

Ultrasonic thalamic stimulation in chronic disorders of consciousness

Dear Editor,

Despite great advances in the field of intensive care, when patients survive a severe brain injury but remain in a chronic Vegetative State (VS) or Minimally Conscious State (MCS) (i.e., a disorder of consciousness; DOC), little can be done to promote recovery [1]. To date, several restorative strategies have been investigated in DOC patients—all proposed to exert their effects via direct or indirect upregulation of excitatory thalamic output and, in turn, upregulation of a large scale cortico-striato-pallido-thalamo-cortical mesocircuit [1,2]. For instance, high-quality evidence supports the use of amantadine and transcranial direct current stimulation (tDCS) in sub-acute patients [1]; however, considerably less evidence exists in chronic patients. Indeed, despite the remarkable results obtained with thalamic deep brain stimulation (DBS) in one chronic patient [2], a 7-year prospective clinical trial evaluating the use of this technique in a larger sample highlights the limited applicability of the technique [3], inviting the development of alternative approaches to direct thalamic stimulation.

The rapid (re)development of low intensity focused ultrasound (LIFU) as a means of reversible modulation of (subcortical) brain tissue offers a potential alternative to DBS for restorative intervention in DOC. The bioactivity of LIFU in neural tissue has now been shown *in vitro*, in non-human animal models, and in healthy human volunteers [4]. Relevant here, thalamic LIFU has been associated with faster behavioral recovery from anesthesia in animal models [5], and a case report of thalamic LIFU in acute DOC confirms this approach's clinical viability [6]. We report the very first application of thalamic LIFU in three patients with chronic DOC, as part of a *first-in-man* clinical trial (NCT02522429; UCLA approved IRB #14–001749).

Patients underwent two MR-guided thalamic LIFU sessions one week apart while behavioral assessments using the JFK Coma Recovery Scale–Revised (CRS-R) [7] were utilized at 12 time points to assess the therapeutic potential of the LIFU procedure. In each session, LIFU was applied at 100 Hz pulse repetition frequency (PRF), 0.5 ms pulse width (PW), 650 kHz carrier wave frequency, 5% duty cycle, and $14.39 \frac{\text{W}}{\text{cm}^2}$ $I_{\text{SPPA.3}}/719.73 \frac{\text{mW}}{\text{cm}^2}$ $I_{\text{SPTA.3}}$. The transducer (Brainsonix) was positioned using MR-guidance such that its focus (55mm from its surface) lay over the left central thalamus [2], at which point sonication was delivered inside the MRI scanner for ten 30-s blocks, separated by 30s off periods (cf., Fig. 1a and b).

Phenotypes of Patients at Baseline: At baseline, Patient 1 (male, age 56, 14.5 months PI [post-injury]—hemorrhagic stroke) displayed behaviors consistent with a minimally conscious state “plus” (MCS+), including reproducible response to command, object recognition, and non-functional communication (CRS-R: 16; CRS-R index [8]: 55.9). Patient 2 (female, age 50, 32 months

PI—cardiac arrest/hypoxia) demonstrated behaviors consistent with MCS “minus” (MCS–), including visual fixation and no response to command (CRS-R: 9; CRS-R index: 15.96). Patient 3 (male, age 58, 66 months PI—motor vehicle accident) displayed behaviors consistent with MCS+, including response to command (finger movement) and object recognition (distinguishing relatives in pictures) (CRS-R: 16; CRS-R index: 65.28).

Results, Phenotypes of Patients Following LIFU: We highlight three initial results. First, this report shows that MR-guided LIFU is feasible in (outpatient) chronic DOC patients. Second, the intervention appears to be well tolerated and safe; no alteration in vital parameters (blood pressure, heart rate, blood oxygen), evidence of structural damage, or any other adverse event were noted. Third, although these results must be understood as preliminary, two out of three patients exhibited clinically significant increases in behavioral responsiveness after exposure to each dose of thalamic LIFU, compared to baseline. In the week following the first LIFU exposure, Patient 1 (baseline MCS+) demonstrated, for the first time, the ability to perform consistent response to two distinct commands and a highly accurate rate of response to autobiographical questions (i.e., 5/6). In the days following the second LIFU exposure, patient 1 also demonstrated, for the first time, the ability to functionally use two different objects (i.e., proper use of a pen on paper, bottle-to-mouth) as well as to functionally communicate (6/6 question-response pairs). Importantly, these behaviors are diagnostic markers of emergence from MCS and thus from a disorder of consciousness. Nonetheless, at 3-month and 6-month follow-up visits, the patient regressed to a neurobehavioral profile consistent with MCS+. Patient 2 (baseline MCS–) demonstrated, also for the first time, reproducible response to command (head, finger movement, 3/4 times each) shortly after the first LIFU exposure, with this behavior becoming systematic (head motion, 4/4 times) in the days following (prior to the second LIFU exposure). This behavior is consistent with MCS+. The patient also exhibited, for the first time, the ability to recognize different objects (pencil, comb) following the first LIFU. MCS+ categorization was maintained throughout follow-up assessments. Importantly, these novel behaviors had not been observed prior to the procedure by our team or their families (see supplement), despite the years since onset. Finally, patient 3, who began as MCS+, did not show any benefit of either exposure to LIFU. In fact, the patient only exhibited lower-level behaviors, consistent with MCS– (visual pursuit and automatic motor response), until the first follow-up, when higher-level behaviors typical of MCS+ were observed again (cf., Fig. 1c for CRS-R (index)) over assessments).

While exciting, alternative explanations should be considered. First, the CRS-R assessment has been shown to minimize diagnostic error (where, importantly, diagnosis is based on the highest level of

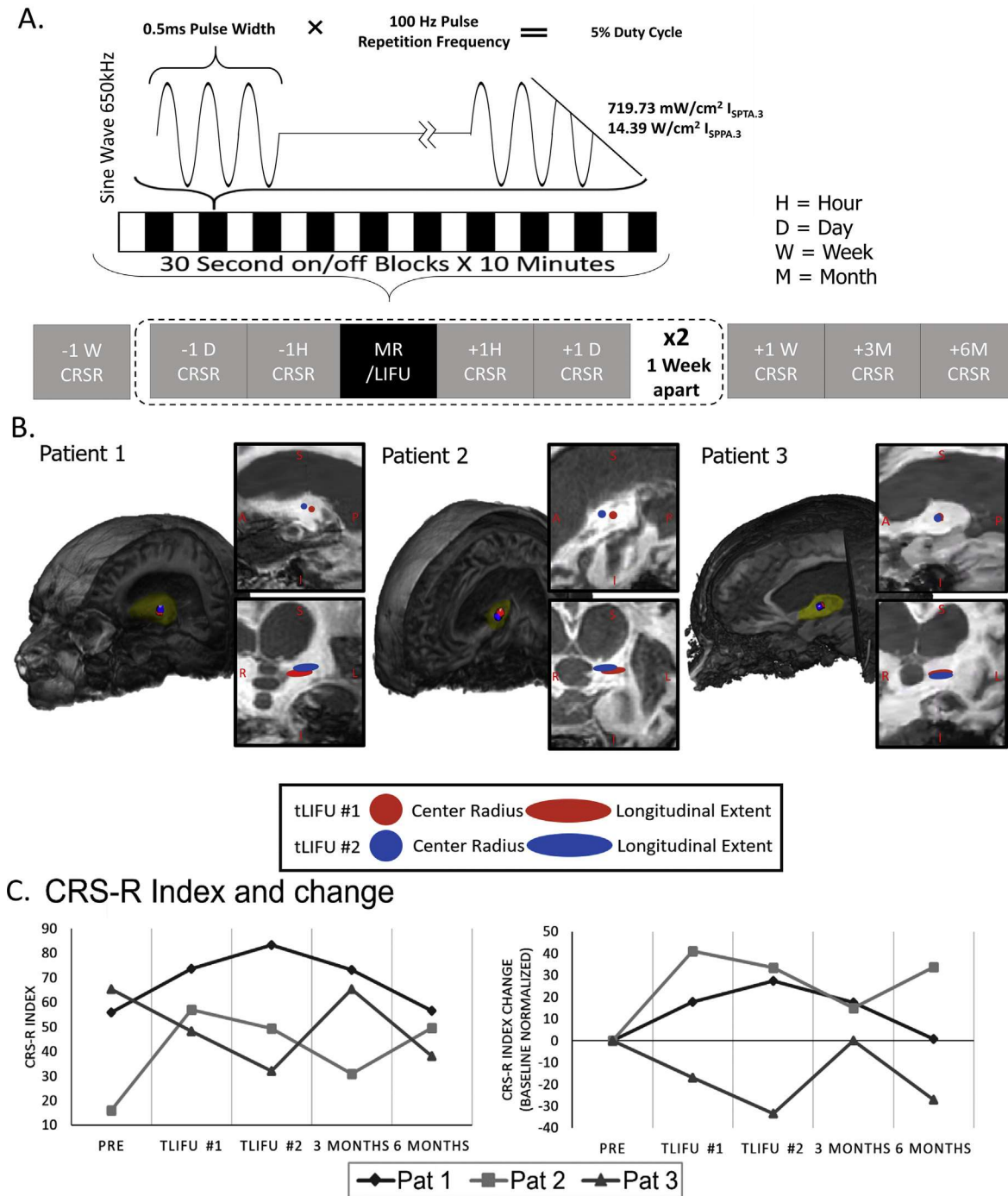


Fig. 1. A) Depiction of study protocol involving LIFU parameters and CRS-R (Coma Recovery Scale — Revised) assessments. ISPTA.3 = Spatial Peak Temporal Average Intensity.3. ISPPA.3 = Spatial Peak Pulse Average Intensity.3 (“0.3” denotes deration (attenuation) due to absorption by tissue at 0.3 dB/cm-MHz). B) Estimated LIFU target for each patient and session. Inferred center of stimulation (approximately 0.25 cm radius, corresponding to the -3 dB focal radius in water) and longitudinal extent (approximately 1.5 cm length perpendicular to the transducer, corresponding to -3dB focal length in water) for LIFU #1 (Red) and LIFU #2 (Blue). The likely location of residual thalamic tissues are lightly highlighted in Yellow. C) Best CRS-R index score during each period (pre, post LIFU #1, post LIFU #2, 3 months, 6 months) (left) and change in best CRS-R index relative to the best baseline assessment (right). Note that here (t) LIFU = (thalamic) LIFU. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

responding) to less than 5% only after 5 administrations whereas our baseline only included three (17% chance of error [9]). However, patient 1 exhibited novel behaviors consistent with eMCS (emergence from MCS) on the 10th examination and patient 2 exhibited systematic response to command on the 6th examination, while published estimates show no benefit of additional assessments beyond the 5th [9]. Yet, future investigations should be mindful

of the recently shown need for extended baseline measurements [9]. Second, albeit less frequently than in acute DOC, spontaneous recovery does occur in chronic patients [10]. Nonetheless, this has been characterized over the course of months and years post-injury, not over the span of days and weeks, making it unlikely that our findings are simply due to spontaneous recovery, particularly for non-traumatic patients. Third, assessments were

unblinded with respect to the LIFU procedure—which produced indicators (e.g., hair removal)—and thus could be susceptible to biases. These findings should compel double-blind and controlled procedures in future confirmatory work. Nonetheless, these preliminary findings suggest that LIFU has potential as a novel, safe, and broadly applicable intervention for patients with chronic DOC.

Author contributions

MMM and CS conceived the study. JAC, MMM, and NMS administered the ultrasound. CS supervised behavioral assessments. JAC, NMS, and CS performed behavioral assessments. JPC, JSC, MAJ, and ESL assisted in planning, preliminary data collection, and ultrasound device management. JAC, MMM, and CS wrote the first draft of the paper. CR, MBB, and PMV oversaw patient wellbeing while in Ronald Reagan hospital, provided medical guidance, and assisted in the patient admission process. All listed authors reviewed this paper and provided feedback.

Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2021.01.008>.

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