to a long-term replacement for treatment. Nonetheless, 3 points of evidence suggest that the sham procedure could not be reliably identified from the active procedure; (1) The sham successfully elicited a temporary placebo response (**Fig. 3**); (2) The time dynamics of the pain reduction effects were comparable across the active and sham conditions regardless of randomization (Supplemental Fig. 4, available at http://links.lww.com/PAIN/C85); (3) There was no significant difference in the dropout rates between active and sham stimulation. The final limitation is that the crossover study design has limited the evaluation of each subject to 7 days, before crossing into the opposite arm. Future studies should evaluate the effect duration over several weeks or longer. The effects of repeated treatments should also be evaluated.

The ultrasonic intervention is conceptually related to TMS applied to the motor cortex, which can provide improvements in chronic pain in certain groups of patients.[18,19] The key difference is that ultrasonic waves can directly modulate the deep brain regions involved in chronic pain, including the ACC. Transcranial magnetic stimulation is believed to modulate deep brain regions only indirectly, which may contribute to its variable response and the need for frequent re-administrations. Nonetheless, the effects of both modalities may be complementary, and their combined application may provide stronger effects than either approach alone.

In summary, this article reports a noninvasive targeted approach to modulate the deep brain circuits involved in chronic pain. The approach provides proof-of-concept data of effective, rapid, and durable reduction in chronic pain. The procedure is incisionless, medication-free, and can be applied to patients within minutes. This approach could therefore be administered to a large spectrum of patients, potentially contributing to the effort of reducing[21] the administration of opioid medications or drugs that cause systemic side effects.

Conflict of interest statement

J. Kubanek is an inventor on a patent related to the device function. The other authors have no conflicts of interest to declare.

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