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Research report

Abnormal structural connectivity between the basal ganglia, thalamus, and frontal cortex in patients with disorders of consciousness

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ABSTRACT

Consciousness loss in patients with severe brain injuries is associated with reduced functional connectivity of the default mode network (DMN), fronto-parietal network, and thalamo-cortical network. However, it is still unclear if the brain white matter connectivity between the above mentioned networks is changed in patients with disorders of consciousness (DOC). In this study, we collected diffusion tensor imaging (DTI) data from 13 patients and 17 healthy controls, constructed whole-brain white matter (WM) structural networks with probabilistic tractography. Afterward, we estimated and compared topological properties, and revealed an altered structural organization in the patients. We found a disturbance in the normal balance between segregation and integration in brain structural networks and detected significantly decreased nodal centralities primarily in the basal ganglia and thalamus in the patients. A network-based statistical analysis detected a subnetwork with uniformly significantly decreased structural connections between the basal ganglia, thalamus, and frontal cortex in the patients. Further analysis indicated that along the WM fiber tracts linking the basal ganglia, thalamus, and frontal cortex, the fractional anisotropy was decreased and the radial diffusivity was increased in the patients compared to the controls. Finally, using the receiver operating characteristic method, we

Abbreviation: AD, axial diffusivity; BG, basal ganglia; DOC, disorders of consciousness; DTI, diffusion tensor imaging; EMCS, emerged minimally conscious state; FA, fractional anisotropy; HC, healthy control; LIS, locked-in syndrome; MCS, minimally conscious state; NBS, network based statistic; RD, radial diffusivity; ROC, receiver operating characteristic; VS/UWS, vegetative state/unresponsive wakefulness syndrome; WM, white matter.

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found that the structural connections within the NBS-derived component that showed differences between the groups demonstrated high sensitivity and specificity (>90%). Our results suggested that major consciousness deficits in DOC patients may be related to the altered WM connections between the basal ganglia, thalamus, and frontal cortex.

1. Introduction

Disorders of consciousness (DOC), which exhibit different levels of dissolution of consciousness including coma, vegetative state/unresponsive wakefulness syndrome (VS/UWS), and minimally conscious state (MCS), have attracted considerable attention from various fields of study and have, therefore, advanced our knowledge of consciousness (Fernandez-Espejo & Owen, 2013; Giacino, Fins, Laureys, & Schiff, 2014; Gosseries, Di, Laureys, & Boly, 2014; Koch, Massimini, Boly, & Tononi, 2016). However, because consciousness is not a unitary construct but a catch-all term that includes wakefulness, awareness, and other phenomena (MacDonald, Naci, MacDonald, & Owen, 2015; Shadlen & Kiani, 2011, pp. 27–46), we still lack an understanding of the neural basis of consciousness. This may block the precise diagnosis of DOC (Steven Laureys & Tononi, 2011). Using non-invasive neuroimaging technology to explore the brain functional and structural alterations in DOC may enable researchers to identify precise diagnostic markers (Owen, 2013; Stender et al., 2014).

A growing number of neuroimaging studies suggest that DOC is a disconnection syndrome (Fernandez-Espejo et al., 2012). For example, Laureys et al. (1999) used Positron Emission Eomography (PET) to reveal functional disconnections in the cortico-cortical and cortico-thalamo-cortical pathways in VS/UWS patients. And resting-state fMRI (R-fMRI) studies showed that the consciousness loss is associated with disrupted functional connections primarily in the default mode network (DMN) (Fernandez-Espejo et al., 2012; Monti et al., 2010), fronto-parietal network (Long et al., 2016), and thalamo-cortical network (Cauda et al., 2009; Crone et al., 2015; Boly et al., 2009). Moreover, several studies indicated that the recovery of consciousness depends to some extent on connectivity between the thalamus and the frontal cortex and parietal regions (Crone et al., 2014; Laureys & Schiff, 2012). A task fMRI study reported that thalamo-frontal connectivity mediates top-down cognitive functions in DOC patients and identified thalamo-frontal connectivity as a neurophysiologic marker that may distinguish patients who can engage in top-down processing from patients who cannot (Monti et al., 2015). Recently, Demertzi et al. (2015) investigated the DMN, fronto-parietal, salience, auditory, sensorimotor and visual networks based on multi-center R-fMRI data (73 DOC patients) by using a multiple-seed correlation approach, and found that the regions in the auditory network were more functionally connected in MCS compared to VS/UWS. Di Perri, Bastianello, and Barrtsch (2013) studied brain functional connectivity between the DMN and other networks in 18 DOC patients, and found the limbic hyperconnectivity in VS/UWS and MCS patients. Annen et al. (2016) studied brain function (fluorodeoxyglucose FDG-PET metabolism)-structure (DTI) relationship in 25 severely brain injured patients (19 DOC: 7 VS/UWS and 12 MCS; 6 EMCS), and detected regional metabolism was declined in inferior-parietal, precuneus, and frontal regions, as well as abnormal fractional anisotropy (FA) in the thalamo-frontal tracts. To understand the underlying forebrain dysfunction and interventions in severe brain injuries, Schiff (2008, 2010) proposed the "mesocircuit" hypothesis, consisting of striatum, thalamus, frontal cortex, and parietal/occipital/temporal cortex, which provides the conceptual foundation for the key role of the central thalamus as a privileged node for neuromodulation to support forebrain arousal regulation or for a causative role of connectivity from the central thalamus to different cortical areas in DOC patients (Schiff, 2008, 2010, 2016; Giacino et al., 2014). And some studies have tested the "mesocircuit" hypothesis on the basis of R-fMRI connectivity (Lant, Gonzalez-Lara, Owen, & Fernández-Espejo, 2016) and FDG-PET technique (Chatelle et al., 2014; Fridman, Beattie, Broft, Laureys, & Schiff, 2014). Considering that the functional disconnection of the thalamo-frontal circuit may originate from pathological white matter (WM) connectivity and that the thalamo-cortical network plays a role in the cortico-basal ganglia (BG) circuit (Draganski et al., 2008), we attempted to know if the brain WM structural disconnection exists between the BG, thalamus, and frontal cortex in DOC patients.

Diffusion tensor imaging (DTI) is the only available non-invasive technique for detecting the distribution of brain WM *in vivo* (Le Bihan & Johansen-Berg, 2012). It can provide valuable information about WM microstructure and the WM injury severity in DOC patients (Galanaud et al., 2012; Luyt et al., 2012). Fernandez-Espejo et al. (2011) used DTI to study the degrees of axonal injury and damage to the thalami and brainstem regions in 25 VS/UWS and MCS patients by using DTI data. They found significantly different mean diffusivity (MD) value in subcortical white matter and thalamic regions, but not in brainstem, between VS/UWS and MCS patients. And Edlow et al. (2013) mapped brain WM pathways in a post-mortem brain (a 62 years-old woman) with acute traumatic coma by using high angular resolution diffusion imaging (HARDI) data, and found the disrupted WM pathways connecting brainstem arousal nuclei to the basal forebrain and thalamic intralaminar and reticular nuclei. They proposed that traumatic coma may be a subcortical disconnection syndrome related to the disconnection of specific brainstem arousal nuclei from the thalamus and basal forebrain. van der Eerden et al. (2014) reported that DOC patients by Hypoxic Ischemic Encephalopathy (HIE) showed a predominant cerebral hemisphere axonal injury accompanied by a markedly decreased axial diffusivity (AD). Lant et al. (2016) found that DOC patients showed lower FA in the subcortico-cortical and