NeuroImage: Clinical 20 (2018) 260–266

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Subdivisions of the posteromedial cortex in disorders of consciousness

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ARTICLE INFO

Keywords:
Default mode network
Diffusion tensor imaging
Disorders of consciousness
Parcellation
Parietal cortex
Persistent vegetative state

ABSTRACT

Evidence suggests that disruptions of the posteromedial cortex (PMC) and posteromedial corticothalamic connectivity contribute to disorders of consciousness (DOCs). While most previous studies treated the PMC as a whole, this structure is functionally heterogeneous. The present study investigated whether particular subdivisions of the PMC are specifically associated with DOCs. Participants were DOC patients, 21 vegetative state/unresponsive wakefulness syndrome (VS/UWS), 12 minimally conscious state (MCS), and 29 healthy controls. Individual PMC and thalamus were divided into distinct subdivisions by their fiber tractography to each other and default mode regions, and white matter integrity and brain activity between/within subdivisions were assessed. The thalamus was represented mainly in the dorsal and posterior portions of the PMC, and the white matter tracts connecting these subdivisions to the thalamus had less integrity in VS/UWS patients than in MCS patients and healthy controls. In addition, these tracts had less integrity in DOC patients who did not recover after 12 months than in patients who did. The structural substrates were validated by resting state fMRI finding impaired functional activity within these PMC subdivisions. This study is the first to show that tracts from dorsal and posterior subdivisions of the PMC to the thalamus contribute to DOCs.

1. Introduction

Patients surviving severe brain damage may develop a long-term disorder of consciousness (DOC), such as vegetative state/unresponsive wakefulness syndrome (VS/UWS) or minimally conscious state (MCS). Evidence from brain imaging studies suggests that disconnections within thalamocortical areas of the default mode network (DMN) are implicated in DOCs (Boly et al., 2009; Fernández-Espejo et al., 2011; Fernandez-Espejo et al., 2012; He et al., 2015; Rosazza et al., 2016; Soddu et al., 2012; Vanhaudenhuyse et al., 2010). The posteromedial cortex (PMC, i.e., precuneus/posterior cingulate cortex) is the structural (Hagmann et al., 2008) and functional (Utevsky et al., 2014) core of the DMN, and is involved in a variety of functions, including self-processing, self-awareness, and consciousness (Cavanna and Trimble, 2006). Diffusion magnetic resonance imaging (dMRI) of DOC patients has revealed white matter damage in connections between the PMC and thalamus (Fernandez-Espejo et al., 2012). A resting state functional magnetic resonance imaging (fMRI) study found reduced PMC-thalamic fluctuations in DOC patients compared with healthy controls (Boly et al., 2009), which accords well with our previous findings of disrupted functional connectivity between the PMC and thalamus in DOC patients (He et al., 2015). These findings suggest that the PMC and thalamus play important roles in determining levels of consciousness. Other studies have shown fMRI or PET can help in predicting recovery from a DOC. For example, functional connectivity strength discriminated between DOC patients who regained consciousness within 3 months and

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https://doi.org/10.1016/j.nicl.2018.07.025
Received 16 April 2018; Received in revised form 28 June 2018; Accepted 25 July 2018
Available online 26 July 2018

those who did not, with the most discriminative region being the PMC (Wu et al., 2015), and PET predicted long-term recovery (i.e., 12 months after baseline assessment) of patients with VS/UWS (Stender et al., 2014).

Previous studies of the PMC in DOC patients have investigated this large region as a whole (Boly et al., 2009; Fernandez-Espejo et al., 2012; He et al., 2015; Laureys et al., 1999a; Vanhaudenhuyse et al., 2010). However, some work provides strong evidence of anatomical diversity and functional heterogeneity in the PMC (Cavanna and Trimble, 2006; Margulies et al., 2009; Zhang et al., 2014). We previously used whole brain white matter tractography in healthy participants to reveal particularly strong connections between dorsal parts of the PMC and the thalamus (Zhang et al., 2014). Dorsal parts of the PMC are reported to have fundamental roles in self-awareness (Den Ouden et al., 2005; Kjaer et al., 2002) and in altered state of consciousness (Maquet et al., 1999), which suggests that, rather than the structure as a whole, particular parts of the PMC may be specifically involved in determining levels of consciousness. If so, this could have implications for using neuroimaging to facilitate more accurate diagnoses of DOCs and more reliably predict patient outcomes. The aim of the present study was to identify subdivisions of the PMC that may be specifically implicated in DOCs. We first used fiber tractography within regions of the DMN to identify subdivisions of the PMC and thalamus. White matter integrity between PMC and thalamus subdivisions, and brain activity within PMC subdivisions, was then compared across VS/UWS patients, MCS patients, and healthy controls, and between DOC patients who recovered after 12 months and those who did not.

2. Materials and methods

2.1. Participants

We recruited 79 patients with a DOC (VS/UWS, n = 62; MCS, n = 17) from the PLA Army General Hospital in Beijing between January 2014 and May 2016. All patients had received a severe brain injury caused by trauma, anoxia or stroke/cerebrovascular accident more than one month prior to recruitment. Patients were evaluated at least twice weekly within the two weeks before baseline, and their diagnosis of either VS/UWS or MCS was based on the Coma Recovery Scale-Revised (CRS-R) assessment with the highest diagnostic level during this time, as per Giacino et al. (2004). Exclusion criteria were having brain damage exceeding 30% of total brain volume, any contraindications to MRI scanning, being sedated or anesthetized during MRI acquisition, or having died during follow-up. The duration of follow-up was at least 12 months after baseline, with clinical examinations using the CRS-R and Glasgow Outcome Scale (GOS) (Jennett and Bond, 1975). Patients with a GOS level of 3–5 were considered to have recovered from their DOC (levels 1 and 2 represent dead and VS/UWS or MCS, respectively) The GOS is commonly used to assess recovery from DOCs (e.g., Norton et al., 2012; Perlbarg et al., 2009; Qin et al., 2015; Van Der Eerden et al., 2014; Wu et al., 2015). The GOS has the advantage of being easy to administer and has a good inter-rater reliability of 92% (Wilson et al., 1998) that suggests the potential for bias across multiple raters is minimal. Most patients were evaluated at follow-up as outpatients, with those outside Beijing evaluated by local health care physicians. After excluding patients with incomplete follow-up assessments (n = 6), severe motion artifacts and poor quality MRI (n = 27), or failed registration or preprocessing because of severe structural deformations (n = 13), our study sample comprised 21 VS/UWS and 12 MCS patients. A group of 29 gender-matched healthy controls (HCs) were recruited. None of the HCs had a history of psychiatric or neurological illness, head injury, or drug or alcohol abuse. The study was approved by the Ethics Committee of the PLA Army General Hospital. All HCs and surrogates for the DOC patients provided written informed consent.

2.2. MRI data acquisition

All participants underwent dMRI, resting state fMRI and T1-weighted MRI scanning on a 3 T GE Discovery MR750 scanner (GE Medical Systems). The major acquisition parameters for dMRI data included: repetition time (TR)/echo time (TE) = 9000/81.9 ms, thickness/gap = 2.0/0 mm, flip angle = 90°, matrix size = 128 × 128 × 75, voxel size = 2 × 2 × 2 mm^3. For each participant, a total of 67 volumes were acquired, including 3 non-diffusion-weighted volumes ($b = 0\ s\,mm^{-2}$) and 64 non-collinear gradient directions ($b = 1000\ s\,mm^{-2}$). Resting state fMRI data were acquired axially using an echo-planar imaging sequence sensitive to blood oxygen level-dependent contrast. The acquisition parameters were TR/TE = 2000/30 ms, thickness/gap = 4.0/0.6 mm, flip angle = 90°, matrix size = 64 × 64 × 39, voxel size = 3.75 × 3.75 × 4 mm^3, 210 volumes were obtained for each participant. Sagittal T1-weighted structural MRI scans were obtained using the following optimized acquisition parameters: TR/TE = 8.16/3.18 ms, thickness/gap = 1.0/0 mm, flip angle = 7°, matrix size = 256 × 256 × 188; and voxel size = 1 × 1 × 1 mm^3.

2.3. MRI data preprocessing

The diffusion MR data were preprocessed using the FSL Diffusion Toolbox (FMRIB Software Library, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL). First, corrections for eddy current distortions and head motion were performed by aligning all diffusion-weighted images to the non-diffusion-weighted image (the b0 volume). To ensure accurate brain masks and anatomical registration, T1-weighted images were processed with the Computational Anatomy Toolbox (CAT12, Structural Brain Mapping Group, http://dbm.neuro.uni-jena.de/cat/). The brain mask in diffusion space was then separated from the skull using the binarized skull-stripped T1-weighted images. Next, the skull-stripped T1-weighted image was aligned with b0 volume and diffusion images. In addition, each coregistered T1-weighted image was first linearly then nonlinearly warped to the Montreal Neurological Institute (MNI) template. The derived transformation parameters were then inverted and used to warp the seed and target masks from MNI space to the native dMRI space using a nearest neighbor interpolation. The registration procedures were performed using Aladin and F3D tools from the NiftyReg package (https://sourceforge.net/projects/niftyreg/). The diffusion-weighted data for each participant were visually inspected to ensure there were no apparent artifacts arising from acquisition or data processing procedures.

Resting state fMRI data were preprocessed in the native space of each participant using Data Processing & Analysis for Brain Imaging toolbox (DPABI) (Yan et al., 2016). Of the 210 volumes for each participant, the first 10 were discarded and the remainders underwent slice timing and motion correction, and were resampled to a stereoscopic 3 mm^3. In order to retain the temporal structures of patients with large head displacement, images with maximum displacement in the cardinal direction > 3 mm, or maximum spin > 3° from the previous frame were treated as outliers and included as nuisance regressors (Demertzi et al., 2015). In subsequent functional statistical analysis, we included head motion indexed by mean framewise displacement (Power et al., 2012) as a confounding factor in the statistical models. Linear regression was performed to remove the influence of head motion, linear trends, white matter and CSF signals. Finally, data were temporally filtered to keep frequencies of 0.01–0.08 Hz, to reduce low-frequency drift and high-frequency noise. Images were smoothed with a Gaussian filter of full width at half maximum value of 6 mm.

2.4. Structural connectivity-based parcellation of the PMC and thalamus to the DMN

We investigated 6 ROIs: the PMC, thalamus, superior frontal gyrus