NCT02522429

Thalamic Low Intensity Focused Ultrasound in Brain Injury

10/30/2020

Background

Few neurological conditions are as scientifically mysterious and clinically, legally, and ethically challenging as disorders of consciousness (DOC) [1]. Typically developed after severe brain injury, this set of related conditions includes Coma, the Vegetative State (VS) and the Minimally Conscious State (MCS) [2]. In the past 20 years, an increasing amount of research has broken many conventions about these disorders, including the once widespread belief that these patients are entirely *apallic* – that is, lack any kind of "higher" activity [3]. Since then, it has been shown that a lot of brain activity, including relatively high-level cognitive processes, can remain in DOC patients. *Nonetheless, to date there exists no standard intervention for patients suffering from these devastating conditions.* Developing interventions for this population is extremely important first and foremost for the well-being of patients, who – today – remain completely dependent on assisted care, are often unable to participate in rehabilitative programs because of their lack of behavioral responsiveness, and thus find themselves prisoners of a condition characterized by uncertainty at the medical, legal and ethical decision-making levels [4]. In addition, these conditions, which can last indefinitely, also place great emotional and monetary strain on families, large burdens on care-takers – often leading to increased rates of burn-out [5] – and large financial stress on medical structures and public finances due to the large costs imposed by prolonged intensive care.

The present project is aimed at evaluating the potential of non-invasive Low Intensity Focused Ultrasound Pulsation (LIFUP) of thalamus as a neuro-restorative stimulation for patients with severe brain injury.

The **rationale** for this proposal hinges upon four premises:

(i) To date, there exists ***no standard intervention*** for severe brain injury patients who develop disorders of consciousness

(ii) Recent advances in our understanding of the physiological mechanisms accompanying the loss and recovery of consciousness and cognitive function after severe brain injury suggest ***specific neural targets for therapeutic intervention*** [6-8]

(iii) Invasive surgical techniques based on permanently implanting neurostimulating electrodes in the brain (i.e., Deep Brain Stimulation – DBS) have shown that ***thalamic stimulation can lead to behavioral improvements in patients with severe brain injury*** [9-13]

(iv) Low-Intensity Focused Ultrasound Pulsation (LIFUP) stimulation [14] has been shown to be an ***effective and safe neuromodulation technique*** in humans [15], consistent with data from animal models, including rodents [16] and non-human primates [17]. The empirical safety data is also well justified from a theoretical point of view considering that LIFUP delivers stimulation of intensities ***below*** those of commonly used ultrasound applications (e.g., pre-natal ultrasonography, doppler ultrasounds), as well other neuromodulatory techniques (e.g., Transcranial Magnetic Stimulation – TMS)

In this project, we propose to assess, in a small number of patients with severe-TBI, the feasibility of LIFUP as a non-invasive alternative to stimulation via neuro-surgical insertion of brain electrodes (i.e., DBS). More specifically, we have three main aims:

Aim 1: Assess the feasibility and preliminary efficacy of LIFUP thalamic stimulation, as measured by changes in clinical assessments measures of consciousness and behavioral responsiveness.

Aim 2: Assess the brain effects of LIFUP stimulation, as measured by functional MRI and the degree to which they correlate with clinical/behavioral changes.

The **main hypotheses** underlying the project are:

H1: As shown by previous literature [15-18], LIFUP stimulation is a safe and effective neuro-modulatory technique.
H2: LIFUP thalamic stimulation is associated with an increase in clinical measures of patient arousal and/or awareness to an extent at least comparable to that demonstrated with neurosurgical thalamic stimulation procedures (i.e., DBS) [9-13].
H3: The neuro-restorative effects of LIFUP stimulation are associated with detectable changes in brain function as detected with fMRI.

Protocol

The **research strategy** is to recruit patients who have suffered a severe TBI and are in a Disorder of Consciousness (18 years or older and no contraindications to entering the MRI environment). Patients will be recruited either as Acute DOC patients or Chronic DOC patients.

Inclusion Criteria:

Acute patients

< 6 weeks since injury
A Glasgow Coma Score < 9 (at the time of injury)
Abnormal CT
Prolonged loss of consciousness (>24h)
Behavioral profile consistent with a VS or MCS as assessed with the Coma Recovery Scale Revised.

Chronic patients

> 3 months post injury for non-traumatic injuries, >12 months post-injury for traumatic injuries
Behavioral profile consistent with a VS or MCS as assessed with the Coma Recovery Scale Revised.

Exclusion Criteria (all patients):

deep sedation
history of neurological illness prior to injury
inability to safely enter the MR environment (e.g., ferromagnetic non MR safe implants)

Neurobehavioral Assessment Procedure

Neurobehavioral assessments will be conducted using the Coma Recovery Scale Revised (CRS-R). [19] Baseline responsiveness will be assessed prior to LIFUP exposure. Responsiveness will also be assessed immediately following, as well as on the days following each LIFUP exposure. The Coma Recovery Scale – Revised, is a standard clinical protocol used to assess a patient's level of consciousness. This test allows us to assess your level of response to sensory stimulation, ability to understand language and to communicate. This procedure is typically administered at bedside. This testing should take 25 minutes.

In addition, the Glasgow Outcome Scale extended score will be assessed to evaluate outcome at protocol end and follow-up

.

Paramedical Measurements

(1) Clinical EEG: data from the clinical recordings will be collected.
(2) MR acquisition (performed in MR suite):
  (A) Structural MRI acquisition:
    (i) T1-weighted (MPRAGE)
    (ii) Diffusion Tensor Imaging (DTI)
  (B) Functional MRI acquisition:
    (ii) Resting state task (BOLD, during sonication)

Electroencephalography (EEG) is a widely employed technique that measures electrical brain activity. In order to acquire EEG data we will fit you with a small elastic cap that you will wear on your head. This procedure (expected duration: 10 minutes + set-up time, up to 20 minutes) will allow us to measure electrical brain activity as you rest. This procedure is entirely non-invasive.

Magnetic Resonance Imaging (MRI) is a widely used method to assess body tissues, including the brain, in a non-invasive manner. In the context of this study, MRI will be used to assess brain structure and function (in response to LIFU). MRI protocols include T1 MPRAGE, Diffusion Tensor Imaging (DTI), and T2* BOLD sequences.

Procedure

The temporal sequence of events, for each cycle, is as follows:
- Clinical EEG (baseline): 10 min of EEG data, from the clinical recordings, will be collected for analysis
- Baseline clinical measures collection (25 min)
- Baseline f/MRI measures collection (in MRI suite; 30 min+20 min set-up)
- Administration of LIFUP (in MRI suite; 10 min + 20 min set-up)
- Post-LIFUP f/MRI measures collection (in MRI suite; 30 min)
- Post-LIFUP clinical measures collection (25 min)
- Clinical EEG (post-LIFUP): 10 min of EEG data, from the clinical recordings, will be collected for analysis

LIFU Procedure. The area surrounding the planned LIFU entry point on the head will be shaved prior to positioning in order to minimize the impedance of ultrasound due to air bubbles. Ultrasound gel (aquasonic) will be first applied to this region and smoothed in order to remove air pockets. The ultrasound transducer will then positioned so that its center lay on the squamous portion of the temporal bone (the thinnest part of the human skull) in order to minimize ultrasound scatter and refraction through the bone. A thin layer of gel will be applied to the surface of the transducer, and bubbles will be similarly smoothed from this layer. The transducer will then be coupled to the head with gel filling any open space between the transducer membrane and the scalp with two straps—one horizontal and one vertical—securing the device to the patient. Conventional soft foam padding and pillows will be used to further secure the positioning of the device and decrease the potential for head motion during the procedure. Next, we will acquired a rapid (95 s) T1-weighted MPRAGE anatomical image. Using a circular MR fiducial and the visible center of the transducer, reference lines will be drawn in the transverse and coronal planes, using the Siemens 3D display GUI available as part of the MRI device's console software to visually locate the target of the LIFU beam

in three dimensions. Adjustments to the positioning of the transducer on the head will be made iteratively, re-acquiring a T1-weighted MPRAGE at each iteration, until the beam trajectory from the center of the transducer is assessed to be in-line with the intended target.

Statistical Plan and Analysis

- **Change in CRS-R related to LIFUP**. *Maximum CRS-R score prior to LIFUP will be compared to the maximum CRS-R score following LIFUP*. Behavioral responsiveness in patients was assessed using the total score on the CRS-R. Prior to analysis, the highest CRS-R prior-to and following LIFUP exposure will be calculated in order to best capture patients' maximal performance. A matched samples T-test analysis will be performed. Where a violation of normality is detected (using a Shapiro-Wilk test) a non-parametric Wilcoxon signed rank test will be used to compare Pre-LIFUP and Post-LIFUP scores for all patients.
- **Change in BOLD signal during LIFUP**. *Brain BOLD signal during exposure to LIFUP will be compared to the brain BOLD signal during inter-stimulation intervals*. MRI data preprocessing and analysis will be conducted using FSL (FMRIB Software Library v6.0.1) with in-house Bash shell scripts. Preprocessing will include brain extraction (using optiBET), spatial smoothing (using a Gaussian kernel of 5 mm full-width half-max), slice timing correction (Fourier-space time-series phase-shifting), highpass temporal filtering (Gaussian-weighted) at 0.01 Hz, and motion correction (MCFLIRT). With the exception of brain extraction, these procedures will be performed in fsl FEAT. Following recent data, in-scanner head motion will be mitigated by including in the statistical model a number of nuisance regressors, including individual time points with excessive motion (i.e., spike regression) derived from the output of fsl FLIRT, head-motion parameters, and regressors for white matter and CSF components. White matter and CSF regressors will be produced by segmenting T1 images for each patient using FSL Fast (visually inspected for accuracy). Tissue segmentations for white matter and CSF will be transformed into functional space and binarized (and again visually inspected for accuracy). Time series for white matter and CSF will then be extracted from functional images using fslmeants. Framewise displacements for each volume will be derived from FSL MCFLIRT and used to exclude unwanted volumes with a framewise displacement exceeding 0.5 mm (25% of voxel width). In order to register structural images to functional space, we will employ a combination of FSL epi_reg and conventional 12 dof linear coregistration (using FSL FLIRT). In order to register structural images to standard space, nonlinear registration (FSL FNIRT) will be used. BOLD data collected during LIFUP will first be analyzed employing a univariate general linear model (GLM) approach, including pre-whitening correction for autocorrelation (FILM). A univariate analysis will be conducted using a single "task" regressor, which represents the onset time of 30 s blocks of LIFUP administration. Thus, here the "baseline" conditions used will be the inter-sonication periods where no LIFUP is applied. For each BOLD sequence, we will compute the contrast LIFUP > Rest. For patients with two LIFU exposures, results from the two runs will be averaged at level two prior to third-level analysis. At the third level, data will be cluster corrected for multiple comparisons using a familywise cluster correction ($p < 0.05$).
- **Structural MRI – Diffusion Tensor Imaging (DTI)**. The aim of this analysis is to assess any changes, in terms of structural connectivity, and in particular thalamo-frontal connectivity, induced

by the LIFUP stimulation. Data will be first preprocessed following standard pipelines in the field (Behrens et al., 2003b); then, streamlines from thalamus to the whole brain will be calculated, for every subject individually, between thalamus and cortex (Behrens et al., 2003a). The streamlines will then be entered, the dependent variable, in the group analysis (i.e., the mixed-design ANCOVA). This analysis is a direct test of whether thalamo-cortical connectivity is affected (as the mesocircuit hypothesis predicts) by our intervention.

- **Electroencephalography**. This analysis is aimed at assessing whether LIFUP session alters the spectral profile of electroencephalographic recordings (EEG). Indeed, it is known that patients at different levels of consciousness after severe brain injury exhibit different electrocortical patterns (e.g., patients with severe disorder of consciousness exhibit large "delta" -- that is: slow -- waves of activity, as compared to the more rapid "alpha" waves typically seen in healthy individuals). Data will be preprocessed following previous literature (Lechinger et al., 2013), then for each channel we will derive a characterization of each patient's spectral profile. This information will then be entered in the group analysis.

1. Monti MM. Ethics, Neuroimaging and Disorders of Consciousness: What Is the Question? AJOB Neuroscience. 2013;4(4):1-2.
2. Monti MM, Laureys S, Owen AM. The vegetative state. BMJ. 2010;341:c3765. Epub 2010/08/04. doi: 10.1136/bmj.c3765. PubMed PMID: 20679291.
3. Monti MM. Cognition in the vegetative state. Annu Rev Clin Psychol. 2012;8:431-54. Epub 2012/01/10. doi: 10.1146/annurev-clinpsy-032511-143050. PubMed PMID: 22224835.
4. Jennett B. Thirty years of the vegetative state: clinical, ethical and legal problems. Prog Brain Res. 2005;150:537-43. Epub 2005/09/28. doi: 10.1016/S0079-6123(05)50037-2. PubMed PMID: 16186047.
5. Gosseries O, Demertzi A, Ledoux D, Bruno MA, Vanhaudenhuyse A, Thibaut A, Laureys S, Schnakers C. Burnout in healthcare workers managing chronic patients with disorders of consciousness. Brain Inj. 2012;26(12):1493-9. Epub 2012/06/26. doi: 10.3109/02699052.2012.695426. PubMed PMID: 22725684.
6. Lutkenhoff ES, McArthur DL, Hua X, Thompson PM, Vespa PM, Monti MM. Thalamic atrophy in antero-medial and dorsal nuclei correlates with six-month outcome after severe brain injury. Neuroimage Clin. 2013;3:396-404. Epub 2013/11/26. doi: 10.1016/j.nicl.2013.09.010. PubMed PMID: 24273723; PMCID: 3815017.
7. Monti MM, Lutkenhoff ES, Rubinov M, Boveroux P, Vanhaudenhuyse A, Gosseries O, Bruno MA, Noirhomme Q, Boly M, Laureys S. Dynamic change of global and local information processing in propofol-induced loss and recovery of consciousness. PLoS Comput Biol. 2013;9(10):e1003271. Epub 2013/10/23. doi: 10.1371/journal.pcbi.1003271. PubMed PMID: 24146606; PMCID: 3798283.
8. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. Trends Neurosci. 2010;33(1):1-9. Epub 2009/12/04. doi: 10.1016/j.tins.2009.11.002. PubMed PMID: 19954851; PMCID: 2931585.
9. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, Fritz B, Eisenberg B, Biondi T, O'Connor J, Kobylarz EJ, Farris S, Machado A, McCagg C, Plum F, Fins JJ, Rezai AR. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature. 2007;448(7153):600-3. Epub 2007/08/03. doi: 10.1038/nature06041. PubMed PMID: 17671503.
10. Yamamoto T, Katayama Y, Kobayashi K, Kasai M, Oshima H, Fukaya C. DBS therapy for a persistent vegetative state: ten years follow-up results. Acta Neurochir Suppl. 2003;87:15-8. Epub 2003/10/02. PubMed PMID: 14518516.
11. Yamamoto T, Katayama Y, Kobayashi K, Oshima H, Fukaya C, Tsubokawa T. Deep brain stimulation for the treatment of vegetative state. Eur J Neurosci. 2010;32(7):1145-51. Epub 2010/11/03. doi: 10.1111/j.1460-9568.2010.07412.x. PubMed PMID: 21039954.
12. Yamamoto T, Katayama Y, Oshima H, Fukaya C, Kawamata T, Tsubokawa T. Deep brain stimulation therapy for a persistent vegetative state. Acta Neurochir Suppl. 2002;79:79-82. Epub 2002/04/27. PubMed PMID: 11974994.
13. Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C, Katayama Y. DBS therapy for the vegetative state and minimally conscious state. Acta Neurochir Suppl. 2005;93:101-4. Epub 2005/07/01. PubMed PMID: 15986737.

14. Bystritsky A, Korb AS, Douglas PK, Cohen MS, Melega WP, Mulgaonkar AP, DeSalles A, Min BK, Yoo SS. A review of low-intensity focused ultrasound pulsation. Brain Stimul. 2011;4(3):125-36. Epub 2011/07/23. doi: 10.1016/j.brs.2011.03.007. PubMed PMID: 21777872.
15. Legon W, Sato TF, Opitz A, Mueller J, Barbour A, Williams A, Tyler WJ. Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. Nat Neurosci. 2014;17(2):322-9. Epub 2014/01/15. doi: 10.1038/nn.3620. PubMed PMID: 24413698.
16. Tufail Y, Yoshihiro A, Pati S, Li MM, Tyler WJ. Ultrasonic neuromodulation by brain stimulation with transcranial ultrasound. Nat Protoc. 2011;6(9):1453-70. Epub 2011/09/03. doi: 10.1038/nprot.2011.371. PubMed PMID: 21886108.
17. Deffieux T, Younan Y, Wattiez N, Tanter M, Pouget P, Aubry JF. Low-intensity focused ultrasound modulates monkey visuomotor behavior. Curr Biol. 2013;23(23):2430-3. Epub 2013/11/19. doi: 10.1016/j.cub.2013.10.029. PubMed PMID: 24239121.
18. Tufail Y, Matyushov A, Baldwin N, Tauchmann ML, Georges J, Yoshihiro A, Tillery SI, Tyler WJ. Transcranial pulsed ultrasound stimulates intact brain circuits. Neuron. 2010;66(5):681-94. Epub 2010/06/16. doi: 10.1016/j.neuron.2010.05.008. PubMed PMID: 20547127.
19. 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. Epub 2004/12/18. doi: 10.1016/j.apmr.2004.02.033. PubMed PMID: 15605342.