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Selective Mapping of Deep Brain Stimulation Lead Currents Using Acoustoelectric Imaging

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Abstract

We describe a new application of acoustoelectric imaging (AEI) for noninvasive mapping of the location, magnitude, and polarity of current generated by a clinical deep brain stimulation (DBS) device. Ultrasound at 1 MHz was focused near the DBS device as short current pulses were injected across different DBS leads. A recording electrode detected the high frequency AE interaction signal. Linear scans of the US beam produced time-varying images of the magnitude and polarity of the induced current, enabling precise localization of the DBS leads within 0.70 mm, a detection threshold of 1.75mA at 1MPa, and sensitivity of $0.52 \pm 0.07 \mu\text{V}/(\text{mA} \cdot \text{MPa})$. Monopole and dipole configurations in saline were repeated through a human skullcap. Despite 13.8 dB ultrasound attenuation through bone, AEI was still >10 dB above background with a sensitivity of $0.56 \pm 0.10 \mu\text{V}/(\text{mA} \cdot \text{MPa})$. This proof-of-concept study demonstrates selective mapping of lead currents through a DBS device may be possible using noninvasive AEI.

Keywords

Acoustoelectric effect; current source density; Parkinson's; essential tremor; ultrasound imaging; DBS; transcranial

INTRODUCTION

Deep brain stimulation (DBS) is an effective treatment for motor symptoms resulting from Parkinson's disease (PD) (Bronstein et al., 2011), essential tremor (Nazzaro et al., 2013), and dystonia (Vidailhet et al., 2005). This success encouraged further investigations for using DBS as a treatment for other neurological disorders, including epilepsy (Laxpati et al., 2014), depression (Morishita et al., 2014), Tourette's syndrome (Ackermans et al., 2013) and obsessive-compulsive disorder (Hamani et al., 2014). DBS for PD appears to work by

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normalizing pathological low frequency oscillations in the basal ganglia (McConnell et al., 2012) and basal ganglia-cortical circuits, but the exact mechanisms underlying therapeutic DBS remain unknown. Regardless, success for DBS strongly depends on the accurate placement of the DBS electrodes in the subthalamic nucleus or globus pallidus interna (Anheim et al., 2008, Ellis et al., 2008, Richardson et al., 2009). Although computed tomography and magnetic resonance imaging are commonly used to help guide placement during surgery, these techniques are unable to directly visualize the contacts or map current patterns for real-time feedback during surgery (Bot et al., 2017, Starr et al., 2010). Computational models are also employed for pre-surgical planning to predict current spread in the brain (Wei and Grill, 2005) and optimal placement of the leads (Kuncel et al., 2008, McIntyre et al., 2004, Iacono et al., 2014, Maks et al., 2009, Gross and Rolston, 2008). These models, however, are primarily theoretical and lack valuable empirical *in vivo* data for validation and optimization.

In this study, we propose acoustoelectric imaging (AEI) as a new technique to noninvasively map the location, magnitude and polarity of current source densities generated by a clinical DBS device. AEI exploits an interaction between US pressure and tissue resistivity to remotely detect and map current densities with high spatial and temporal resolution (Jossinet et al., 1999). As an US beam is pulsed and swept in a conductive medium, a recording electrode detects the high frequency AE interaction signal, which is proportional to the local pressure and current. Feasibility of AEI for mapping current densities has been demonstrated in a variety of preparations, including time-varying dipoles (Olafsson et al., 2008, Wang et al., 2011, Wang et al., 2016, Berthon et al., 2017) and imaging of the cardiac depolarization wave in the live rabbit heart (Olafsson et al., 2009, Qin et al., 2015). The primary goals for this study are to 1) assess the performance (spatial resolution, sensitivity, and accuracy) of AEI for detecting and resolving current densities near a DBS device using stimulation parameters resembling those used clinically, and 2) demonstrate feasibility and benchmark performance of AEI through a human skullcap.

MATERIAL AND METHODS

Acoustoelectric Imaging: Background and Theory

The acoustoelectric (AE) effect describes the interaction of an acoustic wave propagating through a conductive medium. As the US wave propagates, the density of the medium is modulated by the pressure resulting in changes in the medium's resistivity (Jossinet et al., 1998). In accordance with Ohm's law, a voltage can be measured based on the product of this induced change in resistivity with the inner product of the current density ($\mathbf{J}_I(\mathbf{x}, \mathbf{y}, \mathbf{z}, t_{slow})$) and a recording lead field from a pair of recording electrodes ($\mathbf{J}_L(\mathbf{x}, \mathbf{y}, \mathbf{z})$) integrated over a volume. With an US transducer centered at coordinates x_1 and y_1 , the recorded voltage of the AE signal, V_{AE} , includes additional terms related to the US parameters due to the AE effect:

$$V_{AE}(x_1, y_1, t_{fast}, t_{slow}) = -K \int \int \int (\mathbf{J}_L \cdot \mathbf{J}_I) \rho_0 b(x - x_1, y - y_1, z) P_0 a(t_{fast} - z/c) dx dy dz, \quad (1)$$

with ρ_0 the initial resistivity, P the varying acoustic pressure, K an acoustoelectric interaction constant (e.g., 0.034 in 0.9% saline) (Li et al., 2012), US beam pattern $b(x, y, z)$, pulse amplitude P_0 , and US pulse waveform $a(t_{fast})$. The expression includes both fast and slow time components, where fast time (t_{fast}) refers to the propagation of US waves (μs) with wave velocity c along the z axis, and slow time (t_{slow}) refers to the time frame of the injected current waveform (ms), referring to how the measured current densities, $\mathbf{J}_I$, change as the injected current varies over time. See (Olafsson et al., 2008) for a thorough derivation. The AE signal is further separated from the recorded potential using a high pass filter.

Based on (1), an AE M-Mode image (z vs. t_{slow} ; analogous to M-Mode pulse echo) is formed by recording V_{AE} while producing a sequence of US pulses. A raster scan of the US transducer along x and y produces volumetric AE images and 4D movies (volume vs. t_{slow}) (Wang et al., 2011). Note, the AE signal is confined to the US beam such that the spatial resolution for AEI depends on the acoustic wavelength ($\sim 1.5mm$ at 1 MHz in water) and size of the focus.

Experimental Setup

A commercial DBS device (Medtronic model #3389, Medtronic, Inc., Minneapolis, MN, USA) with four platinum-iridium electrodes was placed in a bath of 0.9% NaCl. The device has 4 symmetric contacts numbered 0–3 beginning at the distal tip. Each contact has a length of 1.5mm, diameter of 1.27mm, and separation (kerf) of 0.5mm. The array of electrodes on the device were positioned perpendicular to the propagation of the US beam. A single element transducer (1 MHz, 4.40 MPa peak-to-peak at the focus of 63 mm; NDT A392S, Olympus, Shinjuku, Tokyo, Japan) was submerged in deionized water to deliver focused US pulses near the DBS device.

Figure 1A depicts the timing diagram for acquiring AE signals along one line (depth, z) with the center of the transducer at coordinates x, y . Time-varying pulses of injected current (3V, 200Hz, 1 ms rectangular pulse) were delivered from a function generator (33220A, Agilent, Santa Clara, CA, USA) to either two DBS contacts (dipole configuration) or one DBS contact and a distant stainless-steel ground electrode (monopole configuration). The stimulation waveform was similar to those used clinically (Kuncel and Grill, 2004). A burst of US pulses was focused near the stimulating contacts at a pulse repetition frequency of 4 kHz simultaneous with the injected current. A distant reference electrode (dipole configuration) or adjacent contact on the DBS (monopole configuration) was used to record the AE interaction signal (Fig. 1B). For dipole imaging, 12 bipolar configurations were theoretically possible when considering all leads and polarities; however, we implemented

only three unique combinations (3–2, 3–1, and 3–0) to demonstrate spatial selectivity of AEI.

The AE signal passed through a custom 10 MHz differential amplifier with analog filtering (–3 dB frequency cutoffs at 0.2 and 2 MHz) and a gain of 40dB. The signal was then digitized at 20 MHz on an eight channel, 12-bit NI PXI-5105 acquisition card (National Instruments, Austin, TX, USA). The injected current was measured across a 1 Ohm resistor in series with the stimulating electrodes, amplified 10X by a differential amplifier (PA1855A, Teledyne Lecroy, Chestnut Ridge, NY, USA) and digitized at 20 kHz on a NI PXI-6289 acquisition card (National Instruments, Austin, TX, USA). AE M-Mode images (depth vs. t_{slow}) were generated with the US beam at one location along the lateral and elevational axes. The US transducer was also mechanically scanned in the lateral plane at step sizes of 0.33mm to form cross sectional 2D AE images (lateral vs depth) and movies over time related to the location, direction and amplitude of the local current densities. Standard pulse echo US was simultaneously captured on a pulser-receiver (5077PR, Olympus, Shinjuku, Tokyo, Japan) and digitized on the same NI PXI-5105 acquisition card at 20 MHz to determine the position and orientation of the tip of the DBS device co-registered to the AE signal.

Acoustoelectric Imaging through Human Skullcap

A skullcap was placed upside down in a chamber filled with 0.9% saline, 36 mm below the DBS contacts and 25 mm above the US transducer such that the propagating beam passed through the 6.0-mm thick parietal bone 2 cm lateral from the coronal suture. The AE signals were averaged up to 50 times per location along the lateral axis for the monopole and dipole images and for calculating sensitivity and SNR. A capsule hydrophone (HGL-0200, Onda Corporation, Sunnyvale, CA, USA) was used to calibrate the pressure field with and without the skullcap.

Post Processing and Analysis

AE signals were bandpass filtered with –3dB cutoffs at 0.5 and 1.5 MHz (along US propagation time; t_{fast}) and 100 and 1000 Hz (along current waveform time; t_{slow}). The real AE signals were Hilbert transformed and basebanded to form the complex envelope. Whereas the absolute value of the complex envelope determined the magnitude of the local current densities, the sign of the complex envelope determined polarity. AE images are displayed on hot/cold color maps to indicate the magnitude (intensity) and polarity (color) of the local current densities. Co-registered pulse echo B-mode images are displayed in grayscale.

The signal-to-noise ratio (SNR) was calculated for different amounts of trial averaging (from 1 to 64) to assess background noise and variability. SNR was calculated from the peak of the envelope of the AE signal divided by the maximum voltage in a region devoid of signal. The SNR in dB was then calculated as $20 \cdot \log_{10}(\text{signal/noise})$.

Sensitivity in $\mu\text{V}/\text{mA}$ was determined by calculating the slope between the AE signal and injected current. This was then normalized to peak-to-peak pressure at the US focus to determine sensitivity in $\mu\text{V}/(\text{MPa} \cdot \text{mA})$. The detection threshold for determining minimum

detectable current was defined as the mean + twice the standard deviation of the noise. Six trials using a 200 Hz stimulating sine wave was passed through the DBS device in a monopole configuration for these calculations. Ultrasound pulsed at 4 kHz focused at the monopole provided a temporal resolution of $250\mu\text{s}$ for the AE amplitude measurements. Peak negative pressures were less than 1.9 MPa for all experiments (i.e., the mechanical index was <1.9 , the FDA safety limit for diagnostic imaging) (Harris, 2008).

The spatial extent of monopoles generated by the DBS device were calculated at full-width half-maximum (FWHM) in both axial and lateral directions ($n = 12$ for monopoles, 9 for dipoles). The center of each stimulating contact was estimated from the peak of the local current densities. The location of the DBS device in physical space was determined by the pulse echo (PE) signal (two-way US travel), which was co-registered and superimposed with AEI (one-way US travel). The expected distance between the peaks was expected to close to the 2-mm pitch between consecutive DBS contacts.

RESULTS

AEI of Monopole Current Pulses

The AE M-Mode image (Fig. 2B) displays bright peaks at the time of the current pulses and depth corresponding to contact 3 on the DBS device. A slight deflection below baseline is also observed (blue region), consistent with the current waveform measured simultaneously. Fig 2A depicts the AE M-Mode signal (red line) at a single depth (67.5 mm = depth of the DBS device), which is superimposed and highly correlated ($R^2 = 0.886$) with the injected current waveform (black), illustrating the fast temporal resolution of AEI.

Next, the US beam was scanned along the DBS leads to form 3D (lateral, depth and time) images depicting time-varying current densities (Supplemental Movie 1) for monopoles at each of the four contacts. Figure 3A illustrates the PE image of the DBS with the superimposed AE image for each monopole configuration. The peak amplitude (mean $\pm$ std) of the AE signals from the monopoles were $42.5 \pm 4.5 \mu\text{V}$. The dimensions of the AE signals in the lateral and axial directions were $3.67 \pm 0.18\text{mm}$ and $3.11 \pm 0.21\text{mm}$, respectively. The coordinates of the peak signal along the lateral axis were also calculated for each monopole and were within 0.41mm of the actual location of the stimulating contact estimated by PE. The line profiles in Fig. 3B compare the AE images with the physical location of the contacts.

AEI of Dipole Current Pulses

AEI was also used to map dipoles generated by the DBS electrodes to examine effects of polarity on the sensitivity and accuracy of AEI. The anode was fixed (contact 3) for all scans, while the cathode was shifted among the remaining contacts. Three dimensional movies were generated for these 3 dipole configurations (see supplemental movie 2 for the 3–1 dipole). The 2D images taken at the peak of the AE signal (Fig. 4A) clearly illustrate the shift in the location of the cathode (blue). The peak magnitude, SNR and width of each pole were measured for the bipolar stimulating configurations (summarized in Table 1). The 3–1 and 3–0 dipoles had comparable peak amplitudes, but slightly less than the monopole

configuration. The 3–2 configuration had a lower amplitude for both poles. Additionally, the lateral extent of each pole detected by AEI decreased from configuration 3–0 to 3–2, most likely due to volume integration over the US focus (see discussion).

The centers of the anode from AEI for the 3–0 and 3–1 configurations were 5.82 and 6.11 mm, which were close to the expected position of 6 mm (Fig. 4B). In contrast, the center of the anode determined by AEI using the 3–2 configuration was 6.81 mm. Finally, the distance between the cathode and anode was measured for each configuration and subtracted from the actual distance of the center of the stimulating contacts. The differences were –0.06mm (narrower), +0.75mm (wider), and +1.74 mm for the 3–0, 3–1, and 3–2 configurations, respectively.

AEI Sensitivity and SNR

The sensitivity determined from the 200Hz sine wave stimulation was $0.52 \mu V/(MPa \cdot mA)$ with $R^2 = 0.985$ (see Fig. 5). Based on a detection threshold of $0.91 \mu V$ at 1 MPa, the smallest detectable current was 1.75 mA.

A plot of SNR vs number of repeated stimulations (N) revealed the effect of averaging for detecting current generated by the DBS device (Fig. 5C). With no averaging, SNR was 8 dB and increased logarithmically (base 2) with the number of averages ($R^2 = 0.978$) with a slope of 2.74 dB/octave, reaching 25 dB at 64 averages. This pattern followed closely the assumption of independent background noise between trials ($\sqrt{N}$).

Transcranial AEI of DBS current densities

Peak pressure at the depth of the DBS electrode decreased from 4.40 MPa to 0.868 MPa (80.3% attenuation) after the US beam passed through the skull (at normal incidence) corresponding to an attenuation coefficient of 2.74 Np/m. The beam width (lateral FWHM) was 21.3% larger after propagating through the skull with minimal change to the axial (transverse normal) focus (Fig. 6). The speed of sound of the 6.0-mm thick bone was calculated at 3157 m/s based on the time delay through the skull of $-2.11 \mu s$.

Although the tip of the DBS was discernible on PE images through the skullcap, these images were low quality due to skull reflections and two-way attenuation of the acoustic wave (Fig. 7A). The AE signal, on the other hand, remained fully detectable and characterizable (Fig. 7B). The lateral and axial dimensions of the monopole through skull were 4.71 and 3.24 mm, respectively. The peak locations of the monopoles generated at contacts 1, 2, and 3 were 1.56, 3.81, and 6.15mm away from the peak of the contact 0 monopole. Compared to the expected distances of 2, 4, and 6mm, the error in relative accuracy of the monopole locations was 0.44mm. The distance between each pole in the 0–3 dipole configuration was 6.14mm, compared to the expected 6 mm (Fig 7B - bottom). Sensitivity for detecting the AE signal was $0.56 \mu V/(MPa \cdot mA)$ with $R^2 = 0.971$. At the detection threshold of $0.91 \mu V$ at 1 MPa, the corresponding threshold for current detection was 1.65 mA.

DISCUSSION

Resolution and Accuracy for Identifying Current Sources Generated by DBS

AEI provided quantitative maps of local current densities generated by a DBS device using stimulation parameters resembling those used in patients. At 1 MHz, AEI was able to spatially resolve monopole and dipole sources generated by DBS with sub-mm accuracy and a detection threshold below 0.40 mA at safe US pressures. This was verified by systematically switching the stimulation contacts and scanning the US transducer to form co-registered 3D AE and pulse echo US images. AEI was also able to temporally resolve the peak magnitude, SNR, and pulse width at with 250 μ s sampling limited only by the US pulse repetition rate of the transmitter. The integration of AEI with pulse echo US could help quantify spatial patterns of current flow and enable estimating volumes of tissue activated during therapeutic DBS. Such empirical feedback in the human brain would help validate and optimize computational models of DBS while also enhancing our understanding of mechanisms underlying effective DBS. It may also be possible to register current density maps from AEI with structural MR images to help guide placement of the DBS device with sub-mm accuracy. AEI was able to accurately resolve the direction and amplitude of dipoles generated by the DBS device. The decrease in amplitude of the source and sink (illustrated in Fig. 4A) as the stimulating contacts merged suggests that the two poles begin to cancel due to the volume integration of the US beam focus (~ 3.0 mm) according to equation (1). This effect could be reduced by employing a high frequency transducer to improve spatial resolution for AEI.

Noninvasive AEI Through Human Skull

The effects of AEI through the skullcap were consistent with US attenuation and aberrations and aberrations through bone. The SNR of the AE signal when focusing through the skull decreased on average by 13.8 dB. This matched closely with the expected drop in SNR of 14.3 dB given the 80.3% attenuation in pressure. The width and height of the monopoles measured by AEI increased 28.3% and 5%, respectively, through skull, which was consistent with the corresponding increase in the US focal size (Table 2). Our resulting attenuation coefficient of 2.74 Np/cm is slightly larger than that measured by Ammi et al., who calculated a mean attenuation coefficient for human skull of 2.00 Np/cm when using a 1.03 MHz unfocused US transducer (Ammi et al., 2008). This difference may be explained by different properties or condition of the skull. Our measured speed of sound in the skull of 3157 m/s is within range of other studies that report a range between 2800 and 3300 m/s (Fry and Barger, 1978, Ammi et al., 2008). After normalizing to pressure, the sensitivity for detecting AE signals increased only slightly (7.6%) through the skullcap (Table 2). Because the skull did not increase background noise on the recording electrodes, the threshold for current detection was primarily affected by the reduction in pressure.

The significant reduction in the PE signal paired with focal aberrations explain the degradation of the pulse echo images of the DBS through the skullcap. A phased-array US transducer combined with correction algorithms (e.g., forward beamforming or time reversal) should help reduce distortion of the US beam through bone (Wang and Jing, 2013, Kyriakou et al., 2014, Clement et al., 2000). The reflection artifact on PE due to the skull

(see Fig. 7A) introduces another potential complication for AEI. In any practical clinical setting, however, the US transducer would be directly coupled to the skin over the skull such that the distance to the skull interface would be small, resulting in a reflection that is far removed from the target location of the implanted DBS electrode.

Ultimately, as a noninvasive modality for imaging the human brain, any post-operative AEI performed through the skull would benefit from the highest US frequency possible through skull. Transcranial Doppler (TCD) arrays operate near 2 MHz (Naqvi et al., 2013, Purkayastha and Sorond, 2012) and are commonly used to deliver US through the temporal window. A study investigating the interaction between US and the human temporal bone reported a mean attenuation coefficient of 4.76 Np/cm at 2.00 MHz (Ammi et al., 2008). Given a 2.5mm thick temporal window, the estimated attenuation of the US beam would be 69.6% and less than the 80.3% attenuation reported in our study, which still maintained an SNR >10 dB for AEI. Therefore, it seems possible that AEI could be performed through the temporal window for targeting deep brain structures and mapping local current densities near the DBS with sub-mm precision. In this fashion, it would also be possible to fuse real-time AEI and pulse echo US images of the DBS implant onto anatomical MR images for lead localization (Ahmadi et al., 2015) or for guiding placement during surgery (Walter et al., 2016).

One common complication in TCD is known as temporal bone window insufficiency, where the thickness of the skull at the temporal window is too large, preventing effective imaging. This occurs based on normal variations in bone thickness between people and is estimated to reduce or prevent TCD in 29% of the global population (Hashimoto et al., 1992). Future studies will have to investigate thresholds for transcranial AEI at US frequencies >1 MHz. Because AEI only requires one-way propagation of US, there is considerably less attenuation through the skull than for TCD or PE imaging. Although deep brain structures are accessible through temporal windows, it may also be possible to deliver US directly through thicker part of the skull for AEI. In fact, we have recently designed a 0.6 MHz planar matrix array and demonstrated feasibility in a human head phantom using artificial current sources for 4D AEI through thick skull (Qin et al., 2017). However, with a resolution >3mm, this low frequency array may not be ideal for selective imaging of contacts on a DBS device. Regardless, most common DBS applications (e.g., PD, ET, Dystonia) target deep brain structures accessible through the temporal window.

Current Steering and Orientation-specific DBS

Accurate placement of the DBS electrodes is key to its success in alleviating motor symptoms and minimizing side-effects. Intraoperative MRI guided (Starr et al., 2010) and CT (Bot et al., 2017) techniques have been developed to enhance the accuracy of electrode placement from preoperative anatomical MRI. However, errors in both prediction and placement still occur, limiting the overall success of DBS. For example, a DBS lead implanted in the subthalamic nucleus that lies too close to its lateral boundary can also excite the internal capsule due to its laterally symmetrical field shaping (Hariz, 2014). Omni-directional DBS devices with current steering capability, such as the Sapiens *SureStim*TM, and Abbot *Infinity*TM, have recently been introduced for clinical use (Pollo et

al., 2014). These newer DBS devices allow for current to be steered toward a select side of the device, which may help overcome misplacement during surgery by maintaining optimal volumetric stimulation. AEI presents an elegant way to verify and troubleshoot the complex electric field patterns produced by a steerable DBS device during or after surgery without the need for additional or invasive electrodes.

Precise current steering and field shaping is one approach for optimizing DBS parameters through selective excitation of volumes of tissue, which would allow for circuit selective excitation and strict control of the second spatial derivative of extracellular electric fields driving neuronal excitation (Rattay, 1986). Several studies have demonstrated that DBS electrode designs can exploit the orientation dependence of neurons (Lehto et al., 2017, Howell and Grill, 2014, Howell et al., 2015). AEI may be able to provide access to *in-vivo* data from DBS in humans and enable feedback regarding the population of neurons and circuits responsible for optimal relief of PD symptoms. In this manner, AEI can help guide and validate models of therapeutic DBS for PD by providing real-time spatiotemporal feedback of current densities as they are steered around the implant.

CONCLUSION

This study demonstrated feasibility of AEI for selectively mapping the magnitude and polarity of current source densities generated by a clinical DBS device with high resolution, sub-mm and sub-ms accuracy, and detection thresholds below 1.75 mA at 1 MPa. Because most deep brain structures are readily accessible with US through the temporal window, high resolution AEI may be possible for a variety of applications relevant to DBS. As a clinical tool, AEI could help guide placement of an implant during surgery, optimize stimulation parameters, or monitor its performance in patients. Finally, as a noninvasive modality for mapping local current densities, AEI would provide quantitative empirical data in the human brain for validating computational models and improving our understanding of therapeutic DBS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

- Ackermans L, Neuner I, Temel Y, Duits A, Kuhn J, Visser-Vandewalle V. Thalamic deep brain stimulation for Tourette syndrome. *Behav Neurol*. 2013; 27:133–8. [PubMed: 23242353]
- Ahmadi SA, Milletari F, Navab N, Schuberth M, Plate A, Botzel K. 3D transcranial ultrasound as a novel intra-operative imaging technique for DBS surgery: a feasibility study. *Int J Comput Assist Radiol Surg*. 2015; 10:891–900. [PubMed: 25861056]

- Ammi AY, Mast TD, Huang IH, Abruzzo TA, Coussios CC, Shaw GJ, Holland CK. Characterization of ultrasound propagation through ex-vivo human temporal bone. *Ultrasound Med Biol*. 2008; 34:1578–89. [PubMed: 18456391]
- Anheim M, Batir A, Fraix V, Silem M, Chabardes S, Seigneuret E, Krack P, Benabid AL, Pollak P. Improvement in Parkinson disease by subthalamic nucleus stimulation based on electrode placement: effects of reimplantation. *Arch Neurol*. 2008; 65:612–6. [PubMed: 18474736]
- Berthon B, Dansette PM, Tanter M, Pernot M, Provost J. An integrated and highly sensitive ultrafast acoustoelectric imaging system for biomedical applications. *Phys Med Biol*. 2017; 62:5808–5822. [PubMed: 28436918]
- Bot M, Van Den Munckhof P, Bakay R, Stebbins G, Verhagen Metman L. Accuracy of Intraoperative Computed Tomography during Deep Brain Stimulation Procedures: Comparison with Postoperative Magnetic Resonance Imaging. *Stereotact Funct Neurosurg*. 2017; 95:183–188. [PubMed: 28601874]
- Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkmann J, Stefani A, Horak FB, Okun MS, Foote KD, Krack P, Pahwa R, Henderson JM, Hariz MI, Bakay RA, Rezai A, Marks WJ Jr, Moro E, Vitek JL, Weaver FM, Gross RE, Delong MR. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. *Arch Neurol*. 2011; 68:165. [PubMed: 20937936]
- Clement GT, White J, Hynynen K. Investigation of a large-area phased array for focused ultrasound surgery through the skull. *Phys Med Biol*. 2000; 45:1071–83. [PubMed: 10795992]
- Ellis TM, Foote KD, Fernandez HH, Sudhyadhom A, Rodriguez RL, Zeilman P, Jacobson CET, Okun MS. Reoperation for suboptimal outcomes after deep brain stimulation surgery. *Neurosurgery*. 2008; 63:754–60. discussion 760–1. [PubMed: 18981887]
- Fry FJ, Barger JE. Acoustical properties of the human skull. *J Acoust Soc Am*. 1978; 63:1576–90. [PubMed: 690336]
- Gross RE, Rolston JD. The clinical utility of methods to determine spatial extent and volume of tissue activated by deep brain stimulation. *Clin Neurophysiol*. 2008; 119:1947–50. [PubMed: 18632306]
- Hamani C, Pilitsis J, Rughani AI, Rosenow JM, Patil PG, Slavin KS, Abosch A, Eskandar E, Mitchell LS, Kalkanis S, American Society For, S., Functional, N., Congress of Neurological, S., Cns & American Association of Neurological, S. Deep brain stimulation for obsessive-compulsive disorder: systematic review and evidence-based guideline sponsored by the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (CNS) and endorsed by the CNS and American Association of Neurological Surgeons. *Neurosurgery*. 2014; 75:327–33. quiz 333. [PubMed: 25050579]
- Hariz M. Deep brain stimulation: new techniques. *Parkinsonism Relat Disord*. 2014; 20(Suppl 1):S192–6. [PubMed: 24262179]
- Harris GPR. Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers. Food and Drug Administration; 2008.
- Hashimoto H, Etani H, Naka M, Kinoshita N, Nukada T. Assessment of the rate of successful transcranial Doppler recording through the temporal windows in Japanese with special reference to aging and sex. *Nihon Ronen Igakkai Zasshi*. 1992; 29:119–22. [PubMed: 1583798]
- Howell B, Grill WM. Evaluation of high-perimeter electrode designs for deep brain stimulation. *J Neural Eng*. 2014; 11:046026. [PubMed: 25029124]
- Howell B, Huynh B, Grill WM. Design and in vivo evaluation of more efficient and selective deep brain stimulation electrodes. *J Neural Eng*. 2015; 12:046030. [PubMed: 26170244]
- Iacono MI, Neufeld E, Bonmassar G, Akininagbe E, Jakab A, Cohen E, Kuster N, Kainz W, Angelone LM. A Computational Model for Bipolar Deep Brain Stimulation of the Subthalamic Nucleus. *Conf Proc IEEE Eng Med Biol Soc*. 2014
- Jossinet J, Lavandier B, Cathignol D. The phenomenology of acousto-electric interaction signals in aqueous solutions of electrolytes. *Ultrasonics*. 1998
- Jossinet J, Lavandier B, Cathignol D. Impedance Modulation by Pulsed Ultrasound. *Ann N Y Acad Sci*. 1999
- Kuncel AM, Grill WM. Selection of stimulus parameters for deep brain stimulation. *Clin Neurophysiol*. 2004; 115:2431–41. [PubMed: 15465430]

- Kuncel AM, Cooper SE, Grill WM. A method to estimate the spatial extent of activation in thalamic deep brain stimulation. *Clin Neurophysiol.* 2008; 119:2148–58. [PubMed: 18632304]
- Kyriakou A, Neufeld E, Werner B, Paulides MM, Szekely G, Kuster N. A review of numerical and experimental compensation techniques for skull-induced phase aberrations in transcranial focused ultrasound. *Int J Hyperthermia.* 2014; 30:36–46. [PubMed: 24325307]
- Laxpati NG, Kasoff WS, Gross RE. Deep brain stimulation for the treatment of epilepsy: circuits, targets, and trials. *Neurotherapeutics.* 2014; 11:508–26. [PubMed: 24957200]
- Lehto LJ, Slopsema JP, Johnson MD, Shatillo A, Teplitzky BA, Utecht L, Adrian G, Mangia S, Sierra A, Low WC, Grohn O, Michaeli S. Orientation selective deep brain stimulation. *J Neural Eng.* 2017; 14:016016. [PubMed: 28068296]
- Li Q, Olafsson R, Ingram P, Wang Z, Witte R. Measuring the acoustoelectric interaction constant using ultrasound current source density imaging. *Phys Med Biol.* 2012; 57:5929–41. [PubMed: 22954500]
- Maks CB, Butson CR, Walter BL, Vitek JL, McIntyre CC. Deep brain stimulation activation volumes and their association with neurophysiological mapping and therapeutic outcomes. *J Neurol Neurosurg Psychiatry.* 2009; 80:659–66. [PubMed: 18403440]
- McConnell GC, So RQ, Hilliard JD, Lopomo P, Grill WM. Effective deep brain stimulation suppresses low-frequency network oscillations in the basal ganglia by regularizing neural firing patterns. *J Neurosci.* 2012; 32:15657–68. [PubMed: 23136407]
- McIntyre CC, Mori S, Sherman DL, Thakor NV, Vitek JL. Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. *Clin Neurophysiol.* 2004; 115:589–95. [PubMed: 15036055]
- Morishita T, Fayad SM, Higuchi MA, Nestor KA, Foote KD. Deep brain stimulation for treatment-resistant depression: systematic review of clinical outcomes. *Neurotherapeutics.* 2014; 11:475–84. [PubMed: 24867326]
- Naqvi J, Yap KH, Ahmad G, Ghosh J. Transcranial Doppler ultrasound: a review of the physical principles and major applications in critical care. *Int J Vasc Med.* 2013; 2013:629378. [PubMed: 24455270]
- Nazzaro JM, Lyons KE, Pahwa R. Deep brain stimulation for essential tremor. *Handb Clin Neurol.* 2013; 116:155–66. [PubMed: 24112892]
- Olafsson R, Witte RS, Huang SW, O'donnell M. Ultrasound current source density imaging. *IEEE Trans Biomed Eng.* 2008; 55:1840–8. [PubMed: 18595802]
- Olafsson R, Witte RS, Jia C, Huang SW, Kim K, O'donnell M. Cardiac activation mapping using ultrasound current source density imaging (UCSDI). *IEEE Trans Ultrason Ferroelectr Freq Control.* 2009; 56:565–74. [PubMed: 19411215]
- Pollo C, Kaelin-Lang A, Oertel MF, Stieglitz L, Taub E, Fuhr P, Lozano AM, Raabe A, Schupbach M. Directional deep brain stimulation: an intraoperative double-blind pilot study. *Brain.* 2014; 137:2015–26. [PubMed: 24844728]
- Purkayastha S, Sorond F. Transcranial Doppler ultrasound: technique and application. *Semin Neurol.* 2012; 32:411–20. [PubMed: 23361485]
- Qin Y, Li Q, Ingram P, Barber C, Liu Z, Witte RS. Ultrasound current source density imaging of the cardiac activation wave using a clinical cardiac catheter. *IEEE Trans Biomed Eng.* 2015; 62:241–7. [PubMed: 25122512]
- Qin Y, Ingram P, Xu Z, O'donnell M, Witte RS. International Ultrasound Symposium. Washington D.C.: IEEE; 2017. Performance of a transcranial US array designed for 4D acoustoelectric brain imaging in humans.
- Rattay F. Analysis of models for external stimulation of axons. *IEEE Trans Biomed Eng.* 1986:BME-33.
- Richardson RM, Ostrem JL, Starr PA. Surgical repositioning of misplaced subthalamic electrodes in Parkinson's disease: location of effective and ineffective leads. *Stereotact Funct Neurosurg.* 2009; 87:297–303. [PubMed: 19641340]
- Starr PA, Martin AJ, Ostrem JL, Talke P, Levesque N, Larson PS. Subthalamic nucleus deep brain stimulator placement using high-field interventional magnetic resonance imaging and a skull-

mounted aiming device: technique and application accuracy. *J Neurosurg.* 2010; 112:479–90. [PubMed: 19681683]

Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Benabid AL, Cornu P, Lagrange C, Tezenas Du Montcel S, Dormont D, Grand S, Blond S, Detante O, Pillon B, Ardouin C, Agid Y, Destee A, Pollak P, French Stimulation Du Pallidum Interne Dans La Dystonie Study, G. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N Engl J Med.* 2005; 352:459–67. [PubMed: 15689584]

Walter U, Muller JU, Rosche J, Kirsch M, Grossmann A, Benecke R, Wittstock M, Wolters A. Magnetic resonance-transcranial ultrasound fusion imaging: A novel tool for brain electrode location. *Mov Disord.* 2016; 31:302–9. [PubMed: 26362398]

Wang T, Jing Y. Transcranial ultrasound imaging with speed of sound-based phase correction: a numerical study. *Phys Med Biol.* 2013; 58:6663–81. [PubMed: 24018632]

Wang Z, Da-Ho W, Leung CS, Park SW. Polarity detection in ultrasound current source density imaging. *IEEE UFFC.* 2016

Wang ZH, Olafsson R, Ingram P, Li Q, Qin Y, Witte RS. Four-dimensional ultrasound current source density imaging of a dipole field. *Appl Phys Lett.* 2011; 99:113701–1137013. [PubMed: 21998486]

Wei XF, Grill WM. Current density distributions, field distributions and impedance analysis of segmented deep brain stimulation electrodes. *J Neural Eng.* 2005; 2:139–47. [PubMed: 16317238]

Figure 1. Timing Diagram and Experimental Setup

(A) Timing diagram acoustoelectric (AE) and pulse echo (PE) ultrasound (US) acquisition. An event trigger initiates a burst of electrical stimulation pulses (3V, 1 ms pulse, 200 Hz) and US pulses ($t = 250 \mu s$). Each US pulse was used to generate an AE signal along the depth axis (A line) detected on the recording electrode. The amplitude of the AE signal was proportional to the local and instantaneous current densities generated by the deep brain stimulation (DBS) device (lower left, displaying a monopole at contact 3). The backscattered echo was also detected by the US transducer to form standard pulse echo images co-registered with AEI. (B) Side view of setup with wiring diagram for both monopole (red hashed) and dipole (black solid) stimulating configurations. The US transducer is mechanically steered along the x axis to form 3D datasets (X, Z, t_{slow}). Experiments were performed with and without the human skullcap. Not drawn to scale.

Figure 2. AE M-Mode Images of Time-varying Current

(A) Black trace: measured current waveform injected between contacts 0 and 3 of the DBS implant. Red trace: waveform of AE(t) at a depth of 67.5mm (indicated by white hashed line in B). Amplitude of red trace is normalized to the amplitude of the measured current to highlight the similarities in the waveform; y-axis labels refer to the black trace in mA. (B–E) Corresponding AE M-Mode images related to the time-varying injected current in A, indicating raw AE amplitude signals (B), AE amplitude signal filtered in slow (t_{slow}) and fast (t_{fast}) time (C), magnitude of Hilbert-transformed signal in B with 6 dB dynamic range (D), and signed magnitude of the basebanded and filtered signal indicating polarity (color) and amplitude (intensity) of injected current at the anode with ± 6 dB dynamic range (E). The US transducer is located at a depth of 0mm. Blue arrows from A to B indicate the peak of the injected current pulses, which correspond well to the positive peak of the AE signals located at the depth of the DBS implant (~ 67.5 mm from the US transducer).

Figure 3. AE images of DBS Monopoles in Saline

(A) 2D cross-sectional images of the AE signals during monopole stimulation patterns at peak current ($t = 5.5\text{ms}$; see supplementary movie 1). Gray represents co-registered PE image of the DBS device at depth of 67.5mm. Hot colors represent the magnitude of the AE signal. Below each image is a sized to scale depiction of the DBS device with the contact used to generate the monopole indicated by a solid red circle. (B) Plot of the envelope of the AE signal along the long axis of the DBS device for each monopole configuration. Vertical red hashed lines indicate center of contact used for stimulation.

Figure 4. AE images of DBS Dipoles in Saline

(A) 2D AEI of dipoles generated using the clinical DBS device at peak current ($t_{\text{slow}} = 5.5\text{ms}$; see supplementary movie 2). Gray indicates PE image. Color indicates the polarity and magnitude of the AE signal; hot and cold colors describe positive and negative voltages. The DBS device is depicted to-scale below each image with a red and blue circle indicating the anode and cathode, respectively. (B) Plot comparing the lateral position of the AEI peaks to the center location of the contacts used as the cathode and anode. AE peaks and contact locations are displayed relative to the center of contact 0 (determined by PE). Contact 3 was used as the anode for the dipole configuration. Legend: circles are labeled with numbers corresponding to the contacts used in the different dipole configurations. The slope of the dashed red line is determined from the actual distance from contact 0.

Figure 5. AE Sensitivity and Current Detection Thresholds

(A) Waveform of the injected current (black) overlaid with the measured AE signal from a monopole (red). (B) AE Sensitivity per unit pressure using a monopole generated by a DBS contact (averages = 20). (C) Plot of SNR vs. number of averages for measuring the AE signal. The solid line represents the best fit through the data (2.74 dB/octave). The red dotted line represents the expected slope for completely independent observations (3 dB/octave).

Figure 6. Calibrating US Beam through Human Skullcap

(A) Photograph of human skullcap used for transcranial AEI experiments. Red dashed circle and arrow denote region for delivering US. (B–C) Time waveform and frequency spectrums of US pulses recorded by the hydrophone. (D) Lateral pressure profiles of US beam at focus with and without skullcap.

Figure 7. AEI of DBS Monopoles and Dipole through Human Skull

(A) B-Mode PE image of the DBS electrode through the skull (gray) superimposed on the AE signal from a dipole at peak current generated between contacts 0 and 3. The green dashed box between 60 and 68 mm indicates the zoomed region-of-interest for images in B. (B) (Top) 2D AE images of monopoles through skull with a dynamic range of 6 dB. (Bottom) 2D AE image of a dipole (± 6 dB) superimposed on the PE image (gray) of the DBS electrode. Red and blue circles on the photograph of the DBS electrode above each image indicates the contact used as the anode and cathode, respectively.

Table 1
AEI quantification using different dipole configurations

Peak refers to peak of AE signal envelope. Width was measured at -6 dB. SNR was calculated with an injected current of 11.5 mA. Mechanical Index = 1.7. A = Anode; C = Cathode.

DBS Contacts (A-C)	3-0	3-1	3-2
Anode AE Peak (μV)	32.8	35.6	21.5
Cathode AE Peak (μV)	30.1	31.0	23.0
Anode SNR (dB)	19.4	20.1	15.8
Cathode SNR (dB)	18.7	19.0	16.4
Anode Width (mm)	3.27	3.57	2.13
Cathode Width (mm)	3.27	3.17	1.98

Table 2
AEI quantification with and without human skullcap

Width (lateral) and height (transverse normal) were calculated at –6 dB. DBS lead dimensions were 1.5 mm (width) and 1.27 mm (height). SNR was calculated at 11.5 mA. Mechanical indices at US focus were 0.386 (skull) and 1.70 (no skull). Monopole data represents the average for all four lead configurations.

	No Skull	Skull
Pk-Pk Pressure (MPa)	4.40	0.868
Beam Width (mm)	3.34	4.05
Beam Height (mm)	2.34	2.38
Monopole Width (mm)	3.67 ± 0.18	4.71 ± 0.41
Monopole Height (mm)	3.11 ± 0.21	3.24 ± 0.25
Sensitivity ($\mu\text{V}/\text{MPa}/\text{mA}$)	0.52 ± 0.07	0.56 ± 0.10
SNR (dB)	24.7 ± 1.6	10.9 ± 1.1