


TAKE A CLOSER LOOK AT TRIALS



Personalized Connectome Mapping to Guide Targeted Therapy and Promote Recovery of Consciousness in the Intensive Care Unit

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Abstract

There are currently no therapies proven to promote early recovery of consciousness in patients with severe brain injuries in the intensive care unit (ICU). For patients whose families face time-sensitive, life-or-death decisions, treatments that promote recovery of consciousness are needed to reduce the likelihood of premature withdrawal of life-sustaining therapy, facilitate autonomous self-expression, and increase access to rehabilitative care. Here, we present the Connectome-based Clinical Trial Platform (CCTP), a new paradigm for developing and testing targeted therapies that promote early recovery of consciousness in the ICU. We report the protocol for STIMPACT (Stimulant Therapy Targeted to Individualized Connectivity Maps to Promote ReACTivation of Consciousness), a CCTP-based trial in which intravenous methylphenidate will be used for targeted stimulation of dopaminergic circuits within the subcortical ascending arousal network (ClinicalTrials.gov NCT03814356). The scientific premise of the CCTP and the STIMPACT trial is that personalized brain network mapping in the ICU can identify patients whose connectomes are amenable to neuromodulation. Phase 1 of the STIMPACT trial is an open-label, safety and dose-finding study in 22 patients with disorders of consciousness caused by acute severe traumatic brain injury. Patients in Phase 1 will receive escalating daily doses (0.5–2.0 mg/kg) of intravenous methylphenidate over a 4-day period and will undergo resting-state functional magnetic resonance imaging and electroencephalography to evaluate the drug's pharmacodynamic properties. The primary outcome measure for Phase 1 relates to safety: the number of drug-related adverse events at each dose. Secondary outcome measures pertain to pharmacokinetics and pharmacodynamics: (1) time to maximal serum concentration; (2) serum half-life; (3) effect of the highest tolerated dose on resting-state functional MRI biomarkers of connectivity; and (4) effect of each dose on EEG biomarkers of cerebral cortical function. Predetermined safety and pharmacodynamic criteria must be fulfilled in Phase 1 to proceed to Phase 2A. Pharmacokinetic data from Phase 1 will also inform the study design of Phase 2A, where we will test the hypothesis that personalized connectome maps predict therapeutic responses to intravenous methylphenidate. Likewise, findings from Phase 2A will inform the design

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of Phase 2B, where we plan to enroll patients based on their personalized connectome maps. By selecting patients for clinical trials based on a principled, mechanistic assessment of their neuroanatomic potential for a therapeutic response, the CCTP paradigm and the STIMPACT trial have the potential to transform the therapeutic landscape in the ICU and improve outcomes for patients with severe brain injuries.

Keywords: Coma, Consciousness, Brain injury, Connectome, Clinical trial, Biomarker

Introduction

For patients with severe brain injuries in the intensive care unit (ICU), the range of possible outcomes includes death, a persistent disorder of consciousness (DoC), recovery of consciousness with functional disability, and recovery of functional independence [1]. Early recovery of consciousness in the ICU is a strong predictor of long-term outcome [2–4] and a critical determinant of decisions to continue or withdraw life-sustaining therapy [5]. However, there are currently no treatments proven to promote early recovery of consciousness in the ICU. Without knowing whether a patient can recover consciousness, many families—guided by intensive care clinicians—withdraw life-sustaining therapy, a decision that accounts for up to 70% of deaths in ICU patients with severe traumatic brain injury (TBI) [6, 7] and over 40% of deaths in patients with hypoxic-ischemic injury [8]. Furthermore, decisions to withdraw life-sustaining therapy often occur in the first 3 days of hospitalization [6], when prognosis is most uncertain. A new treatment that promotes early recovery of consciousness in the ICU would benefit patients and families by reducing the likelihood of premature withdrawal of life-sustaining therapy and could decrease ICU complications related to immobility, facilitate self-expression, enable autonomous decision-making, and increase access to specialized rehabilitative care.

Two barriers currently prevent the development of consciousness-promoting therapies in the ICU. First, prior to enrollment in clinical trials, patients' injuries are not rigorously classified. Instead of selecting patients based on the precise pathophysiologic mechanism underlying coma, trials enroll patients based on behavioral measures, such as the Glasgow Coma Scale (GCS) score, that stratify brain injuries into crude categories of severity. This approach is ineffective because coma is a highly heterogeneous condition. Traumatic and hypoxic-ischemic coma, for example, are associated with variable patterns of axonal disconnections within the subcortical ascending arousal network (AAN), cortical default mode network (DMN), and other networks that contribute to consciousness [9–14]. Without precision tools to map preserved network connections in individual patients, it is not possible to identify patients whose connectomes are amenable to therapeutic modulation.

Second, in early-phase clinical trials, therapeutic responses are not routinely tested with direct measures of brain function. Rather, early-phase trials rely on indirect serologic markers of brain injury or insensitive, delayed measures of functional disability [15, 16]. Without biomarkers that directly and quantitatively measure brain function, fundamental questions about a therapy's neurobiological effects are not being answered in Phases 1 and 2 before moving to Phase 3 trials. Clearly, a new approach to clinical trial design is of scientific and ethical import for this vulnerable population [5]. Indeed, experts in civilian and military brain injury [15–17], including leaders at the National Institute of Neurological Disorders and Stroke [18], are now calling for new approaches to clinical trial design for patients with coma and other DoCs. This goal is also a central component of the Curbing Coma Campaign launched by the Neurocritical Care Society in 2019.

To address the call for clinical trial design innovation, we propose the Connectome-based Clinical Trial Platform (CCTP), a new mechanistic paradigm for developing and testing targeted therapies that promote early recovery of consciousness in the ICU. The CCTP incorporates two innovations: (1) predictive biomarkers to enroll patients in clinical trials based on connectomes that can be targeted by new therapies; and (2) pharmacodynamic biomarkers to measure how targeted therapies modulate networks, reactivate the cerebral cortex and restore consciousness. By enrolling patients in clinical trials based on a principled, mechanistic assessment of their neuroanatomic potential for a therapeutic response, the CCTP will generate enhanced study samples of patients with similar connectomes, thereby increasing treatment effect sizes, decreasing sample sizes needed to power trials, and ultimately reducing trial duration, cost and risk to subjects [16]. Most importantly, by enhancing the scientific rigor of early-phase clinical trials, we hypothesize that the CCTP will improve the success rate of late-phase trials so that investigators can bring new therapies to clinical practice in the ICU.

To demonstrate the feasibility and utility of implementing the CCTP in the ICU, we report the protocol for STIMPACT (*Stimulant Therapy Targeted to Individualized Connectivity Maps to Promote ReACTivation of Consciousness*), a CCTP-based clinical trial in which

intravenous methylphenidate (IV MPH) will be used to promote recovery of consciousness in severely brain-injured ICU patients. STIMPACT will begin with a Phase 1, open-label, safety and dose-finding study of IV MPH in patients with DoC caused by acute severe TBI (ClinicalTrials.gov NCT03814356). The findings from the primary and secondary outcomes of Phase 1 of STIMPACT will dictate whether we will proceed to Phase 2A. Below, we describe the conceptual framework of the CCTP, and we present the STIMPACT Phase 1 trial protocol as well as the prespecified criteria for proceeding to Phases 2A and 2B.

Conceptual and Empiric Basis for the CCTP

Current theories propose that consciousness requires the integrated function of multiple brain networks, not any single node or connection [19, 20]. This network-based model of consciousness is supported by histologic and radiologic data demonstrating that coma can be caused by variable network disconnections [9, 10, 21–23] and that consciousness requires dynamic network interactions [24]. For a patient to recover consciousness, it is believed that the subcortical AAN, which modulates wakefulness [25, 26], must reconnect with the DMN and other cortical networks that mediate awareness [13, 27]. However, the precise mechanisms underlying this reintegration of subcortical and cortical networks are poorly understood. Furthermore, it may be weeks, months, or even years before these recovery mechanisms allow preserved AAN connections to reactivate the cerebral cortex [28–30]. For patients whose families face time-sensitive, life-or-death decisions in the ICU, treatments that promote recovery are needed within days. The CCTP will accelerate recovery of consciousness via targeted therapeutic modulation of structurally preserved brain network connections. The ultimate goal of the CCTP is to provide ICU clinicians with an armamentarium of targeted therapies that promote recovery of consciousness in patients with a broad range of DoC etiologies.

Testing the CCTP: Patient and Target Selection for STIMPACT

STIMPACT will test the CCTP in patients with acute severe TBI who are being treated in the ICU. We selected this patient population for our inaugural CCTP trial because prior evidence suggests that components of the AAN may be spared, and therefore serve as therapeutic targets, in patients with severe TBI. Histopathological studies show that although the AAN is invariably injured in animals and humans with coma caused by severe TBI [10, 31], not all AAN nuclei are lesioned and not all axons are disconnected. For example, both histopathological and MRI studies reveal that the ventral midbrain, home

to the dopaminergic ventral tegmental area (VTA), is heterogeneously injured by severe TBI, remaining partially intact in some patients [22, 32–34]. This phenomenon pertains not only to VTA neuronal cell bodies in the midbrain, but also to VTA axons that connect with the diencephalon, basal forebrain, and cortex (Figs. 1, 2). Consistent with these observations, nuclear imaging studies show that signal transmission in dopaminergic circuits is variably altered by severe TBI [35–37]. These converging lines of evidence support the hypothesis that preserved VTA connections are a potential target for therapeutic modulation in ICU patients with severe TBI.

Testing the CCTP: Therapy Selection for STIMPACT

We selected IV MPH as the therapeutic agent for STIMPACT because of its well-established mechanism of action on the VTA, compelling rodent data suggesting its role in promoting consciousness, and decades of data indicating its safe use in humans. IV MPH is a dopamine reuptake inhibitor that potentiates dopaminergic neurotransmission by VTA neurons [38, 39]. Although multiple neurotransmitters contribute to arousal [25], empiric evidence strongly supports the role of dopamine in therapeutic modulation of consciousness. In rodent models, it has been shown that a dopamine D1 receptor agonist (but not a D2 agonist) restores consciousness from anesthetic coma [40]. Furthermore, optogenetic [41] and electrical stimulation [42] of dopaminergic VTA neurons promotes recovery of consciousness in anesthetized rodents. This effect was strongly inhibited by a D1 receptor antagonist, suggesting that the arousal effects of VTA dopaminergic stimulation are D1 receptor-dependent. Collectively, these observations suggest that IV MPH promotes reemergence of consciousness by stimulating dopaminergic VTA neuronal signaling via D1 receptors [38, 42].

In humans, multiple enteral and subcutaneous therapies that stimulate dopaminergic neurotransmission have been shown to benefit patients with subacute or chronic TBI, including enteral MPH [43, 44]. Moreover, enteral amantadine, the only therapy shown to promote recovery of consciousness in a randomized controlled trial of patients with subacute TBI [45], increases dopamine release and blocks dopamine reuptake, thereby increasing synaptic levels of dopamine. Prior clinical trials of MPH investigated the enteral formulation, which is approved by the FDA to treat attention deficit disorder [39] and prescribed “off-label” to promote recovery in patients with TBI [46, 47]. However, positron emission tomography studies show that the IV formulation of MPH has a far more rapid uptake in the human brain than does the enteral formulation (~10 min versus ~90 min) [39]. These positron emission tomography data also indicate

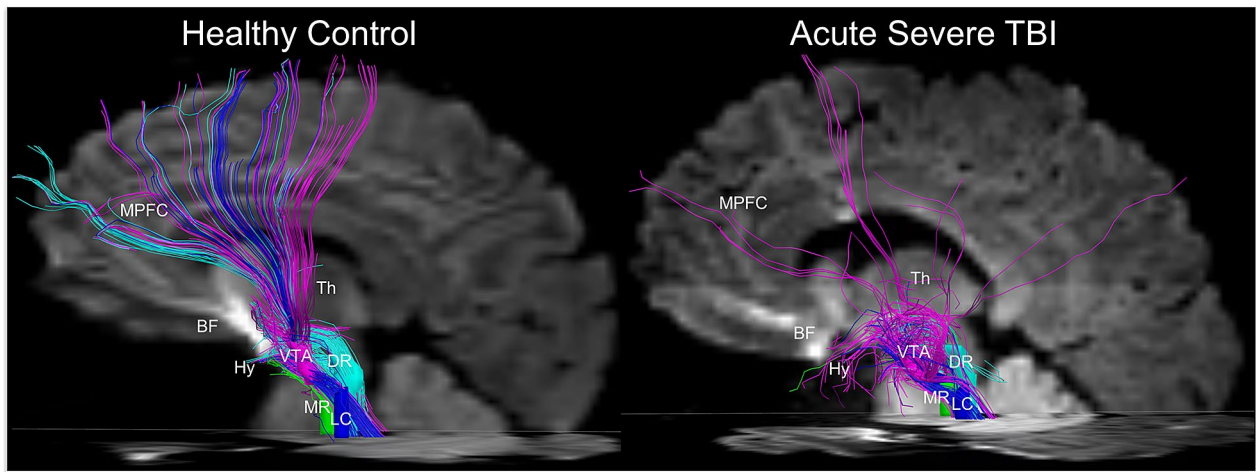


Fig. 1 Personalized connectome mapping in the ICU reveals preserved ventral tegmental area (VTA) connections. VTA tracts are shown from a left lateral view in a 33-year-old healthy male control and a 29-year-old man with acute severe TBI. The patient was comatose on arrival to the hospital and in a minimally conscious state at the time of this scan on post-injury day 7, as determined by a Coma Recovery Scale-Revised assessment. Tractography analysis was performed using TrackVis, as previously described [26]. All tracts are color-coded by sites of VTA connectivity: turquoise with dorsal raphe (DR), blue with locus coeruleus (LC), green with median raphe (MR), and pink with cortex, thalamus (Th), hypothalamus (Hy), or basal forebrain (BF). Multiple VTA connections are preserved in the patient, including with the medial prefrontal cortex (MPFC), which is a node of the default mode network. The patient recovered consciousness and functional independence by 6 months. Even in a patient with acute severe traumatic brain injury, the VTA may be a hub through which multiple brainstem AAN nodes connect with the Th, Hy, BF and cerebral cortex

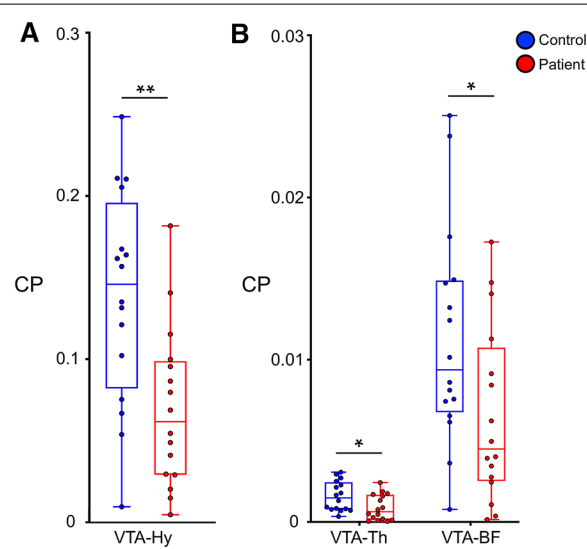


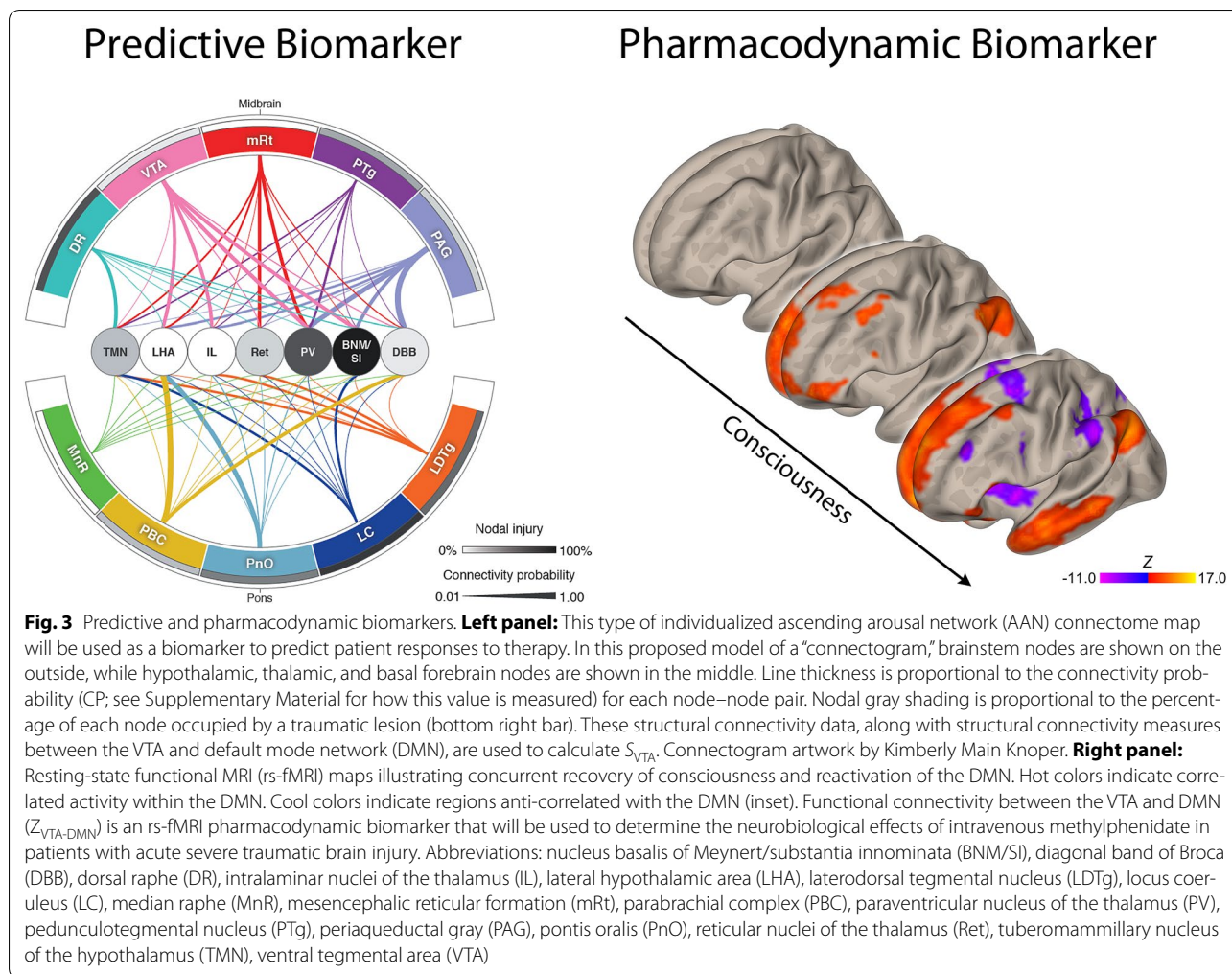
Fig. 2 Ventral tegmental area (VTA) axonal connections are spared in a subset of patients. We analyzed VTA connectivity with the hypothalamus (Hy), thalamus (Th), and basal forebrain (BF) in 16 patients, as well as in 16 matched controls. We calculated a connectivity probability (CP) between the VTA and each target ascending arousal network (AAN) node using previously described methods [9, 48, 84]. On a group level, median CP values were lower between the VTA and each AAN node in patients compared with controls. However, there is significant variance in control-group CP values, and many patients fall within the control-group interquartile range (IQR). These results indicate relative sparing of VTA connections in a subset of patients with acute severe TBI. See the Supplementary Material for a detailed description of the CP calculation algorithm

that the IV formulation of MPH generates higher levels of dopamine signaling than does the enteral formulation. Collectively, prior animal and human data thus provide a biological basis for using IV MPH to upregulate structurally intact, functionally dormant dopaminergic VTA circuits in ICU patients with severe TBI.

Testing the CCTP: Predictive Biomarker Selection for STIMPACT

To identify patients with preserved VTA connections, we will map the structural AAN connectome on a clinical MRI scanner. We will use high angular resolution diffusion imaging (HARDI) tractography, an MRI technique that maps axonal connectivity based on directional water diffusion [48]. We have previously shown that HARDI tractography can map the AAN connectome in the ex vivo human brain [26], detect acute AAN disconnections ex vivo [10], and detect disruptions in vivo in ICU patients with acute severe TBI [9].

Given that the VTA and cerebral cortex are connected both monosynaptically and polysynaptically [26, 49] (Fig. 3), it is unlikely that a single preserved VTA connection will predict a patient's response to IV MPH. Rather, we will use a graph theoretical analysis measure, VTA hub strength (S_{VTA}), as a predictive biomarker for the STIMPACT trial, because this biomarker measures both direct (monosynaptic) and indirect (polysynaptic) VTA connections. We selected subcortical AAN and cortical



DMN nodes as targets in the S_{VTA} measurement because functional connectivity studies suggest that DMN reactivation is essential for recovery of consciousness after severe brain injury [12, 50–53] and that the VTA activates the DMN via the AAN [54].

STIMPACT Hypothesis

The overarching hypothesis of the STIMPACT trial is that preservation of VTA connections within the AAN connectome predicts a response to IV MPH in patients with acute severe TBI. We hypothesize that for the subset of patients with preserved VTA connections, IV MPH will reconnect the cerebral cortex, accelerate reemergence of consciousness, and transform the course of their recovery.

STIMPACT Design Overview for Phases 1, 2A and 2B

The Phase 1 STIMPACT protocol described here focuses on safety (primary outcome measure). IV MPH will be administered as daily boluses (via IV push at a rate not

to exceed 20 mg/min) on Days 1–4: 0.5 mg/kg on Day 1, 1.0 mg/kg on Day 2, 2.0 mg/kg on Day 3, and the maximum tolerated dose on Day 4 (see Supplementary Material for a detailed rationale of dose selection). In Phase 1, we will also assess MPH pharmacokinetics and pharmacodynamic biomarkers of MPH responses (secondary outcome measures; see Fig. 4 for study schematic). Inclusion and exclusion criteria for STIMPACT Phase 1 are reported on ClinicalTrials.gov (NCT03814356) and in the Supplementary Material. Because the STIMPACT Phase 1 trial is focused on safety and dose-finding, all patients will receive IV MPH, regardless of their S_{VTA} measures.

The decision to proceed from Phase 1 to Phase 2A will depend upon the safety data and pharmacodynamic biomarker data obtained in Phase 1. Pharmacokinetic data from Phase 1 will inform the inter-dose intervals for Phase 2A, which is being planned as a double-blinded, placebo-controlled crossover design trial. Predictive biomarker data acquired in Phase 1 will inform the power

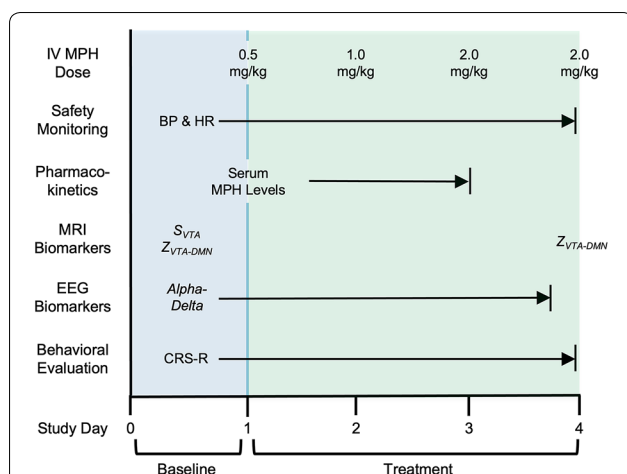


Fig. 4 STIMPACT study design schematic. Each patient in Phase 1 of the STIMPACT Trial will undergo 5 days of data acquisition, with predictive biomarker data and baseline pharmacodynamic biomarker data collected on Day 0, and treatment-related biomarker data collected on Days 1–4. Hence, each patient's biomarker responses to IV MPH will be measured against his/her own baseline biomarker variance. *BP* blood pressure, *CRS-R* Coma Recovery Scale-Revised, *HR* heart rate, *IV MPH* intravenous methylphenidate, S_{VTA} ventral tegmental area hub strength, $Z_{VTA-DMN}$ functional connectivity between the ventral tegmental area and the default mode network

calculation for the number of patients needed in Phase 2A to detect a difference in pharmacodynamic responses to MPH between patients with preserved versus lost VTA connectivity (i.e., high S_{VTA} versus low S_{VTA}). If our hypothesis that S_{VTA} predicts pharmacodynamic responses to IV MPH is supported in Phase 2A, then in Phase 2B we will select patients based on the S_{VTA} predictive biomarker, thus realizing the individualized, precision medicine goal of the CCTP.

Rationale for a STIMPACT Phase 1 Trial

IV MPH has been administered to over 1700 human subjects since 1957 [55–69]. In these prior studies, mostly conducted in healthy subjects and patients with psychiatric disease, no serious adverse events (SAEs) were reported. Common drug-related adverse events (AEs) included hypertension, tachycardia, agitation, and nausea [70], which will be readily manageable in the ICU environment of the STIMPACT trial.

Yet despite its reassuring safety record in human subjects, IV MPH has never been administered to a patient with acute severe TBI. Experience with IV MPH in comatose humans is limited to small case series of patients with barbiturate overdoses [61, 71, 72]. Because patients with acute severe TBI have increased hepatic drug metabolism and clearance, we cannot rely on prior dose-finding and pharmacokinetic studies of healthy humans

[39, 70]. Rather, it is essential to determine the maximum tolerated dose and pharmacokinetics of IV MPH in our population of interest. Thus, we believe that it is scientifically and ethically appropriate to begin STIMPACT with a Phase 1 safety and dose-finding study.

Methods

Primary Outcome Measure

The primary outcome measure of STIMPACT Phase 1 is the number of drug-related AEs at each of three IV MPH doses: 0.5, 1.0 and 2.0 mg/kg. The incidence of drug-related AEs (including SAEs) will be calculated as the ratio of the number of events divided by the number of administrations of IV MPH at each dose. The percentage of subjects experiencing each documented AE and SAE will be reported for each dose. AEs and SAEs will be classified according to the Medical Dictionary for Regulatory Activities (<https://www.meddra.org>).

In Phase 1, we aim to detect, with high probability, a drug-related SAE that would prevent STIMPACT from moving to Phase 2a. We therefore designed the Phase 1 trial to have a 90% chance of detecting any drug-related SAE that occurs with a frequency of $\geq 10\%$ at any given dose. Based on these criteria, we used the binomial equation to calculate our sample size: $1 - (1 - p)^n = y$, where p = drug-related SAE rate, n = number of subjects, and y = chance of detecting the SAE. Using a drug-related SAE rate of 10% ($p = 0.10$) and requiring a 90% probability of detecting the SAE at least once ($y = 0.90$) at each dose, we calculate that a 22-subject cohort will be necessary to enroll in Phase 1.

If two drug-related SAEs occur at a dose (frequency $\sim 10\%$), that dose and all higher doses will be removed from the trial. If two drug-related SAEs occur at the lowest dose, the trial will be stopped and Phase 1 will be repeated at a lower dose range. Any patient who experiences a drug-related AE at a dose of 1.0 or 2.0 mg/kg will continue in the study at the previously tolerated dose. If a drug-related AE occurs at the lowest dose of 0.5 mg/kg, the patient will be withdrawn from the study. A patient who experiences an SAE at any dose will be withdrawn from the study. Additional details regarding the definitions and criteria for AEs and SAEs are provided in the Supplementary Material.

Secondary Outcome Measures

Pharmacokinetics

For analysis of IV MPH pharmacokinetics, blood samples (1 mL) will be obtained via arterial or central venous catheters at baseline (immediately pre-dose), 5 min, 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 8 h, 12 h, and 16 h after each dose. Samples will be stored at -70°C until liquid chromatography/tandem mass spectrometry analysis

is performed by Worldwide Clinical Trials (Austin, TX). Plasma samples will be analyzed for total MPH (ng/mL) and ritalinic acid metabolic (ng/mL) concentrations.

As pharmacokinetic and pharmacodynamic potency may differ between MPH enantiomers [73], serum samples will also be analyzed for d-threo-MPH and l-threo-MPH enantiomer concentrations (ng/mL). Non-compartmental analysis will be used to calculate pharmacokinetic parameters using Pheonix WinNonLin (Version 8.1; Certara, L.P; Princeton, NJ) to determine time to maximum concentration (T_{max}) and elimination half-life ($T_{1/2}$), as well as maximum concentration (C_{max}) and area under the concentration–time curve (AUC_{inf}). Pharmacokinetic data will be summarized using descriptive statistics.

Pharmacodynamics

The pharmacodynamic outcome measures in STIMPACT Phase 1 are the effect of IV MPH on resting-state functional MRI (rs-fMRI) and EEG biomarkers of brain function, which will provide a direct assessment of IV MPH on its target brain network. On Days 1–3, we will record EEG continuously to measure the EEG biomarker response to each dose. On Day 4, each patient will receive his/her maximum tolerated dose during an rs-fMRI scan to measure the rs-fMRI biomarker response to this dose. The rs-fMRI scan will begin 10 min before administration of IV MPH and will continue for 30 min after IV MPH administration. Based upon prior positron emission tomography data [39], we anticipate that the peak MPH response in the brain will occur approximately 10 min after MPH administration. Thus, we expect to capture the peak brain concentration of MPH during the 30-min of rs-fMRI data acquisition that follow drug administration. We will use a self-controlled design, whereby each patient's baseline, pre-dose biomarker data (i.e., obtained immediately prior to IV MPH administration) are compared to the post-dose biomarker data.

For the rs-fMRI analysis, we and others have demonstrated the feasibility of using rs-fMRI to map functional brain networks in ICU patients with acute severe TBI (Figs. 3, 5) [12, 51, 52]. Given that brainstem functional network mapping of VTA-DMN connectivity requires high spatial and temporal resolution, we implemented a simultaneous multislice [74] blood-oxygen level dependent (BOLD) sequence on the 3 Tesla Siemens Skyra MRI scanner in the Massachusetts General Hospital Neurosciences ICU (2 mm isotropic voxels, $TR = 1.25$ s). To control for the effects of physiological fluctuations on the BOLD signal [75], we measure and statistically regress cardiac and respiratory activity during rs-fMRI (Fig. 6 and Supplementary Figures 1 and 2). Additional details regarding rs-fMRI sequence parameters, as well as

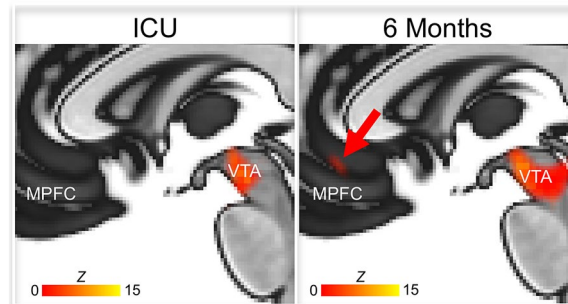
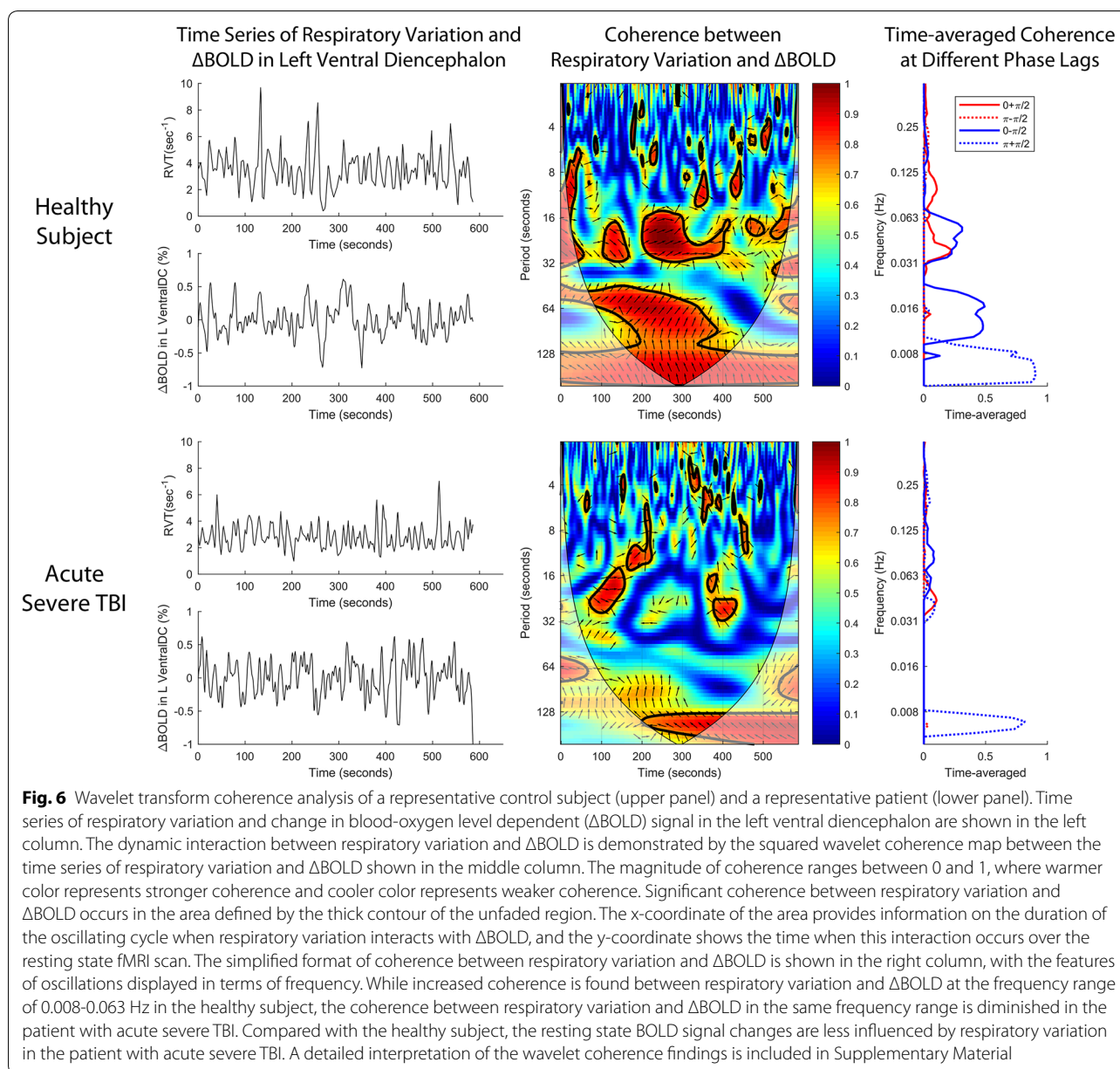


Fig. 5 Functional connectivity between the ventral tegmental area (VTA) and default mode network (DMN) reemerges during recovery. Eight patients with acute severe TBI underwent resting-state functional MRI (rs-fMRI) in the ICU and at 6-month follow-up, by which time all had recovered consciousness. Mean group-level VTA functional connectivity maps are shown, based on Fisher Z-transformed correlations in the BOLD signal (color bar). Correlations are adjusted for significance with $p < 0.01$ height-level and $p < 0.05$ false discovery rate (FDR)-corrected cluster-level thresholds. There were no VTA-DMN connections acutely, but VTA connections with the medial prefrontal cortex (MPFC) node of the DMN reemerged during recovery of consciousness (red arrow). The statistical threshold used here is more liberal than in our recent studies of DMN connectivity [12, 51], which underscores the need for the higher-resolution rs-fMRI sequence that we developed for the CCTP

physiologic data acquisition and analysis, are provided in the Supplementary Material.

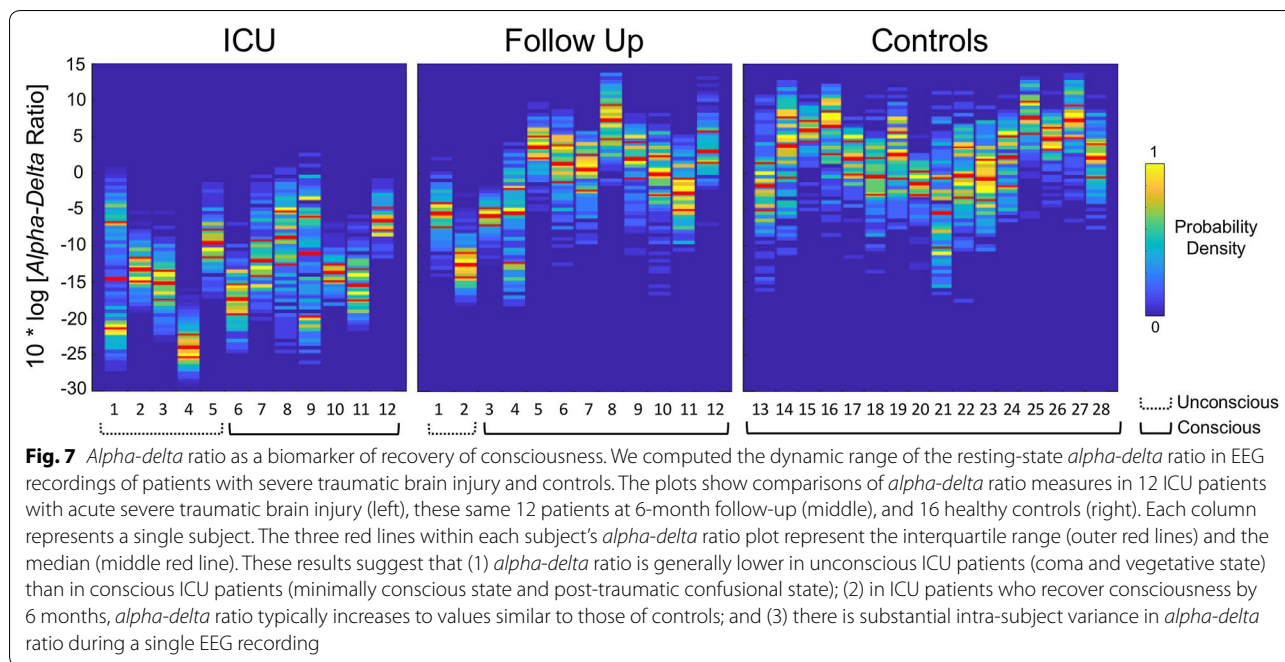
To test for an rs-fMRI biomarker response to the maximum tolerated IV MPH dose, we will perform a patient-specific, change-point analysis [76, 77] that detects whether time-series values deviate between two epochs of data (i.e., pre- versus post-dose). First, we will generate averaged rs-fMRI time-series in VTA and DMN regions of interest and regress physiological heart rate and respiration data from these time-series (see Supplementary Material). Then, we will use dynamic functional connectivity (DFC) [24, 78] to calculate a correlation value (r) between the VTA and DMN for every 10 s of rs-fMRI data. We will Fisher-Z transform the r values into Z values to generate 60 $Z_{VTA-DMN}$ (pre IV MPH) values across the 10 min of rs-fMRI data acquisition before IV MPH is administered and 180 $Z_{VTA-DMN}$ (post IV MPH) values across the 30 min of rs-fMRI data acquisition after IV MPH is administered. We will analyze the time-series, composed of $Z_{VTA-DMN}$ (pre IV MPH) and $Z_{VTA-DMN}$ (post IV MPH) using the R *change-point* program [79]. A patient will be considered a responder to IV MPH if the change-point analysis identifies a deviation in the $Z_{VTA-DMN}$ (post IV MPH) time-series compared to $Z_{VTA-DMN}$ (pre IV MPH) time-series.

With respect to the EEG pharmacodynamic data, we aim to identify a resting-state EEG biomarker that measures the effect of IV MPH on cortical circuit function.



Crucial to this effort is the development of statistical methods that quantify EEG oscillatory dynamics. Patients with DoC experience frequent fluctuations in arousal [80], and the dynamic range and robustness of EEG biomarkers during these fluctuations in the ICU environment is unknown. Therefore, to minimize confounders and optimize the signal-to-noise ratio of the EEG data, we will again use a self-controlled design in which we compare post-dose EEG data to each patient's immediate pre-dose EEG data. This design allows therapeutic responses to be compared to each patient's baseline biomarker data on the same clinical medication regimen.

We considered a broad range of candidate EEG biomarkers for the EEG pharmacodynamic biomarker analysis (see Supplementary Material). Recent studies of patients with chronic DoC suggest that spectral measures perform better than other EEG-based cortical measures as biomarkers of consciousness [81]. Our preliminary results suggest that ICU patients with severe TBI experience wide-ranging fluctuations in frequency band-specific spectral measures over the course of a clinical recording (Fig. 7). Nevertheless, the ratio of alpha to delta power appears to reliably distinguish ICU patients with acute DoC from patients who have recovered



consciousness. We therefore selected *alpha-delta* ratio as the EEG-based pharmacodynamic biomarker for STIMPACT Phase 1. Details of EEG data acquisition and processing are provided in the Supplementary Material.

The analytic approach for the EEG *alpha/delta* pharmacodynamic biomarker data will parallel the approach for the rs-fMRI $Z_{VTA-DMN}$ pharmacodynamic biomarker described above. To test for an EEG biomarker response at the maximum tolerated IV MPH dose, we will generate a time-series composed of the *alpha/delta* statistic calculated from 10-s time windows before ($\alpha/\delta_{(pre\ IV\ MPH)}$) and after ($\alpha/\delta_{(post\ IV\ MPH)}$) MPH administration. A patient will be considered a responder to IV MPH based on EEG data if the change-point analysis identifies a deviation in the $\alpha/\delta_{(post\ IV\ MPH)}$ time-series compared to $\alpha/\delta_{(pre\ IV\ MPH)}$ time-series.

Criteria for Proceeding from Phase 1 to Phase 2A

We will proceed from Phase 1 to Phase 2a if predetermined safety *and* pharmacodynamic biomarker criteria are met. The safety criterion is that an IV MPH dose will be used in Phase 2A only if there are fewer than 2 drug-related SAEs at that dose in Phase 1. The pharmacodynamic biomarker criterion is that there must be a pharmacodynamic response in $\geq 10\%$ of patients, in either the rs-fMRI biomarker *or* the EEG biomarker, at the maximum tolerated dose. Without such a response, we will repeat Phase 1 at a higher dose range. The rationale for this second criterion is that even though our dose range of 0.5–2.0 mg/kg is broader than the 0.5–0.9 mg/

kg dose range used in most prior human studies [39, 70], our dose range may still be insufficient to detect a pharmacodynamic response in patients with severe TBI.

The safety and pharmacodynamic criteria for proceeding to Phase 2A yield three possible outcomes for STIMPACT Phase 1 (Supplementary Fig. 3): (1) IV MPH is safe and $\geq 10\%$ of the 22 patients show a response in $Z_{VTA-DMN}$ or *alpha/delta* \rightarrow we will proceed to Phase 2a at the maximum tolerated dose; (2) IV MPH is not safe, even at the lowest dose \rightarrow we will repeat Phase 1 in 22 new patients at a lower dose range; (3) IV MPH is safe, but $< 10\%$ show a response \rightarrow we will explore alternative rs-fMRI [12, 24] and EEG analytic biomarkers [81, 82], as well as different statistical models of the pharmacodynamic response (see Supplementary Material), and will consider repeating Phase 1 at a higher dose range. Recognizing that rs-fMRI and EEG biomarker development is an active area of investigation in the field of DoC, the CCTP provides alternate approaches at each stage of trial design while maintaining the central focus on connectome-based measures of therapeutic responses.

Overview of Phase 2A and Phase 2B

The study design for Phase 2A will be finalized upon completion of Phase 1. STIMPACT Phase 2A is being planned as a double-blind, placebo-controlled, crossover trial to test the primary hypothesis that pharmacodynamic biomarkers respond to IV MPH more than to placebo. The secondary hypothesis of Phase 2A is that preserved S_{VTA} predicts a pharmacodynamic biomarker

response to IV MPH relative to placebo. As in Phase 1, patients will be enrolled in Phase 2A regardless of their S_{VTA} measures. If the secondary hypothesis of Phase 2A is supported by the pharmacodynamic biomarker data, suggesting that S_{VTA} predicts a response to IV MPH, we will select patients for enrollment in Phase 2B based upon their S_{VTA} measures.

In Phase 2A, we will also investigate the effect of IV MPH versus placebo on the change in level of consciousness on behavioral assessment with the Coma Recovery Scale-Revised (CRS-R) [83]. CRS-R data will be used to inform the power calculation for Phase 2B. The primary hypothesis in Phase 2B will be that there is a greater behavioral response to IV MPH relative to placebo, as assessed by the CRS-R. Phase 2B thus represents a realization of the fundamental premise of the CCTP—that a principled, mechanistic approach to study design in early phase clinical trials leads to enriched study samples in late phase trials that are more likely to show a drug effect.

Trial Oversight

Between July 2018 and February 2020, we convened a Clinical Oversight Committee, led by an experienced Independent Medical Monitor (Dr. Thomas P. Bleck), which approved the protocol for the Phase 1 STIMPACT trial. To ensure that the TBI community's interests are represented, we also convened a Patient and Family Advisory Board, which reviewed the research plan and made recommendations regarding recruitment, study activities, and data dissemination. The investigational new drug (IND) application was approved by the FDA in August, 2018 (IND# 140675), and the study protocol was approved by the Partners Healthcare Institutional Review Board in May, 2019.

Summary

We propose a mechanistic clinical trial paradigm, the Connectome-based Clinical Trial Platform (CCTP), to predict and measure responses to new targeted therapies in the ICU. We also describe a CCTP-based trial, STIMPACT, which will test the safety of IV MPH in Phase 1, and then in later phases will ultimately test the hypothesis that IV MPH promotes recovery of consciousness in patients who have preserved VTA connections within their AAN connectomes. The CCTP will allow clinicians to provide targeted treatments that are personalized to each patient's connectome, ensuring that each patient is given the best possible chance to recover consciousness in the ICU. Ultimately, we envision multidisciplinary discussions about optimal treatment selection at a *Coma Board*, akin to the *Tumor Board* at which therapeutic decisions are made by a multidisciplinary team for patients with cancer. By providing a clinical trial platform

to test targeted pharmacologic and electrophysiologic therapies that reactivate the injured human connectome, the CCTP has the potential to transform the therapeutic landscape and improve outcomes for patients with DoC.

Electronic supplementary material

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Author Contributions

BLE: study conception and design; data acquisition, processing, and analysis; data interpretation; drafting the article; final approval of the version to be published. MEB: design of treatment compounding and operating procedures and pharmacokinetic monitoring, critical review of manuscript, final approval of the version to be published. DWZ: design of EEG pharmacodynamic biomarker; data acquisition, processing, and analysis; critical review of manuscript, final approval of the version to be published. ASF: design of statistical plan; critical review of manuscript, final approval of the version to be published. SBS: design of structural MRI predictive biomarker; data acquisition, processing, and analysis; critical review of manuscript, final approval of the version to be published. ZDT: design of functional MRI pharmacodynamic biomarker; data acquisition, processing, and analysis; critical review of manuscript, final approval of the version to be published. SC: design of dynamic functional connectivity-based pharmacodynamic analysis; critical review of manuscript, final approval of the version to be published. JEK: design of functional MRI sequence; data acquisition, processing, and analysis; critical review of manuscript, final approval of the version to be published. SC: design of functional MRI physiologic monitoring; data acquisition, processing, and analysis; critical review of manuscript, final approval of the version to be published. SLM: design of functional MRI physiologic monitoring; data acquisition, processing, and analysis; critical review of manuscript, final approval of the version to be published. TPB: study design; critical review of manuscript, final approval of the version to be published. JJF: study design, ethical guidance, final approval of the version to be published. JTG: study design; critical review of manuscript, final approval of the version to be published. LRH: study design; critical review of manuscript, final approval of the version to be published. KS: development of investigational therapy; study design; critical review of manuscript, final

approval of the version to be published. ENB: development of investigational therapy; study design; critical review of manuscript, final approval of the version to be published. YGB: study conception and design; data acquisition, processing, and analysis; data interpretation; drafting the article; final approval of the version to be published.

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Conflict of interest

The authors have no relevant conflicts of interest to disclose.

Ethical approval/Informed consent

All biomarker data reported here were obtained with written informed consent provided by healthy control subjects or by surrogate decision-makers for patients with altered consciousness, as part of a separate Institutional Review Board-approved protocol.

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