



Letter to the Editor

Non-Invasive Ultrasonic Thalamic Stimulation in Disorders of Consciousness after Severe Brain Injury: A First-in-Man Report



Dear Editor:

Modern intensive care medicine has greatly increased the rates of survival after severe brain injury (BI). Nonetheless, a number of patients fail to fully recover from coma, and awaken to a disorder of consciousness (DOC) such as the vegetative state (VS) or the minimally conscious state (MCS) [1]. In these conditions, which can be transient or last indefinitely, patients can lose virtually all autonomy and have almost no treatment options [1,2]. In addition, these conditions place great emotional and financial strain on families, lead to increased burn-out rates among care-takers, impose financial stress on medical structures and public finances due to the costs of prolonged intensive care, and raise difficult legal and ethical questions [3].

Leveraging on a growing scientific understanding of the processes accompanying recovery of function after severe BI [4], neuromodulatory techniques such as deep brain stimulation (DBS) [5] and transcranial direct current stimulation (tDCS) [6] have been employed to enhance the excitability of (central) thalamic efferent neurons. While these neuromodulatory techniques have shown some ability to increase patients' behavioral responsiveness in both subacute and chronic patients, they have severe limitations. Thalamic DBS has shown encouraging results in one patient [5], but requires invasive surgery and can lead to complications tied to implantation, such as intracranial hemorrhage and its sequelae, device failure, and may affect future medical care (e.g., the ability to undergo specific types of MR-imaging). tDCS, although non-invasive, has only superficial penetration and can therefore only modulate thalamus indirectly, through its reciprocal innervations with, for example, (pre-)frontal cortex [6].

As a possible alternative, combining the advantages of DBS and tDCS, and avoiding the respective disadvantages, low intensity focused ultrasound pulsation (LIFUP) can produce direct neuromodulation of deep brain nuclei, such as the thalamus, non-invasively and without affecting intervening tissues. This technique, which has an excellent safety record [7,8], has already been shown to affect the state of tissue excitability, and thus achieve neuromodulation, across a number of animal models as well as in humans [7–9]. In addition, in rodents undergoing intraperitoneal ketamine/xylazine anesthesia, thalamic LIFUP has been shown to speed up the return of behavioral responsiveness [8], thus opening the door to potential use in human patients suffering from a DOC.

As part of a “first-in-man” clinical trial (NCT02522429) aimed at testing the feasibility, safety, and initial efficacy of thalamic LIFUP in patients suffering from post-traumatic DOC, we recruited one patient (25y, male, 19 days post-injury). The patient was brought to the Ronald Reagan Medical Center (RRMC) at UCLA after suffering a road-traffic related severe BI, with a field Glasgow Coma Scale (GCS) of 3, an emergency department GCS of 7, and presenting bi-frontal contusions and sub-dural hemorrhage on the CT. The patient was recruited, after chart review (by PMV), upon meeting the inclusion criteria of: (i) initial GCS < 9 and an abnormal CT, both indicating severe TBI; (ii) prolonged loss of consciousness (>24 h post injury); (iii) an ongoing DOC (assessed by CS); and (iv) at least 18 years old. No change in sedating medicine regimen occurred during the length of the experiment.

The procedure was approved by the UCLA institutional review board, and written consent was given by the patient's legal surrogate.

The procedure included four clinical assessments of level of consciousness and responsiveness. Two assessments occurred pre-LIFUP sonication (performed by CS using the Coma Recovery Scale-Revised; CRS-R [10]), one on the day prior to sonication and one on the day of. Two clinical assessments occurred post-LIFUP, one on the day of sonication and one on the day after. The study utilized a LIFUP device (BXPulsar 1001, Brainsonix Inc.) containing a single-element, air-backed, spherical section ultrasound transducer with a diameter and radius of curvature of 71.5 mm, operating at a fundamental frequency of 650 kHz. The transducer was mounted in a plastic housing that was filled with deionized, de-gassed water and sealed with a thin polyethylene membrane permeable to ultrasound. LIFUP was administered with a pulse repetition frequency of 100 Hz, and pulse width of 0.5 ms. A total of 10 sonications were administered, with a derated spatial-peak temporal-average intensity ($I_{sp,ta}$) of approximately 720 mW/cm², each lasting 30 s, separated by 30 s pause intervals. Sonication was administered within a 3 Tesla Magnetom Tim Trio MR scanner at the RRMC at UCLA.

Prior to sonication, the patient presented a CRS-R of 15 (day prior) and 14 (day of), exhibiting behaviors consistent with an MCS diagnosis (e.g., object reaching). Once the patient was brought to the MR suite, the transducer was manually placed and secured to the right side of the patient's head, by the temporal bone thinning (Fig. 1, left). Using a rapid (92 s) MPRAGE structural sequence (TR = 1900 ms, TE = 2.2 ms) we ascertained that the perpendicular, 7 cm away from the apex of the transducer's concavity, was directly aimed at the patient's thalamus, following the expected trajectory of sound waves at the current parameters (Fig. 1, right). Satisfactory targeting was obtained in 3 trials (when unsatisfactory, the transducer was repositioned to compensate the offset between the perpendicular and the intended target, and a new MPRAGE was acquired). After sonication, the patient presented a CRS-R of 13 (day of) and 17 (day after), demonstrating the ability to reach toward objects and exhibiting new behaviors in both motor and oromotor function (e.g., motor responses, vocalization/oral movement). Three days post-LIFUP the patient demonstrated full language comprehension, reliable

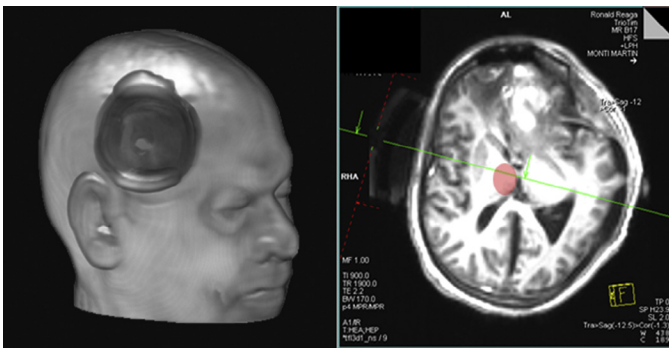


Figure 1. Left: 3D reconstruction of patient's head with transducer; Right: axial view of the transducer, the perpendicular from its concavity apex, and approximate thalamic target (in red). (For interpretation of the reference to color in this figure legend, the reader is referred to the Web version of this article.)

response to command, and reliable communication (by yes/no head gesturing), consistent with emergence from MCS (eMCS). Five days post-LIFUP the patient attempted to walk. The post-LIFUP improvements also suggest that the procedure was well tolerated and safe.

On the basis of results obtained in the animal model [7] and in MCS patients undergoing neuromodulatory stimulations [5,6] as well as pharmacological interventions [2], all of which are believed to act via modulation of cortico-striato-pallido-thalamo-cortical communication [4], the pattern of behavioral progression observed in the patient is exactly what would be expected of thalamic LIFUP. Nonetheless, we currently cannot tell whether the observed effects are causally linked to the LIFUP sonication or whether the patient spontaneously, and serendipitously, emerged from a DOC. Further investigation will be needed to interpret the significance of this intriguing finding.

Acknowledgments

This work was supported by the Dana Foundation [grant #115558] and the Tiny Blue Dot Foundation. Brainsonix Inc. provided, on a no-cost basis, usage of a LIFUP device to the authors. The sponsors had no role in the conduct of the research and/or preparation of the letter.

Martin M. Monti*

Department of Psychology, University of California Los Angeles, Los Angeles, CA 90095, USA

Brain Injury Research Center (BIRC), Department of Neurosurgery, University of California Los Angeles, Los Angeles, CA 90095, USA

Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA 90095, USA

Caroline Schnakers

Brain Injury Research Center (BIRC), Department of Neurosurgery, University of California Los Angeles, Los Angeles, CA 90095, USA

Alexander S. Korb, Alexander Bystritsky

Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA 90095, USA

Paul M. Vespa

Brain Injury Research Center (BIRC), Department of Neurosurgery, University of California Los Angeles, Los Angeles, CA 90095, USA

* Corresponding author. Department of Psychology, University of California Los Angeles, Los Angeles, CA 90095, USA.

Fax: +13102065895

E-mail address: monti@psych.ucla.edu (M.M. Monti)

Received 7 July 2016

Available online 22 July 2016

<http://dx.doi.org/10.1016/j.brs.2016.07.008>

References

- [1] Monti MM, Laureys S, Owen AM. The vegetative state. *Br Med J* 2000;341:c3765.
- [2] Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. *N Engl J Med* 2012;366(9):819–26.
- [3] Monti MM, Sannita WG. Brain function and responsiveness in disorders of consciousness. Switzerland: Springer International Publishing; 2016.
- [4] Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. *Trends Neurosci* 2010;33(1):1–9.
- [5] Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature* 2007;448(7153):600–3.
- [6] Thibaut A, Bruno MA, Ledoux D, Demertzi A, Laureys S. tDCS in patients with disorders of consciousness Sham-controlled randomized double-blind study. *Neurology* 2014;82(13):1112–18.
- [7] Yoo SS, Kim H, Min BK, Franck SP. Transcranial focused ultrasound to the thalamus alters anesthesia time in rats. *Neuroreport* 2011;22(15):783.
- [8] Bystritsky A, Korb AS, Douglas PK, Cohen MS, Melega WP, Mulgaonkar AP, et al. A review of low-intensity focused ultrasound pulsation. *Brain Stimul* 2011;4(3):125–36.
- [9] Legon W, Sato TF, Opitz A, Mueller J, Barbour A, Williams A, et al. Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. *Nat Neurosci* 2014;17(2):322–9.
- [10] Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 2004;85(12):2020–9.