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Relationship between the anterior forebrain mesocircuit and the default mode network in the structural bases of disorders of consciousness

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ABSTRACT

The specific neural bases of disorders of consciousness (DOC) are still not well understood. Some studies have suggested that functional and structural impairments in the default mode network may play a role in explaining these disorders. In contrast, others have proposed that dysfunctions in the anterior forebrain mesocircuit involving striatum, globus pallidus, and thalamus may be the main underlying mechanism. Here, we provide the first report of structural integrity of fiber tracts connecting the nodes of the mesocircuit and the default mode network in 8 patients with DOC. We found evidence of significant damage to subcortico-cortical and cortico-cortical fibers, which were more severe in vegetative state patients and correlated with clinical severity as determined by Coma Recovery Scale—Revised (CRS-R) scores. In contrast, fiber tracts interconnecting subcortical nodes were not significantly impaired. Lastly, we found significant damage in all fiber tracts connecting the precuneus with cortical and subcortical areas. Our results suggest a strong relationship between the default mode network – and most importantly the precuneus – and the anterior forebrain mesocircuit in the neural basis of the DOC.

1. Introduction

Disorders of consciousness (DOC) can result from a variety of focal and widespread patterns of injuries but exact pathological taxonomies for diagnosis have not yet been developed (Giacino et al., 2014). Nevertheless, impairments in thalamocortical and frontoparietal networks appear as consistent findings in recent neuroimaging studies (Cauda et al., 2009; Crone et al., 2013, 2015; Hannawi et al., 2015). Specifically, DOC patients show functional (Cauda et al., 2009; Soddu et al., 2012; Vanhaudenhuyse et al., 2010), metabolic (Laureys et al., 1999) and structural (Fernandez-Espejo et al., 2012) disconnections within thalamocortical and cortico-cortical regions of the default mode network (DMN), which are correlated with clinical severity (Fernandez-Espejo et al., 2012; Vanhaudenhuyse et al., 2010). A recent study has further stressed the importance of thalamocortical connections by revealing specific patterns of impaired metabolic activity in the anterior forebrain mesocircuit (Fridman et al., 2014). The so-called mesocircuit hypothesis proposes that a loss of excitatory output from the central thalamus to diffuse cortical areas has a causative role in DOC (Schiff, 2008, 2010; Schiff and Posner, 2007). Such a loss is proposed to be caused by circuit dysfunction wherein inhibitory striatal output to the globus pallidus is lost, resulting in pallidal disinhibition and subsequent excessive inhibition of the thalamus. This mechanism is theorized to be driven by disinhibition of the globus pallidus interna specifically. Nevertheless, likely due to limitations in spatial resolution of the data, the above metabolic study (Fridman et al., 2014) considered the globus pallidus as a whole.

While recent functional neuroimaging studies seem to support the predictions of the mesocircuit model (see Giacino et al., 2014 for a review), it is unknown whether the hypothesized deafferentations are functional or anatomical. Structural impairments in thalamocortical and cortico-cortical fiber tracts of the DMN have been previously observed in DOC patients (Fernandez-Espejo et al., 2012). However, to our knowledge, the integrity of direct structural connections of the mesocircuit has not been investigated. A mechanistic understanding of the specific structural neural bases underlying DOC will be essential for the development of objective prognostic and diagnostic biomarkers.

The purpose of our study was to investigate structural integrity of the mesocircuit and its cortical projections in DOC patients, in order to lend structural support to observed differences in functional and metabolic brain activity in this poorly understood patient population. We used diffusion tensor imaging (DTI) tractography to reconstruct and

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assess the integrity of white matter connections between the nodes of the mesocircuit and several cortical regions *in vivo* in a group of DOC patients, as compared with healthy participants. DOC patients included those in the vegetative state (VS), minimally conscious state (MCS), and emerging-from-minimally conscious state (EMCS). We predicted that subcortico-subcortical connections would show less evidence of specific structural damage than subcortico-cortical and cortico-cortical connections in DOC patients. This prediction was based on several factors: 1) subcortico-cortical and cortico-cortical connections were previously shown to have evidence of significant structural damage in DOC patients (Fernandez-Espejo et al., 2012), 2) long range connections may be anatomically more susceptible to both diffuse axonal injury (Adams et al., 1982; Blumbergs et al., 1989; Johnson et al., 2013) and hypoxic–ischemic injury (Saab et al., 2013), and 3) the above described subcortical metabolic patterns (Fridman et al., 2014) suggested inhibitory pallidothalamic fibers (*i.e.* subcortico-subcortical) were intact.

2. Materials and methods

2.1. Participants

A convenience sample of 16 DOC patients participated in our study between February 2012 and November 2014. Inclusion criteria for the study were adult patients with a diagnosis of chronic DOC, or EMCS at the time of the study. The only exclusion criterion was unsuitability to enter the MRI environment. Independent functional and structural datasets from subsets of this cohort have been previously reported (Cruse et al., 2012; Fernandez-Espejo and Owen, 2013; Gibson et al., 2014; Naci and Owen, 2013; Naci et al., 2014). From these, 8 patients (4 VS patients, 3 MCS, and one EMCS) met the data quality criteria (see Section 2.3 below) and were included in the study. Patients were clinically assessed with repeated administrations of the Coma Recovery Scale—Revised (CRS-R; Giacino et al., 2004) over a 5 day visit to our center. The highest score achieved by each patient across the different examinations is included in Supplementary Information Table S1. Demographic and clinical data from the patients are summarized in Table 1. A group of 8 sex- (3 females) and age-matched healthy control subjects were also recruited for the study. The Health Sciences Research Ethics Board of The University of Western Ontario provided ethical approval for the study. All volunteers gave written informed consent and were paid for their participation in the experiment. Written assent was obtained from the legal guardian for all patients.

2.2. MRI acquisition

Diffusion-weighted images were acquired in a 3 T MRI scanner at the Centre for Functional and Metabolic Mapping (CFMM) at Robarts Research Institute (London, Canada). Patients were recruited over a time span of 2.5 years, during which the CFMM upgraded their 3 T scanner. Twelve participants (6 patients and 6 healthy controls) were scanned before the upgrade, in a Magnetom Trio system (Siemens, Erlangen, Germany), and the remaining four (2 patients and 2 healthy controls) were scanned in the new system: a Magnetom Prisma system (Siemens, Erlangen, Germany). This resulted in a balanced distribution of patients and healthy controls across the two different scanners. Similarly, the proportion between clinically conscious and clinically unconscious patients was also maintained across scanners. Diffusion-weighted images included sensitizing gradients applied in 64 non-collinear directions with a b-value = 700 s/mm^2, using an EPI sequence (Trio system: TR = 8700 ms, TE = 77 ms, voxel size = 2 × 2 × 2 mm, no gap, 77 slices; Prisma system: TR = 9600 ms, TE = 77 ms, voxel size = 2 × 2 × 2 mm, no gap, 76 slices). A high-resolution, T1-weighted, 3-dimensional magnetization prepared rapid acquisition gradient echo (MPRAGE) image was also acquired (Trio system: TR = 2300 ms, TE = 2.98 ms, inversion time = 900 ms, matrix size = 256 × 240, voxel size = 1 × 1 × 1 mm, flip angle = 9°; Prisma system: TR = 2300 ms, TE = 2.32 ms, inversion time = 900 ms, matrix size = 256 × 256, voxel size = 1 × 1 × 1 mm, flip angle = 8°).

2.3. DTI analyses

Motion related artifacts are a common methodological problem when working with DOC patients. Quality control of the data was performed by one of the authors (N.D.L.), who carefully inspected all diffusion-weighted raw images for the presence of motion related artifacts or macrostructural lesions or abnormalities in the regions of interest. Four DOC patients were excluded after visual inspection of DTI data revealed large artifacts due to excessive movement inside the scanner. An additional four DOC patients were excluded due to widespread and severe structural brain abnormalities that precluded accurate identification of either subcortical (n = 1), or both subcortical and cortical regions (n = 3) in the MRI data. All exclusions were made prior to fiber tracking and were made blinded to the clinical diagnosis of the patients.

Data preprocessing and analysis were performed using the FSL Diffusion Toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/), following a similar pipeline as Fernandez-Espejo et al. (2012) and Fernandez-Espejo et al. (2015). Pre-processing steps included eddy-current correction (Behrens et al., 2003a) and skull and non-brain tissue stripping using the Brain Extraction Tool (Smith, 2002). Fractional anisotropy (FA) maps were obtained using FSL Diffusion Toolbox (FDT; Behrens et al., 2003a). Diffusion modeling and probabilistic tractography were carried out using FDT. Fiber tracking between regions of interest (ROIs) was performed in native space for each subject (see Table 2 for summary of all fiber tracts), using FSL probtrackX (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). Tracking was done in both directions between each set of two ROIs, and the resulting probability distribution was averaged and thresholded to 2% of the maximum intensity for each subject, in order to remove very-low probability paths. While there is currently no convention about the precise percentage, 2% has proven successful in previous studies of both healthy and pathological populations (Fernandez-Espejo et al., 2012; Sala-Llonch et al., 2010). The resulting tracts were visually inspected by one of the authors (N.D.L.) for correspondence with known anatomy and to ensure that our approach did not remove anatomically viable fibers.

Table 1
Summary of demographic and clinical characteristics of patients and controls.

Characteristic	Healthy controls	Patients	Statistic	P	Diagnostic categories			
					VS	MCS & EMCS	Statistic	P
Age, years, mean ± SD	26 ± 2	35 ± 11	t = −2.2	n.s.	31 ± 11	38 ± 10	t = 1.03	n.s.
Sex, M/F	5/3	5/3			3/1	2/2[a]		
Time post-ictus, days, mean ± SD		3523 ± 2914			2576 ± 3348	4472 ± 2492	t = 0.91	n.s.
VS/MCS/EMCS		4/3/1						
TBI/HBI		3/5			2/2	1[a]/3		
Scanner: Trio/Prisma	6/2	6/2			3/1	3/1[a]		

SD: standard deviation, VS: vegetative state, MCS: minimally conscious state, EMCS: emerging from minimally conscious state, TBI: traumatic brain injury, HBI: hypoxic–ischemic brain injury.
[a] Identifies the EMCS patient.