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Study Title: Feasibility Study of the mindBEAGLE Device in Patients with Disorders of Consciousness or Locked-In Syndrome

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PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL

Feasibility Study of the mindBEAGLE Device in Patients with Disorders of Consciousness or Locked-In Syndrome

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I. Background and Significance

Estimates of diagnostic error among clinicians who treat persons with disorders of consciousness (DOC) are consistently reported to be approximately 40% (Andrews *et al.*, 1996; Childs *et al.*, 1993; Schnakers *et al.*, 2009). The absence of a "gold standard" for consciousness is a major driver behind this problem. Behavior, as assessed by expert clinicians, is the standard metric relied upon to judge level of consciousness but, in practice, is a poor proxy for consciousness. Behavioral signs of conscious awareness may be too subtle to detect reliably. Conversely, reflexive or random behaviors may be misjudged as voluntary. Electroencephalography (EEG) offers potential for the development of relatively inexpensive, simple, compact systems that can be readily deployed at bedside to detect conscious processing in DOC patients.

Similarly, there is a small set of patients for whom speech and movement are severely impaired, but cognition remains intact. These patients, some of whom have LIS, need better methods of communication with their clinicians, family, and friends.

Over the last two decades, there has been considerable research into event-related EEG responses (ERs) (Chatelle *et al.*, 2012). This growing literature suggests that EEG-based paradigms may be employed to investigate cognition in severely brain-injured individuals who lack the capacity for speech and active movement (Chatelle *et al.*, 2012; Cruse *et al.*, 2011; Lule *et al.*, 2013; Schnakers *et al.*, 2008). Indeed, if conscious awareness could be identified for individual patients with high accuracy, this would contribute important information to early clinical decision making on a wide variety of medical and surgical issues. Similar EEG techniques can be used to enable communication for people with locked in syndrome (LIS) or other difficulties with communication.

Even if ERs may offer a means to assess human information processing capabilities in the absence of overt behavior, the extent to which DOC patients are capable of processing even simple instructions is unclear, and prognostic indicators predicting the functional outcome of these patients are limited and non-specific. Some studies have demonstrated preserved ERs in coma, vegetative states, and minimally conscious state (Cruse *et al.*, 2011; Cruse *et al.*, 2012; Perrin *et al.*, 2006; Schnakers *et al.*, 2008; Steppacher *et al.*, 2013), but due to the small number of investigated cases and frequent lack of outcome documentation, their clinical and prognostic significance is currently unclear. Almost none of these studies focus on the initial period after injury.

The presence of ERs after brain damage, in particular endogenous ERs that appear relatively late after stimulus onset and reflect more complex cognitive operations, may predict subsequent recovery of consciousness and communicative abilities (Steppacher *et al.*, 2013). These ER components depend on the synchronized activity of multiple brain regions, which may be critical for conscious awareness.

A new, portable technology called "mindBEAGLE" has been developed by an Austrian neurotechnology company with the intent of providing simple and rapid assessment of the presence of auditory and somatosensory evoked EEG responses in people with DOC or LIS. We propose to evaluate the feasibility of this no-to-minimal risk technology with up to 20 inpatient participants at MGH. The EEG data collected from this system will be correlated with behavioral assessments of consciousness using the Coma Recovery Scale-Revised (CRS-R), which has been shown to optimize sensitivity for detecting conscious awareness in patients with DOC and LIS. The same system will be tested in up to 20 healthy controls to provide baseline validation of the technology.

II. Specific Aims

The primary aims of this study are:

1) To determine the **feasibility** of deploying mindBEAGLE, a portable, bedside EEG-based system, in the Neurosciences Intensive Care Unit in patients with DOC or LIS;
2) To determine if mindBEAGLE neurophysiologic markers of cognitive function correlate with bedside behavioral assessments of consciousness;
3) To determine if mindBEAGLE can serve as an assistive communication device for people with LIS.

III. Subject Selection

HEALTHY PARTICIPANTS (n = 20)

Inclusion Criteria

- Minimum age: 18
- Capacity to provide informed consent
- Fluent in English

Exclusion Criteria

- History of developmental, neurologic, or major psychiatric disorder resulting in functional disability

INPATIENT PARTICIPANTS (n = 20)

Inclusion Criteria

- Age 18 - 80
- Fluent in English
- For DOC only:

- Surrogate decision-maker (whomever is consenting for clinical procedures, as described in the consent procedures below) available to provide informed consent
- History of severe acquired brain injury with loss of consciousness
- Diagnosis of coma, vegetative state, minimally conscious state or confusional state
- Inpatient at Lunder 6 (NeuroICU at MGH)

- For LIS only:
  - Ability to maintain wakefulness for ~30 minutes without sedative medication, as assessed by nursing staff.
  - Ability to remain off intravenous sedative medication for ~60 minutes.
  - Inpatient at Lunder 6 (NeuroICU at MGH).
  - (see consent procedures below)

Exclusion Criteria

- Prior history of developmental, neurologic, or major psychiatric disorder resulting in functional disability
- Evidence of uncontrolled seizure disorder
- Patients for whom EEG leads are contraindicated
- Injury preventing the placement of surface EMG-type leads on the hands or back.

IV. Subject Enrollment

We plan to enroll a total of 20 patients treated at Massachusetts General Hospital (MGH) for DOC or LIS. Eligible subjects who meet the inclusion criteria will be identified by study staff at MGH, and consent will be obtained from the patient's surrogate with assent from the patient if possible. We also plan to enroll 20 healthy control subjects. These healthy control subjects will be identified with a recruitment flier that will be posted at MGH. The exact text from this recruitment flier will also be posted on the Partners clinical studies website clinicaltrials.partners.org and circulated via the *All User MGH* email list.

V. Study Procedures

Subject Screening – Subjects will be screened by study staff using the daily Lunder 6 NeuroICU inpatient list.

Consent - Informed consent will be obtained from all subjects (or their surrogates) by study staff prior to all study procedures. Informed consent for participation may be obtained from a representative (surrogate) for those incapable of providing informed consent. The following categories of surrogates in order of preference may provide consent in writing on behalf of potential subjects incapable of providing informed consent on their own behalf:

i) court appointed guardian with specific authority to consent to participation in research or authority to make health care decisions for a class of diagnostic and therapeutic decisions inclusive of the proposed research
ii) health care proxy/person with durable power of attorney with specific authority for making health care decisions inclusive of the proposed research
iii) spouse, adult child, or other close family member who knows the subject well and has been involved in their care

Should surrogate consent be obtained, the investigator will document the relationship of the surrogate to the subject in the research record. The investigator obtaining consent will also ensure that the surrogate understands that her/his decisions should be based on the potential subject's own views when s/he had the capacity to express them ("substituted judgment"). Subject assent will also be a requirement for participation in the research unless the subject is incapable of providing it, given her/his medical condition.

In order to minimize the possibility of patients and/or surrogates feeling obligated to participate in research in the event that one of the investigators is also their physician, a physician colleague or research nurse not involved in their care will initially explain the study to potential subjects. We will also offer patients and/or surrogates the opportunity to review the consent form privately and be contacted once they have been able to do so.

The investigator obtaining consent will explain in detail the protocol of the study, its purpose and potential benefits to society. Surrogates and subjects will be informed about minimal risks of EEG. Subjects will be informed that if they feel uncomfortable with the study, they can choose to terminate the study at any time. Surrogates and subjects will be informed that their refusal to participate in the study or choosing to terminate it at some point will have no effect on care and treatment received by them at any Partners institution (i.e. Spaulding, MGH, etc.) now or in future. Informed consent clearly states that subjects and surrogates may choose to terminate the study at any time. Surrogates and subjects will be informed that their personal information will be protected as per the HIPAA guidelines. Surrogates and subjects will have as much time as they wish to consider participation in the study. Although subjects must be fluent in English in order to participate in the study, there may be circumstances where a subject is consented to the study by a non-English speaking surrogate. In these circumstances, the consenting Investigator will utilize MGH Interpreter Services, and the consent process will be documented on the MGH IRB-approved short form consent document and full English-version consent form, in compliance with PHS IRB.

Organization of the study – Patients with DOC or LIS will be evaluated once, although the technology may be made available to them during their inpatient stay if it is found to provide a more reliable method of communication than the patient's current method (as previously determined by a nurse, physician, or speech-language therapist). A behavioral assessment will be performed at the time of the mindBEAGLE EEG assessment.

Healthy subjects will only be assessed once and will be considered as a control group.

Clinical data collection - Demographic and clinical data recorded in the medical record at the time of admission will be collected in accordance with the common data elements recently proposed by the interagency committee of the TBI Common Data Element Project, including age, gender, injury mechanism, admission Glasgow Coma Scale (GCS) score, CT findings, duration of coma, and brainstem function (e.g. pupillary and corneal reflexes). We will also record standard clinical data about level of consciousness (e.g. CRS-R score), severity of LIS (e.g. cranial nerve and extremity motor examination), and level of functional recovery (e.g. Disability Rating Scale score).

EEG - Each subject will be given an EEG, which will utilize the mindBEAGLE system in order to attempt to assess level of consciousness. The EEG will last up to 120 minutes and the subject will be sitting down or lying down. We may also play recordings of spoken language or music via headphones, or we may ask the subject to perform certain tasks, like saying a word to herself or imagining that she is tapping her fingers. We will give the subject specific instructions about these tasks during the EEG.

Neurobehavioral testing – The primary behavioral measure of level of consciousness will be the CRS-R-derived diagnosis of recovery of consciousness, which will allow for classification of each patient as being in coma, vegetative state, minimally conscious state, emerged from minimally conscious state, confusional state, or in a state of fully recovered consciousness. This assessment will be performed by study staff at MGH. The entire neurobehavioral assessment will last up to 60 minutes.

Neurobehavioral (level of consciousness) data will be shared with the subjects, their surrogates, or their outside physicians, at the subject's and/or the surrogate's request, since these data come from well validated assessment tools that are routinely used in clinical practice. Furthermore, the results from these tests can be compared to prior results from these same tests, which are routinely performed as part of clinical care at MGH.

Sharing EEG results with families and treating clinicians

After extensive consideration of the ethical implications of sharing or not sharing the mindBEAGLE EEG data with the patient's family (or non-family surrogate decision-maker) and treating clinicians, our team has reached the following consensus: we believe that the most appropriate course of action from an ethical standpoint is to make the results of these tests available to the patient's surrogate decision-maker AND clinical team, at the request of the surrogate decision-maker. In reaching this consensus, we considering the following points:

- While tools such as the mindBEAGLE system have not been validated as prognostic tools in large, randomly controlled clinical trials, there are preliminary studies suggesting that stimulus-based EEG techniques may be able to detect signs of cognitive awareness that cannot be detected on bedside exam (Cruse et al. 2011). On the one hand, we are hesitant to share data from tests that have not been fully validated. However, we also believe that it would not be appropriate to withhold critically important information about functional activation of brain networks, especially since this information could potentially impact the surrogate's decisions about goals of care as well as the clinical team's impression of the prognosis.

- Consistent with our team's consensus opinion, experts in the field of DOC research recently published a manuscript supporting the dissemination of EEG results to families (Graham *et al.*, 2015). The authors of this manuscript invoke the same rationale articulated above. There is thus an emerging consensus in the field that sharing these results is the ethically appropriate course of action.

We therefore believe that sharing the mindBEAGLE results is ethically justifiable, given that withholding such information might prevent families and clinicians from making a fully informed formulation of the patient's prognosis.

VI. Biostatistical Analysis

In addition to determination of feasibility of deployment of the mindBEAGLE system in the ICU, we will test correlations between mindBEAGLE neurophysiologic markers of cognitive function with CRS-R diagnosis, as well as with EEG biomarkers of consciousness. For example, univariate correlations will be tested using Pearson's and Spearman's correlation tests. We will also attempt to determine whether mindBEAGLE neurophysiologic markers are stable and informative enough to use the system as an assistive communication device.

VII. Risks and Discomforts

The EEG involves one routine EEG test, for which there are no known or foreseeable risks. Medical risk to subjects during the paradigm is not anticipated. There is a risk of minor superficial skin irritation. However, it is infrequent, easily treated and fully reversible.

Study activities will be deferred or discontinued if subjects become medically unstable prior to, or during, procedures. Continuation will be dependent upon consensual approval of the participant or surrogate and the research team.

There are no anticipated medical risks associated with the neurobehavioral/physical examinations that will be conducted in this study. Some exams sometimes include brief application of noxious stimulation to the finger and/or toenail beds to assess motor responses in the absence of command-following. Discomfort typically lasts less than 10 seconds and resolves completely.

There are no other known risks from participation in this study.

VIII. Potential Benefits

For the participants, there is no direct benefit. However, it may result in significant societal benefit, as the development of new diagnostic tools may help guide clinical management for physicians and families of patients with DOC or LIS.

IX. Monitoring and Quality Assurance

All data and safety monitoring will be done by the Principal Investigator of this study. Adverse events will be reported to the IRB within 24 hours by fax, and within 10 days by interoffice mail, as per IRB regulations. A licensed physician will be available in the ICU to address any unforeseen complications.

Any unanticipated adverse events involving risk to human subjects will be reviewed by the Principal Investigator and will be quickly reported to the Human Research Committee within the required time frame and to all participating investigators by Dr. Edlow according to the Partners Human Research Committee guidelines.

Monitoring of the study data itself will be performed by the investigators at MGH, who have an active interest in the results of the study.

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