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Disrupted Interactions Between Arousal and Cortical Awareness Networks in MCS and VS/UWS Patients: Evidence from Resting-state Functional Imaging Connectivity

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Abstract—Clinical patients in a vegetative state or unresponsive wakefulness syndrome (VS/UWS) demonstrate distinct arousal-awareness dissociation; the neuropathological mechanisms underlying such dissociation remain poorly understood. Here, we systematically examined how functional connectivity from the brainstem areas regulating arousal to the cortical networks supporting internal and external awareness is disrupted in minimally conscious state (MCS) and VS/UWS patients. Resting-state functional imaging was conducted in 23 MCS patients, 31 VS/UWS patients, and 20 age-matched healthy individuals. A hierarchical cluster analysis was conducted using all voxel-based signals in the brainstem to identify the specific areas for arousal. We found that the pontine tegmentum area (PTA) and caudal midbrain area persistently formed a distinct cluster that exclusively showed extensive connections with the cortical networks supporting internal and external awareness in healthy individuals, confirming their role in arousal. We show that functional connectivity from the PTA and caudal midbrain area to the cortical-awareness-supporting networks were significantly reduced in MCS and VS/UWS patients; importantly, as the clinical symptoms of consciousness disorders deepen from MCS to VS/UWS, functional connectivity strength became significantly reduced, changing from presenting no significant connections in MCS to widespread negative connections in VS/UWS. Additionally, we observed increased connectivity from the PTA and caudal midbrain area to limbic structures, the brainstem areas, and the cerebellum in MCS and VS/UWS patients, consistent with prior studies. These findings offer important insights into the neural network mechanisms underlying the long-observed arousal-awareness dissociation in VS/UWS patients and provide additional neuroimaging-based biomarkers for the clinical diagnosis of MCS and VS/UWS patients. © 2018 Published by Elsevier Ltd on behalf of IBRO.

Key words: vegetative state/unresponsive wakefulness syndrome (VS/UWS), minimally conscious state (MCS), resting-state fMRI, functional connectivity, arousal, internal and external awareness.

INTRODUCTION

The neuropathological mechanisms underlying disorders of consciousness (DOC) in vegetative-state or unresponsive wakefulness syndrome (VS/UWS) patients remain incompletely understood (Giacino et al., 2014). VS/UWS patients are distinctively characterized by an absence of the awareness of self and environment with a preservation of autonomic and motor reflexes and sleep-wake cycles (Giacino and Kalmar, 2005). This is in contrast with patients in another severe DOC condition, the minimally conscious state (MCS), who show minimal, inconsistent, but reproducible behavioral evidence of self or environmental awareness. Despite the clear definitions of symptoms, how to correctly differentiate between MCS and VS/UWS patients remains one of the most challenging clinical tasks (Giacino et al., 2014; Noirhomme et al., 2017).

Human consciousness is a multifaceted concept (Tononi et al., 2016). From a theoretical point of view, consciousness has two distinct and dissociable dimen-

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Abbreviations: BOLD, blood-oxygen-level-dependent; DOC, disorders of consciousness; MCS, minimally conscious state; PTA, pontine tegmentum area; rs-fMRI, resting-state functional magnetic resonance imaging; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

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sions or components: level and content (Laureys, 2005; Mashour and Hudetz, 2017). The level of consciousness describes the degree of arousal or wakefulness, while the content of consciousness describes awareness or subjective experience (Laureys, 2005; Calabro et al., 2015). The clinical symptoms of VS/UWS indicate a dissociation between arousal and awareness, the two components of consciousness, in the patients. In comparison, in healthy individuals, arousal in normal conditions (e.g., awaking from sleep) is always accompanied by an immediate presence of the awareness of the self and environment. It is also conceivable that in MCS patients, arousal may be accompanied by a state of consciousness that fluctuates inconsistently around the boundary between awareness possession (probably minimal) and unconsciousness. Although the dissociation between arousal and awareness in VS/UWS patients is conceptually and behaviorally evident in clinical settings, the systems-level neuropathological mechanisms underlying such a dissociation in VS/UWS patients remain poorly understood (Bagnato et al., 2013; Giacino et al., 2014). To date, few studies have directly addressed the potential alteration of functional connections between brain systems regulating arousal and those supporting awareness in healthy and DOC conditions based on measurement from brain imaging modalities (Fischer et al., 2016; Golaszewski, 2016). Filling this gap of knowledge facilitates a better understanding of the neuroanatomy of arousal and consciousness and the systems-level mechanisms underlying DOC in patient populations in the theoretical context of human consciousness (Tononi et al., 2016).

The goal of this study is to promote a better understanding of the dissociation between arousal and awareness in VS/UWS patients by systematically examining and comparing, using resting-state functional magnetic resonance imaging (rs-fMRI), functional connections between the brainstem areas that regulate arousal (e.g., the pontine tegmentum area [PTA]) and the cortical consciousness-supporting networks (Vanhaudenhuyse et al., 2011; Demertzi et al., 2013) among three groups of study participants consisting of MCS patients, VS/UWS patients, and age-matched healthy control individuals, respectively. The brainstem is the well-recognized source of signals that determine the state of arousal (Posner and Plum, 2007). The brainstem contains functionally discrete regions, and the reticular formation in the brainstem has been considered critical for arousal (Parvizi and Damasio, 2003). Our study made two unique efforts to address the proposed goal. First, to better identify the brainstem areas that are specifically associated with arousal, we performed a hierarchical cluster analysis using all voxel-based blood-oxygen-level-dependent (BOLD) fMRI signals in the brainstem in healthy individuals. The hierarchical clustering resulted in four spatially nonoverlapping clusters whose functional connectivities with the rest of the brain were analyzed. Of the four clusters, one cluster uniquely occupies the PTA and caudal midbrain area, which have been considered to play a critical role in arousal (Parvizi and Damasio, 2001, 2003; Posner and Plum, 2007). Second, we specifically examined potential disruptions of functional connectivity from the seed cluster in the PTA and caudal midbrain area to the cortical networks that have been identified to support internal and external awareness in MCS and VS/UWS patients relative to healthy individuals. Specifically, the internal awareness network encompasses the midline anterior cingulate/frontal and posterior cingulate/precuneal cortices, while the external awareness network encompasses mainly the bilateral fronto-temporo-parietal cortices (Vanhaudenhuyse et al., 2011; Demertzi et al., 2013).

Based on the differences between the clinical symptoms of MCS and VS/UWS, we hypothesized that (1) compared with healthy individuals, functional connectivity from the seed cluster in the PTA and caudal midbrain area for arousal to the cortical-awareness-supporting networks is disrupted in both MCS and VS/UWS patients, and (2) as the clinical symptoms of DOC deepen from MCS to VS/UWS, functional connectivity strength between the arousal- and awareness-supporting brain systems further decreases (i.e., connectivity strength changing from the level near zero [fluctuations around zero] in MCS patients to negative [two systems becoming inhibitory to each other] in VS/UWS patients at the group level). We show that, of the four identified brainstem clusters, only the cluster containing the PTA and caudal midbrain area demonstrated extensive functional connections in widespread cortical regions, including those in the cortical-awareness-supporting networks, in healthy individuals, confirming their role in arousal in humans. Moreover, compared with healthy individuals, the reduction of functional connectivity strength from the PTA and caudal midbrain area to the cortical-awareness-supporting networks showed significant DOC-dependent reductions in MCS and VS/UWS patients that support our hypotheses. The findings together offer important insights into the neural-network-level mechanisms underlying the long-observed arousal-awareness dissociation in VS/UWS patients and provide additional functional imaging-based biomarkers that may facilitate the diagnosis and prognosis of MCS and VS/UWS patients in clinical settings.

EXPERIMENTAL PROCEDURES

This study was approved by the ethics committee of Beijing Army General Hospital. Written informed consent was obtained from healthy volunteers and from the legal surrogate of each patient.

Participants

Study participants included 23 patients in the MCS, 31 patients with VS/UWS, and 20 age-matched healthy control subjects enrolled at Beijing Army General Hospital from 2013 to 2016. At the time of enrollment, the patients had remained in MCS or VS/UWS for at least one month after severe brain injury. Table 1 in Appendix summarizes the clinical profiles of the patients enrolled in this study. Patients were excluded if they had