Real-time displacement and cavitation imaging of non-invasive neuromodulation of the peripheral nervous system via focused ultrasound

Stephen A. Lee*, Hermes A.S. Kamimura* Mark T. Burgess*, Antonios Pouliopoulos*, and Elisa E. Konofagou*†
*Department of Biomedical Engineering, †Radiology
Columbia University
New York, NY, USA
Email: ek2191@columbia.edu

***Abstract*— Conventional treatments of neuropathic pain are commonly invasive or non-localized. Focused ultrasound (FUS) is a promising neuromodulation technique that has been shown effective in various animal models. There have been numerous advances in the field of ultrasound neuromodulation with the technology already being applied to humans without a clear understanding of the underlying mechanism. Here, we present a method capable of targeting and monitoring of focused ultrasound (FUS) neuromodulation of the mouse sciatic nerve using high frame-rate displacement and cavitation imaging. Our technique is capable of detecting micron displacements and cavitation activity at the focus. Displacement and cavitation were measured with excitation of the sciatic nerve, indicating that radiation force and cavitation play in parts of the underlying mechanism. Taken together, our imaging technique is a powerful *in vivo* tool for real-time targeting of deep structures and investigation of the FUS neuromodulation mechanism.**

I. INTRODUCTION

Peripheral nerve stimulation (PNS) has been employed as a therapeutic for peripheral neuropathy and other chronic pain through the use of permanent, implanted electrodes [1]–[5]. Other techniques for the treatment of neuropathic pain include brain stimulation include transcutaneous electrical stimulation, transcranial direct-current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS)[6]–[8]. Though these techniques may produce long-lasting effects, they are also non-localized methods with significant heterogeneity among studies[9].

Alternatively, focused ultrasound (FUS) has been shown to evoke neuromodulatory responses in a variety of studies[10]–[21]. In addition to its neuromodulatory effects, FUS also has superior target specificity and depth of penetration compared to other non-invasive technique[10], [17]. Despite the efforts in developing *ex vivo* and *in vitro* models for the investigation of the mechanism of FUS neuromodulation, experimental conditions are different than *in vivo* so that the underlying mechanism of FUS neuromodulation remains largely unknown. In addition, studies investigating FUS CNS modulation are prone to physical artifacts such as the skull which absorbs and distorts ultrasound energy, forcing the practitioner to increase the intensity of the transducer or lowering the frequency in order to reach certain brain regions. Whereas the access to the periphery remains unobstructed and the acoustic energy may reach the nerve. Despite the differences between the central and peripheral nervous systems, FUS-based PNS performed noninvasively may give insights into the mechanisms coupled with FUS that could be associated with neuronal activation such as cavitation, temperature, and acoustic radiation force, while avoiding physical limitations commonly found in central nervous system (CNS) studies.

In this study, we developed a FUS-based imaging technique to monitor and track tissue displacement and measure cavitation during FUS neuromodulation of the sciatic nerve in an *in vivo* mouse model at high frame rates. We demonstrate a connection between displacement, cavitation and corresponding electromyography (EMG). This technique is an important tool to advance the investigations of the mechanisms involved in FUS neuromodulation.

II. EXPERIMENTAL SETUP

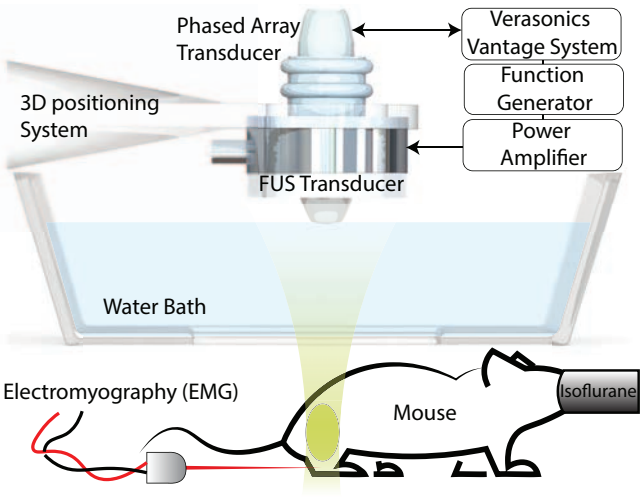

Fig. 1. Schematic of experimental setup for both displacement and cavitation studies

Two commercially available ultrasound transducers were used in a confocally aligned configuration (Fig 1).A FUS

stimulation transducer (H-215, 4MHz center frequency, single-element FUS; SonicConcepts, Bothell, WA) and an imaging transducer (L22-14vX Long Focus, 16 MHz center frequency, 128 elements linear array; Vermon, France). Acoustic stimulation emissions were driven by a function generator (33220a; Keysight Tech., Santa Rosa, CA) amplified by a 150W amplifier (A150; E&I, Rochester, NY). Imaging transmit and receive events were acquired through a Vantage 128 (Verasonics; Redmond, WA) research platform.

All procedures and protocols were approved by the Columbia University Institutional Animal Care and Use Committee (IACUC) and the USAMRMC Animal Care and Use Review Office (ACURO). Male C57BL/6J mice, weighing between 22g to 28g, were used in all experiments (n = 6). Mice were anesthetized with isoflurane: 3% during induction and preparation, 1.2% during the procedure. The mouse was placed in a pronated orientation so that the sciatic nerve was more superficial to the ultrasound transducer.

Electromyography was performed using two bi-polar needle electrodes grounded to either the loose skin on the back of the neck, or the table. One electrode was placed 1 mm into the tibialis anterior and the other 1 mm into the gastrocnemius muscle. The head was fixed in a stereotaxic system and the legs were immobilized to reduce movement artifacts in the EMGs. The mouse was then placed in a custom-built faraday cage to eliminate external noise sources from the recording electrodes. Both the transducer and the Faraday cage were grounded.

III. Displacement Imaging

Plane wave were transmitted at a 50 kHz frame rate and five compounded angles were used to generate subsequent RF data to be tracked. RF data was beamformed using conventional delay-and-sum beamforming and HIFU interference was filtered out using notch filters at the fundamental and up to the 5th harmonic. Axial displacement was calculated through 1-D cross correlation[22], 95% overlap and a 0.733 mm window. Displacement images were overlaid onto B-mode images of the mice for both targeting and mechanism studies.

EMG amplitudes were detected only when higher acoustic pressures (between 15 and 30 MPa) were used and corresponding displacements increased linearly as the pressure increased. Figure 2 shows that when the acoustic focus is placed on the nerve (outlined in white), the nerve will fire and cause electrical muscle activity to be picked up by the EMG electrodes.

IV. Cavitation

Cavitation maps were generated using a receive-only acquisition for the imaging transducer while the FUS transducer transmits enough power to elicit a response. To form an image, the received signals were temporally delayed based on the geometry and propagation times for each element in the transducer. Waveforms were then beamformed to each pixel position by summing up the contributions from each element. The power cavitation image was then log-compressed relative

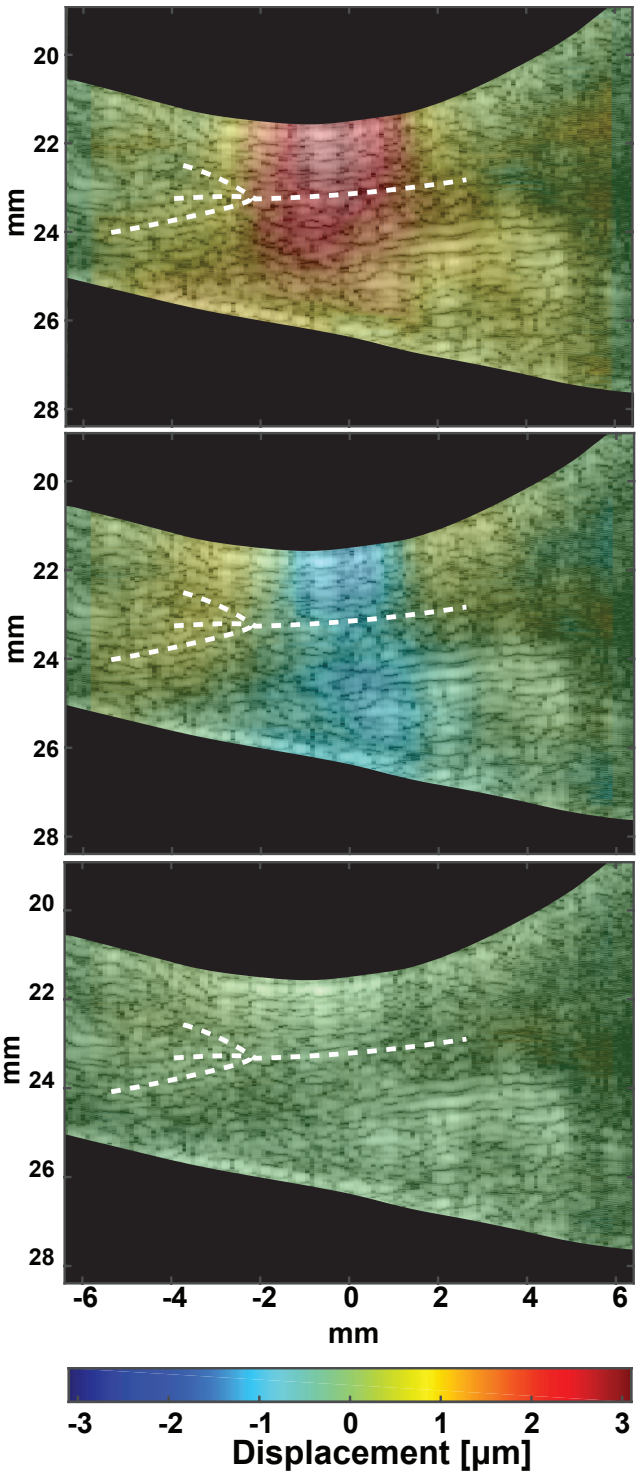

Fig. 2. Interframe displacement images overlaid onto the upper thigh of a mouse. The sciatic nerve and corresponding branches are outlined in each image.

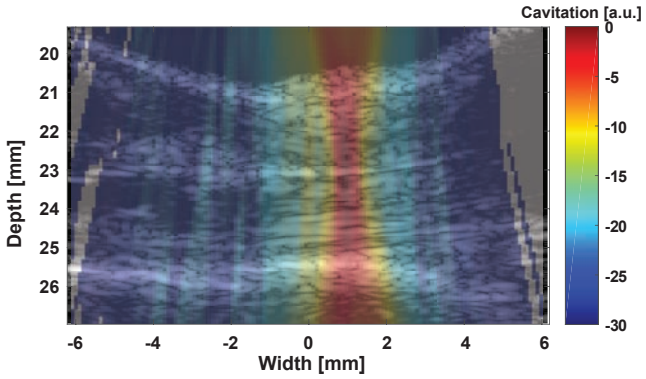

Fig. 3. Power cavitation image overlaid onto the B-mode image of a mouse leg

to the maximum pixel intensity. Contributions over the 1 ms FUS pulse duration were used to generate a single power cavitation image[23].

Figure 3 shows a generated cavitation map at -21 MPa rarefactional pressure. The summation of the cavitational events are seen to be located mostly at the sciatic nerve. Cavitation was shown to be present in FUS neuromodulation events above -10 MPa pressure.

V. Discussion

Displacement and cavitation imaging were shown to be able to detect radiation force and cavitation during individual FUS neuromodulation events. The results indicate that the two mechanisms may have an interconnected relevance to how FUS neuromodulation of the peripheral nervous system works. Since most CNS studies use low intensity pulsed ultrasound, the cavitation events and radiation force are limited. We believe that the mechanism for targeting the nerve bundle and subsequent axons are inherently different than modulating the neuron cell bodies themselves. Furthermore, there may be a dependence of acoustic parameters on the accumulation of nerve fibers. Since many nerve fibers need to be activated to generate an EMG response, there may be more subtle influence of displacement and cavitation on nerve action potentials.

Cavitation becomes more likely, the higher the acoustic pressure used is. However, the amount of displacement shown also increases and it becomes increasingly difficult to separate the two. There may be instances where neuromodulation occurs without the presence of cavitation. We do not expect thermal effects for neuromodulation since the temperature, measured with a thermocouple, indicate that temperatures for these parameters do not exceed 0.1^{o}C.

VI. Conclusions

We present a FUS system that takes advantage of the actual FUS pulse for neuromodulation to provide feedback for mechanistic studies of both cavitation and radiation force. For initial feasibility, we demonstrate that both cavitation and radiation force contribute to the firing of the nerve bundle. Future studies will investigate purely mechanical excitation of the nerve or purely thermal excitation to better inform of the mechanism behind ultrasound neuromodulation. This is important for the scientific understanding but also the clinical translation into a therapeutic technique for pain management.

Acknowledgment

The authors would like to acknowledge Iason Apostolakis, Ph.D. and Nancy Kwon M.S., for their helpful discussions, insights, and assistance.

References

[1] H. Al-Jehani and L. Jacques, "Peripheral nerve stimulation for chronic neurogenic pain." *Prog. Neurol. Surg.*, vol. 24, pp. 27–40, 2011. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/21422774

[2] O. A. de Leon-Casasola, "Spinal Cord and Peripheral Nerve Stimulation Techniques for Neuropathic Pain," *J. Pain Symptom Manage.*, vol. 38, no. 2, pp. S28–S38, aug 2009. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0885392409005429

[3] K. V. Slavin, "Peripheral nerve stimulation for neuropathic pain," *Neurotherapeutics*, vol. 5, no. 1, pp. 100–106, jan 2008. [Online]. Available: http://link.springer.com/10.1016/j.nurt.2007.11.005

[4] R. M. Stuart, "Neurostimulation Techniques for Painful Peripheral Nerve Disorders," *Neurosurg. Clin. N. Am.*, vol. 20, no. 1, pp. 111–120, jan 2009. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1042368008000569

[5] M. Y. Oh, J. Ortega, J. B. Bellotte, D. M. Whiting, and K. Aló, "Peripheral Nerve Stimulation for the Treatment of Occipital Neuralgia and Transformed Migraine Using a C1-2-3 Subcutaneous Paddle Style Electrode: A Technical Report," *Neuromodulation Technol. Neural Interface*, vol. 7, no. 2, pp. 103–112, apr 2004. [Online]. Available: http://doi.wiley.com/10.1111/j.1094-7159.2004.04014.x

[6] J.-P. Lefaucheur, A. Antal, R. Ahdab, D. Ciampi de Andrade, F. Fregni, E. M. Khedr, M. Nitsche, and W. Paulus, "The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain," *Brain Stimul.*, vol. 1, no. 4, pp. 337–344, oct 2008. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1935861X08003215?via{\%}3Dihub

[7] G. Cruccu, T. Z. Aziz, L. Garcia-Larrea, P. Hansson, T. S. Jensen, J.-P. Lefaucheur, B. A. Simpson, and R. S. Taylor, "EFNS guidelines on neurostimulation therapy for neuropathic pain," *Eur. J. Neurol.*, vol. 14, no. 9, pp. 952–970, sep 2007. [Online]. Available: http://doi.wiley.com/10.1111/j.1468-1331.2007.01916.x

[8] J.-P. Lefaucheur, "Cortical neurostimulation for neuropathic pain," *Pain*, vol. 157, pp. S81–S89, feb 2016. [Online]. Available: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage{\&}an=00006396-201602001-00013

[9] M. L. Chen, L. Yao, J. Boger, K. Mercer, B. Thompson, and N. Jiang, "Non-invasive brain stimulation interventions for management of chronic central neuropathic pain: a scoping review protocol." *BMJ Open*, vol. 7, no. 10, p. e016002, oct 2017. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/29042375http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5652613

[10] M. E. Downs, S. A. Lee, G. Yang, S. Kim, Q. Wang, and E. E. Konofagou, "Non-invasive peripheral nerve stimulation via focused ultrasound in vivo," *Phys. Med. Biol.*, vol. 63, no. 3, p. 035011, jan 2018. [Online]. Available: http://stacks.iop.org/0031-9155/63/i=3/a=035011?key=crossref.1f4508614d5b73dc4a990bc4e8859631

[11] Y. Tufail, A. Matyushov, N. Baldwin, M. L. Tauchmann, J. Georges, A. Yoshihiro, S. I. Tillery, and W. J. Tyler, "Transcranial Pulsed Ultrasound Stimulates Intact Brain Circuits," *Neuron*, vol. 66, no. 5, pp. 681–694, jun 2010. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0896627310003764?via{\%}3Dihub

[12] W. J. Tyler, Y. Tufail, M. Finsterwald, M. L. Tauchmann, E. J. Olson, and C. Majestic, "Remote excitation of neuronal circuits using low-intensity, low-frequency ultrasound," *PLoS One*, vol. 3, no. 10, p. e3511, oct 2008. [Online]. Available: http://dx.plos.org/10.1371/journal.pone.0003511

[13] E. . N. Harvey, "The effect of high frequency sound waves on heart muscle and other irritable tissues," *Am. Heart J.*, vol. 5, no. 3, p. 388, feb 1930. [Online]. Available: http://linkinghub.elsevier.com/retrieve/pii/S0002870330903432

[14] M. D. Menz, O. Oralkan, P. T. Khuri-Yakub, and S. A. Baccus, "Precise Neural Stimulation in the Retina Using Focused Ultrasound," *J. Neurosci.*, vol. 33, no. 10, pp. 4550–4560, mar 2013. [Online]. Available: http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.3521-12.2013

[15] W. Lee, S. D. Lee, M. Y. Park, L. Foley, E. Purcell-Estabrook, H. Kim, K. Fischer, L. S. Maeng, and S. S. Yoo, "Image-Guided Focused Ultrasound-Mediated Regional Brain Stimulation in Sheep," *Ultrasound Med. Biol.*, vol. 42, no. 2, pp. 459–470, feb 2016. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0301562915005876

[16] R. L. King, J. R. Brown, W. T. Newsome, and K. B. Pauly, "Effective parameters for ultrasound-induced in vivo neurostimulation," *Ultrasound Med. Biol.*, vol. 39, no. 2, pp. 312–331, feb 2013. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0301562912005753?via{\%}3Dihub

[17] H. A. S. Kamimura, S. Wang, H. Chen, Q. Wang, C. Aurup, C. Acosta, A. A. O. Carneiro, and E. E. Konofagou, "Focused ultrasound neuromodulation of cortical and subcortical brain structures using 1.9 MHz," *Med. Phys.*, vol. 43, no. 10, pp. 5730–5735, sep 2016. [Online]. Available: http://doi.wiley.com/10.1118/1.4963208

[18] J. Kubanek, J. Shi, J. Marsh, D. Chen, C. Deng, and J. Cui, "Ultrasound modulates ion channel currents," *Sci. Rep.*, vol. 6, no. 1, p. 24170, jul 2016. [Online]. Available: http://www.nature.com/articles/srep24170

[19] W. Legon, T. F. Sato, A. Opitz, J. Mueller, A. Barbour, A. Williams, and W. J. Tyler, "Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans," *Nat. Neurosci.*, vol. 17, no. 2, pp. 322–329, jan 2014. [Online]. Available: http://www.nature.com/doifinder/10.1038/nn.3620

[20] W. J. Fry, V. J. Wulff, D. Tucker, and F. J. Fry, "Physical Factors Involved in Ultrasonically Induced Changes in Living Systems: I. Identification of Non-Temperature Effects," *J. Acoust. Soc. Am.*, vol. 22, no. 6, pp. 867–876, 1950. [Online]. Available: http://link.aip.org/link/?JASMAN/22/867/1

[21] W. J. Fry, W. H. Mosberg, J. W. Barnard, and F. J. Fry, "Production of Focal Destructive Lesions in the Central Nervous System With Ultrasound," *J. Neurosurg.*, vol. 11, no. 5, pp. 471–478, sep 1954. [Online]. Available: http://thejns.org/doi/10.3171/jns.1954.11.5.0471

[22] J. Luo and E. Konofagou, "A fast normalized cross-correlation calculation method for motion e ... - PubMed - N ... A fast normalized cross-correlation calculation method for motion estimation . PubMed Commons," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 57, no. 6, pp. 1347–57, 2010.

[23] M. T. Burgess, I. Apostolakis, and E. Konofagou, "Passive microbubble imaging with short pulses of focused ultrasound and absolute time-of-flight information," *J. Acoust. Soc. Am.*, vol. 141, no. 5, pp. 3491–3491, may 2017. [Online]. Available: http://asa.scitation.org/doi/10.1121/1.4987289