Neurocrit Care (2020) 33:358–359
https://doi.org/10.1007/s12028-020-01065-4

NEUROCRITICAL CARE SOCIETY

INVITED COMMENTARY

Precision Medicine for Traumatic Coma

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Trauma is a leading cause of severe neurological injury and the primary etiology in many patients with disorders of consciousness (DOC) [1]. Neurological recovery following traumatic coma is a multidimensional process that involves the reemergence of wakefulness, awareness, sensorimotor function, higher-order cognitive domains, and the progressive restoration of functional independence [2]. When recovery of consciousness fails or is delayed, patients can present with severely impaired phenotypes such as the unresponsive wakefulness or minimally conscious states [2]. The lack of accurate prognostic models to predict the trajectory of recovery following severe traumatic brain injury (TBI) is widely recognized as a major unmet need in intensive care medicine. Additionally, in spite of decades of translational and clinical research, there are no therapeutic interventions that can effectively change the natural history of traumatic coma recovery. In the face of uncertainty, family members and medical teams may elect to withdraw or maintain life-sustaining therapies on the basis of false assumptions and self-fulfilling prophecies [3, 4].

Advances in image acquisition, brain mapping and network science have emerged as major opportunities to not only gain insights on the biological mechanisms of TBI, but also to increase the accuracy of recovery prediction and, perhaps most importantly, to identify targets for therapy [5]. Two innovations have been particularly impactful. Diffusion tensor imaging (DTI) has provided a window on the precise anatomical distribution and prognostic importance of traumatic white matter damage [6]. Resting state functional MRI (rs-fMRI) has shown that the architecture of topographically distinct large-scale networks is massively disrupted after severe brain injury [7]. Additionally, recent work has found that connectivity strength within and between resting-state networks is predictive of long-term functional outcome following severe neurological insults such as anoxic brain injury [8]. These findings support MRI-derived structural and functional connectivity indices as versatile biomarkers in unresponsive patients.

In this issue of *Neurocritical Care*, Edlow et al. [9] propose a clinical trial platform for comatose patients who are in the ICU following severe TBI. Their overarching aim is to identify specific brain connectivity signatures that would guide interventions to promote early recovery of consciousness. In a study designated Stimulant Therapy targeted to Individualized connectivity Maps to Promote reACTivation of consciousness (STIMPACT), the authors plan to administer the stimulant methylphenidate intravenously to comatose patients following severe TBI. The central hypothesis is that a positive response to methylphenidate would be predicted by preserved connectivity within an ascending arousal system that includes the ventral tegmental area (VTA) of the midbrain and structures in the thalamus, hypothalamus, basal forebrain and nodes of the cortically based default mode network (DMN). Integrity of this arousal system would be evaluated using high angular resolution diffusion imaging (HARDI), a tractographic refinement of DTI. Given the complex connectional architecture of the VTA, the authors propose to use a graph theoretical analysis measure, "VTA hub strength", as the primary predictive biomarker.

The study is organized in incremental phases, each building on prior steps. First, the investigators plan to evaluate drug safety and pharmacokinetics with escalating doses of methylphenidate (phase 1). Second, using a double-blind, placebo-controlled, crossover trial design, they will explore the association between VTA hub strength and "pharmacodynamic biomarkers", namely

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This article refers to the original article: https://doi.org/10.1007/s12028-020-01062-7.

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functional connectivity between the VTA and DMN assessed with rs-fMRI, and EEG alpha-delta ratio (phase 2A). Last, they intend to select patients for treatment based on their VTA hub strength and to evaluate the behavioral response using validated metrics (phase 2B).

The STIMPACT investigators deserve praise for designing an innovative mechanistic framework for individualizing therapeutic interventions in the acute phase of severe brain injury. Nevertheless, some limitations need to be mentioned. First, the sole reliance on connectivity biomarkers may be reductive, as there are a number of other variables which influence treatment response (e.g., pharmacogenomic factors determining drug efficacy) and clinical outcome. Second, converging evidence indicates that the relationship between functional and structural connectivity is far from straightforward, particularly in TBI patients; hence, the assumption may not hold that that the structural connectivity predictive biomarker (VTA hub strength defined using tractography) will map effectively to the rs-fMRI pharmacodynamic biomarker. Third, it is unclear whether the ultra-short-term change in dynamic rs-fMRI connectivity, as proposed in phase 2A, would be an appropriate endpoint to determine the efficacy of medications which may have a range of effects on different neuronal systems and at different timescales; in other words, the lack of response to stimulant or other therapeutics over 30 min may not preclude longer-term treatment responses. Fourth, the proposed analysis exclusively focused on the dopaminergic VTA network and fails to consider other arousal systems (e.g., the noradrenergic system based in the locus coeruleus or the glutamatergic/cholinergic system based in the pedunculopontine nucleus). Fifth, the investigators should recognize that resting-state fMRI can be extremely challenging or even unsafe to implement in critically ill TBI patients and that this technique is confounded by concurrent physiological disturbances, movement, and sedation. Last, real-world clinical application of the methods used in STIMPACT would require standardized and automated preprocessing and processing pipelines that could be challenging to implement in centers where advanced analytical expertise is unavailable.

Overall, the authors have designed an appealing protocol with a persuasive conceptual basis for the selected biomarkers. If successfully carried out, this research could be impactful in generating actionable information for clinicians who are deciding which patients are most likely to respond to treatment. The proposed clinical trial platform might be especially valuable in predicting responses to experimental therapies which carry significant risks, for example invasive neuromodulation therapy (thalamic stimulator implantation) or cell-based transplantation. Future precision medicine efforts will need to consider other important factors likely to drive TBI recovery, including variance in gene expression, to answer the difficult questions of how to predict and promote recovery of consciousness at the individual level. This is one of the central objectives of the Neurocritical Care Society's recently established Curing Coma Campaign [10].

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Source of Support
None.

Conflict of interest
Authors report no conflict of interests or disclosures in relation to the content of this manuscript.

Publisher's Note

Received: 20 July 2020 Accepted: 22 July 2020
Published online: 13 August 2020

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