White Matter Connectometry In Patients With Disorders of Consciousness Revealed By 7-Tesla Magnetic Resonance Imaging

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White matter connectometry in patients with disorders of consciousness revealed by 7-Tesla magnetic resonance imaging

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Abstract

White matter disruption plays an important role in disorders of consciousness (DOC). The aim of this study was to analyze the connectometry between DOC patients and healthy controls and to explore the relationship between diffusion connectometry and levels of consciousness. Fourteen patients with DOC and 13 sex- and age-matched controls were included in this study. The participants underwent diffusion magnetic resonance imaging (MRI) and T1-weighted structural MRI at 7 Tesla. Diffusion MRI connectometry was performed to investigate the differences between groups, and to subsequently study the correlation between Coma Recovery Scale-Revised (CRS-R) scores and white matter integrity. In DOC patients, the quantitative anisotropy (QA) was significantly reduced in deep white matter tracts, whereas significantly higher QA values were found in the bilateral cerebellum compared with healthy controls. Moreover, the QA values in many tracts within the right hemisphere were higher in patients in a minimally conscious state compared to those in vegetative state/unresponsive wakefulness syndrome. In contrast, many tracts within the left hemisphere of the latter group showed higher QA than the former, which was reflected by the correlation between diffusion connectometry and CRS-R scores. These results indicate that the cerebellum may play an important role in DOC, and the lateralization of the cerebral hemisphere in affected patients may suggest neural compensation.

Keywords: disorders of consciousness; ultra-high field (7T); Connectometry; cerebellum; Quantitative anisotropy

1. Introduction

Disorders of consciousness (DOC), including vegetative state/unresponsive wakefulness syndrome (VS/UWS) (Laureys et al., 2010) and minimally conscious state (MCS) (Giacino et al., 2002), describe a pathological state usually caused by severe brain injury in which arousal and awareness are separated. Although in VS/UWS patients who have recovered from coma in the acute phase, autonomic functions, including the sleep-wake cycle, are retained, the ability to perceive themselves and the surrounding environment is completely lost (Jennett & Plum, 1972); in contrast, patients in MCS have a weak but certain perceptual ability, whilst exhibiting inconsistent and non-reflexive behavior (Giacino et al., 2002). Accurate and reliable prognostic assessment is essential for the selection of treatment strategies and to guide end-of-life decisions by relatives of patients with DOC (Bernat, 2006). However, the current traditional behavioral scales, such as the Coma Recovery Scale-Revised (CRS-R) (Giacino, Kalmar, & Whyte, 2004) are not sufficient for the detection of residual consciousness and prognosis of patients with DOC.

With the development of neuroimaging technology and the diversification of post-processing analysis methods, many researchers have turned to neuroimaging and neuroelectrophysiological techniques to assess brain function and disease prognosis in DOC patients. Functional magnetic resonance imaging (MRI), a statistical measure of correlation between neuronal activities (Z. Zhou, Wang, Zang, & Pan, 2017), has become a common tool for investigating functional connectivity and deepening our understanding of states of consciousness. A growing number of studies have reported reduced functional connectivity in the default mode network (DMN) (Boly et al., 2009), frontoparietal network (Long et al., 2016), and thalamocortical network (Crone et al., 2014) in patients with DOC.

Recently, white matter (WM) has drawn increasing attention in studies on DOC. Diffusion tensor imaging (DTI) is a non-invasive imaging technique implemented in MRI (Basser & Pierpaoli, 1996), which has dramatically improved our understanding of subcortical WM microstructure alterations. Many articles about WM microstructure and the severity of WM injury in DOC patients have been published (Galanaud et al., 2012; Luyt et al., 2012). In addition, researchers have applied DTI to distinguish between different states of consciousness or to correlate DTI findings with injury severity and clinical outcome (Fernandez-Espejo et al., 2011; Fernandez-Espejo et al., 2012; Newcombe et al., 2011; Perlbarg et al., 2009). Furthermore, widespread abnormalities in WM following severe brain injury have been reported. Weng et al. (2017) observed abnormal structural connectivity between the basal ganglia, thalamus, and frontal cortex in patients with DOC (Weng et al., 2017). Wang et al. (2018) found that the behavioral CRS-R assessment score was positively correlated with WM integrity in the fornix, uncinate fasciculus, pontine crossing tract, and posterior limb of the internal capsule (Wang et al., 2018). In our previous research, which consisted of 22 nodes mainly located in the frontal cortex, limbic system, occipital, and parietal lobes, network-based statistics analysis revealed significantly decreased structural connectivity in DOC patients compared with healthy controls (Tan et al., 2019). Consciousness may depend on key pathways that link distributed brain network regions (Wang et al., 2018). Meanwhile, other studies have attempted to distinguish different levels of consciousness based on diffusion characteristics (Fernandez-Espejo et al., 2011; Fernandez-Espejo et al., 2012; Zheng, Reggente, Lutkenhoff, Owen, & Monti, 2017). However, the structural reasons for impaired consciousness remain unclear.

In the last decade, a novel method called connectometry was proposed to bypass

the limitation of fiber tracking by more accurately reflecting the structure and density of WM tracts, while accounting for crossing fibers and partial volume effects (Yeh, Badre, & Verstynen, 2016). Connectometry extracts the spin distribution function (SDF) in a given fiber orientation as a measure of the water density along that direction. There are numerous diffusion indices derived from SDFs, such as the quantitative anisotropy (QA) (Yeh, Tang, & Tseng, 2013). QA represents the peak density of water diffusion along the main direction of the WM fibers in each fiber tract. The use of QA in dMRI can provide further spatial resolution to identify tracts in regions with kissing or crossing tracts. Compared with traditional DTI measures, decreasing the rates of Type I errors, improving spatial resolution, and reducing sensitivity to partial volume effects are the main advantages of QA in dMRI connectometry (Mojtahed Zadeh, Ashraf-Ganjouei, Ghazi Sherbaf, Haghshomar, & Aarabi, 2018). This method has already been used to study Parkinson's disease (Sobhani, Rahmani, Aarabi, & Sadr, 2019), mood disorders (Olvet et al., 2016), multiple sclerosis (Romascano et al., 2015), and amyotrophic lateral sclerosis (Abhinav et al., 2014), but not in patients with DOC.

In the present study, we used multi-shell high angular resolution diffusion imaging (HARDI) data acquired on a 7-Tesla (7T) MRI scanner to analyze the connectometry between DOC patients and healthy controls. We further explored the relationship between diffusion connectometry and levels of consciousness.

2. Methods

2.1. Participants

Thirty-three patients with severe brain injuries and 13 healthy volunteers were recruited in this study. All the patients were from the Department of Rehabilitation in the Hangzhou Hospital of Zhejiang CAPR, Hangzhou, China. The consciousness

level of the patients was estimated by two experienced medical doctors according to the Coma Recovery Scale-Revised (CRS-R) scale (Giacino et al., 2004) on the 3 consecutive days before 7 T MRI scan. The inclusion criteria were: 1) a diagnosis of VS or MCS; 2) longer than 1 month but shorter than 1 year since onset; 3) no MRI contraindications; 4) no history of psychological disorders; 5) no epilepsy or frequent spontaneous movements; 6) no use of the benzodiazepine class of drugs, 7) no large brain lesion or severe hydrocephalus. Eleven patients with MRI contraindications and seven patients presented extensive focal brain damage were excluded. Additionally, one patient's data were excluded from the analysis due to a diagnosis of locked-in syndrome. Finally, the data from 14 patients with severe brain injuries were included in the analysis. Besides, we also enrolled 13 healthy volunteers as controls.

2.2 Image acquisition

The MRI data were acquired on a Siemens Magnetom 7 T scanner equipped with a Nova 1Tx/32Rx head coil. Multi-shell DWI data were acquired with the following parameters: 112 slices for each shell, 1.25 mm isotropic voxels, acceleration factor = 2, echo time (TE)/repetition time (TR) = 66.2/5100 ms, flip angle (FA) = 90 °, generalized autocalibrating partially parallel acquisitions (GRAPPA) = 3, multi-band (MB) = 2, b = 2000 s/mm^2, 60 directions, acquisition time (TA) = 6'53", performed twice with opposite phase encoding directions for each direction. Six interspersed b0 images (b-value = 0 s/mm^2) were also acquired. Whole brain scanning was performed with sagittal T1-weighted images were obtained using magnetization-prepared rapid gradient echo (MPRAGE) sequence with 0.75 mm isotropic resolution, 208 slices, TE/TR/inversion time (TI) =2.51/2590/1050 ms, FA=7°, GRAPPA=2, TA =5'49".

2.3 Image preprocessing

The preprocessing was conducted using FSL (Jenkinson, Beckmann, Behrens,

Woolrich, & Smith, 2012) (http://fsl.fmrib.ox.ac.uk/fsl). Briefly, diffusion preprocessing included correcting the motion, susceptibility, and eddy current distortion with the FSL's eddy and topup tools (Andersson, Skare, & Ashburner, 2003).

2.4 Reconstruction and group connectometry analysis

A total of 27 dMRI scans were included in the connectometry database and in the analysis. The b-table was checked using an automatic quality control routine to ensure accuracy (Schilling et al., 2019). The diffusion data were reconstructed based on the Montreal Neurological Institute (MNI) coordinate space using q-space diffeomorphic reconstruction (Yeh & Tseng, 2011) to obtain the SDF (Yeh, Wedeen, & Tseng, 2010); the Human Connectome Project 1021 (HCP-1021) template was adopted as dMRI atlas (Yeh & Tseng, 2011). A detailed description was in the Supplementary materials.

2.5 Statistical analysis

IBM SPSS Statistics 22.0 statistical package (SPSS Inc., Chicago, IL) was used to compare demographic differences between DOC patients and healthy controls. Two sample t-test was used for age, and a p value <0.05 was regarded to indicate statistically significant association.

For connectometry analysis, we used a multiple regression model to evaluate between-group differences and the correlation between the WM structure and the CRS-R score; the T-score threshold was set at 2.5. The permutation test (5000 permutations) allowed the estimation and correction of the false discovery rate (FDR) of Type I error inflation due to multiple comparisons (Yeh et al., 2016). A nonparametric Spearman partial correlation was used to derive the correlation, and the effects of age and sex were removed using a multiple regression model. Group

connectometry in DSI Studio (http://dsi-studio.labsolver.org) was used for the connectometry analysis.

3. Results

3.1 Demographic and clinical information

Fourteen patients with DOC (age range: 46.9 ± 16.4 years) were enrolled. Eight patients were diagnosed with VS, and six patients were diagnosed with MCS. Thirteen healthy controls were also assessed (12 males; age range: 40.7 ± 15.9 years). There was no significant difference in age between the two groups (two-sample t-test, $p > 0.05$). The clinical characteristics of the enrolled patients are shown in Table S1. All patients and controls included in the study were right-handed. Demographic data of the two groups are presented in Table 1.

3.2 Connectometry analysis in DOC patients compared to healthy controls

Patients with DOC and healthy controls were matched for age and sex. Healthy controls had significantly higher QA compared with DOC patients in the following WM fibers: corpus callosum, bilateral fornix, bilateral corticospinal tract, bilateral cingulum, right inferior fronto-occipital fasciculus, left corticopontine tract, right corticothalamic pathway, bilateral reticulospinal tract, and left dentato-rubro-thalamic tract (FDR = 0.000024) (Table 2; Figure 1). In contrast, compared with healthy controls, DOC patients had significantly higher QA in two of the WM fibers: bilateral cerebellum (FDR = 0.000094) (Table 2; Figure 2).

3.3 Connectometry analysis between patients in MCS and VS/UWS

The connectometry analysis between patients with MCS and VS/UWS revealed that the QA values of the corpus callosum, right corticopontine tract, right inferior fronto-occipital fasciculus, bilateral corticospinal tract, middle cerebellar peduncle, right uncinate fasciculus, right cingulum, right dentato-rubro-thalamic tract, right

inferior longitudinal fasciculus, right reticulospinal tract, right corticobulbar tract, and right cerebellum were higher in MCS patients (FDR = 0.011136) (Table S2; Figure S1). In contrast, the left arcuate fasciculus, left inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus, anterior commissure, left optic radiation, left superior longitudinal fasciculus, left corticostriatal pathway, and left corticopontine tract showed higher QA in VS/UWS patients compared to those in MCS (FDR = 0.069474) (Table S2; Figure S2).

3.4 Correlation between diffusion connectometry and CRS-R scores

In patients with DOC, the connectometry analysis revealed that the QA values of the right inferior fronto-occipital fasciculus, right corticopontine tract, corpus callosum, bilateral corticospinal tract, uncinate fasciculus, middle cerebellar peduncle, right dentato-rubro-thalamic tract, right reticulospinal tract, right inferior longitudinal fasciculus, right cingulum, and right corticobulbar tract were positively correlated with the CRS-R score (FDR = 0.005977) (Table 3). In contrast, the QA values of the left arcuate fasciculus, left inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, left cingulum, anterior commissure, left cerebellum, left corticostriatal pathway, and left optic radiation were negatively associated with the CRS-R score (FDR = 0.002597) (Table 3).

4. Discussion

This study investigated the whole-brain WM group connectometry in patients with DOC and healthy controls. Firstly, we found that the QA was significantly reduced in the deep WM fibers of DOC patients; and interestingly, the patients had significantly higher QA in the bilateral cerebellum compared with healthy controls. Second, the connectometry analysis between patients with MCS and VS/UWS further revealed that the QA values in many tracts of the right hemisphere were higher in

individuals in MCS, and many tracts within the left hemisphere showed higher QA in VS/UWS patients. Finally, we observed that the QA of many tracts in the right hemisphere positively correlated with the CRS-R score; in contrast, many tracts within the left hemisphere showed a negative correlation between QA and CRS-R score, which was in line with the second result.

Our findings demonstrate that the QA of the deep WM fibers was significantly reduced in patients with DOC compared with healthy controls. This is mostly in line with a previous study indicating multiple abnormal WM ROIs in DOC patients compared with normal controls (Wu et al., 2018). The authors identified 14 WM regions in which the fractional anisotropy differed across levels of consciousness using analysis of covariance. Consistent with their findings, the cingulum, corpus callosum, corticospinal tract, and fornix were disrupted in patients with DOC in the current study. In addition to these tracts, we found the QA of the right corticothalamic pathway to be lower in DOC patients than in controls. This observation is in line with a previous literature showing significant differences between WM tracts of the thalamus and DMN brain regions in VS and MCS patients (Fernandez-Espejo et al., 2012), which may provide anatomical substrates for the deficiencies in thalamocortical functional connectivity in DOCs. Moreover, the right inferior fronto-occipital fasciculus tract, which connects the right temporal lobe (medially) and frontal lobe (inferiorally), was found to be impaired in DOC patients. This tract and inferior longitudinal fasciculus share projections at the posterior temporal and occipital lobes and connect visual association areas of the occipital lobe, auditory and visual association areas, and prefrontal cortex (Catani, Dell'acqua, & Thiebaut de Schotten, 2013). The identification of these impairments in our study match well with the primary sensory deficit observed in patients with DOC. In addition, the left

corticopontine tract and bilateral reticulospinal tracts located around the brainstem were associated with the impairment of consciousness in patients with DOC. This has been previously reported in a TBI study showing that impaired brainstem WM integrity is associated with loss of consciousness (Delano-Wood et al., 2015). Finally, the dentato-rubro-thalamic tract originates from the dentate nucleus in the cerebellum and terminates in the contralateral ventrolateral nucleus of the thalamus after decussating to the contralateral red nucleus, which is known to be involved in the control of movement (Kwon et al., 2011). The abnormalities we observed in the left dentato-rubro-thalamic tract in patients with DOC are consistent with abnormal motor skills in these individuals.

The most striking result to emerge from our analyses was the finding that DOC patients had significantly higher QA in the bilateral cerebellum compared with healthy controls. It has been reported that cerebello-thalamic fibers appear to be relatively preserved across DOC patients, with only unilateral damage in one VS patient, whereas all other patients exhibited no differences compared with controls (Stafford, Owen, & Fernandez-Espejo, 2019). In addition, Zhou et al. (2011) also reported partial preservation of functional connectivity between the thalamus and cerebellum at rest in prolonged DOC (J. Zhou et al., 2011). The cerebellum has a well-established role in controlling motor functions, such as coordination, balance, posture, and skilled learning. However, the role of this brain region in non-motor learning is poorly understood (Sendhilnathan, Semework, Goldberg, & Ipata, 2020). Currently, an increasing number of researchers are beginning to study the role of the cerebellum in higher-order functions, such as emotion, language, and cognition (Adamaszek et al., 2017; Baumann et al., 2015; Koziol et al., 2014; Marien et al., 2014). Regarding the biological structure, it connects to multiple brain regions with

different functions, such as the reticular system, brainstem, hypothalamus, limbic system, paralimbic regions, and association and sensorimotor cortices (Schmahmann, 2004). A two-stage feedforward and feedback system was identified from the cerebellar to the cortical areas. The feedforward system originates in the cerebellum, then passes through the deep cerebellar nuclei and projects to the thalamus and cortical regions. The backward system originates in the cortex and projects to the cerebellum through the pons (Stoodley & Schmahmann, 2010). In our study, why the QA values in the cerebellum of DOC patients were higher still needs to be explored in the future.

The connectometry analysis also revealed that in MCS patients, the QA values were higher in many tracts of the right hemisphere, whereas in VS/UWS patients, many tracts in the left hemisphere showed higher QA. This is consistent with previous findings of left-lateralized thalamic (Fernandez-Espejo et al., 2010; Lutkenhoff et al., 2015) and global gray matter (Guldenmund et al., 2016) atrophy in prolonged DOC. Early studies have reported that left-hemispheric damage could lead to a more severe deficit in motor function compared with right-hemispheric damage in patients with focal brain injuries (Haaland & Harrington, 1989; Kimura, 1977; Wyke, 1966, 1967). On the other hand, left-lateralization might be related to defects in language processing, and clinical assessments (such as CRS-R) are more affected by language (Guldenmund et al., 2016; Lutkenhoff et al., 2015). Therefore, further studies are needed to better understand these associations.

Two potential limitations of this study need to be considered. First, the sample size was relatively small. As no metal in any body part was permitted in patients with DOC undergoing 7T MRI scans, very few patients met the inclusion criteria. Patients with large focal lesions were also excluded from the study. Second, some of the

patients with DOC had TBI while others had hypoxic-ischemic encephalopathy; the different pathogenic backgrounds may have influenced our results. Additional studies need to be conducted with larger cohorts and stratification by etiology.

5. Conclusions

In this study, non-invasive ultra-high field (7 T) MRI and group connectometry analyses were used to reveal WM disruptions in DOC. We found that in DOC patients, the QA was significantly reduced primarily in deep WM tracts. Remarkably, we observed significantly higher QA in the bilateral cerebellum of patients with DOC compared with healthy controls. Moreover, the observed lateralization between MCS and VS/UWS patients was in line with the correlation between diffusion connectometry and CRS-R scores. Our findings emphasize the need for further research examining the unique roles of the cerebellum, particularly with regard to DOC patients, and unravel a lateralization of the cerebral hemisphere in the context of this disorder.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate Informed consent was obtained from healthy participants and the legal guardians of the patients to allow them to participate in the study. and for this article to be published.

Consent to Publish Informed consent was obtained from healthy participants and the legal guardians of the patients for this article to be published.

Authors Contributions XT, XZ, and BL were responsible for the study design, literature search, and manuscript drafting. XT, ZZ, and JG were responsible for data collection and statistical analysis. XT, RW, and ZZ were mainly responsible for administrative, technical, or material support. XZ and BL were responsible for the study concept and critical revision. All the authors contributed to editing of the manuscript.

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Competing Interests All the authors declare that they have no conflict of interest.

Availability of data and material The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

Figure legends

Figure 1 Tracks with QA increased in healthy controls compared with DOC patients

The connectometry analysis found corpus callosum, bilateral fornix, bilateral corticospinal tract, bilateral cingulum, right inferior fronto-occipital fasciculus, left corticopontine tract, right cortico-thalamic pathway, bilateral reticulospinal tract, left dentatorubro-thalamic tract showing QA increased in healthy controls compared with DOC patients (FDR = 0.000024). Axial (A) and Coronal (B) view (radiologic

orientation) of the fibers that showed increased QA in healthy controls compared with DOC patients (red color). (C) Brain regions that showed increased QA. The color of the tract depends on the direction of the fibers (red: left-right, green: anterior-posterior, blue: superior-inferior).

Figure 2 Tracks with QA increased in DOC patients compared with healthy controls
The connectometry analysis found left cerebellum and right cerebellum showing QA increased in DOC patients compared with healthy controls (FDR = 0.000094). Axial (A) and Coronal (B) view (radiologic orientation) of the fibers that showed increased QA in DOC patients compared with healthy controls (blue color). (C) Brain regions that showed increased QA. The color of the tract depends on the direction of the fibers (red: left-right, green: anterior-posterior, blue: superior-inferior).

Tables

Table 1 Demographic and clinical characteristics

	DOC	HC	p-value
Number	14	13	NA
Age/years, mean (±SD)	46.9 ± 16.4	40.7 ± 15.9	0.166
Sex, male (%)	85.71%	92.31%	NA
Handedness, right (%)	100%	100%	NA
Diagnosis (MCS/VS/UWS)	6/8	NA	NA
Etiology (TBI /non-TBI)	6/8	NA	NA

Abbreviations: MCS, Minimally Conscious State; VS/UWS, Vegetative State/Unresponsive Wakefulness Syndrome; HIE, Hypoxic Ischemic Encephalopathy; TBI, Traumatic Brain Injury; CRS-R, Coma Recovery Scale-Revised. N/A, not applicable. [b]p-value was obtained using the two-sample two-tailed t-test.

Table 2 Regions with significantly different connectivity in between group comparing of DOC patients with healthy controls

Healthy controls > DOC patients (FDR = 0.000024)	Healthy controls < DOC patients (FDR = 0.000094)
Corpus callosum	Right cerebellum

Bilateral fornix	Left cerebellum
Bilateral corticospinal tract	
Bilateral cingulum	
Right inferior fronto-occipital fasciculus	
Left corticopontine tract	
Right cortico-thalamic pathway	
Left dentatorubro-thalamic tract	
Bilateral reticulospinal tract	

Table 3 Fibers with significantly association with CRS-R in DOC patients

Fibers with positive association with CRS-R in DOC (FDR= 0.005977)	Fibers with negative association with CRS-R in DOC (FDR = 0.002597)
Right inferior fronto-occipital fasciculus	Left arcuate fasciculus
Right corticopontine tract	Left inferior longitudinal fasciculus
Corpus callosum	Left inferior fronto-occipital fasciculus
Bilateral corticospinal tract	Left cingulum
Uncinated fasciculus	Anterior commissure
Middle cerebellar peduncle	Left cerebellum
Right dentatorubrothalamic tract	Left corticostriatal pathway
Right reticulospinal tract	Left optic radiation
Right inferior longitudinal fasciculus	
Right cingulum	
Right corticobulbar tract	

References

Abhinav, K., Yeh, F. C., El-Dokla, A., Ferrando, L. M., Chang, Y. F., Lacomis, D., . . . Fernandez-Miranda, J. C. (2014). Use of diffusion spectrum imaging in preliminary longitudinal evaluation of amyotrophic lateral sclerosis: development of an imaging biomarker. *Front Hum Neurosci, 8*, 270. doi: 10.3389/fnhum.2014.00270

Adamaszek, M., D'Agata, F., Ferrucci, R., Habas, C., Keulen, S., Kirkby, K. C., . . . Verhoeven, J. (2017). Consensus Paper: Cerebellum and Emotion. *Cerebellum, 16*(2), 552-576. doi: 10.1007/s12311-016-0815-8

Andersson, J. L., Skare, S., & Ashburner, J. (2003). How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *Neuroimage, 20*(2), 870-888. doi: 10.1016/S1053-8119(03)00336-7

Basser, P. J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson B,*

111(3), 209-219. doi: 10.1006/jmrb.1996.0086

Baumann, O., Borra, R. J., Bower, J. M., Cullen, K. E., Habas, C., Ivry, R. B., . . . Sokolov, A. A. (2015). Consensus paper: the role of the cerebellum in perceptual processes. *Cerebellum, 14*(2), 197-220. doi: 10.1007/s12311-014-0627-7

Bernat, J. L. (2006). Chronic disorders of consciousness. *Lancet, 367*(9517), 1181-1192. doi: 10.1016/S0140-6736(06)68508-5

Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Ledoux, D., . . . Laureys, S. (2009). Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. *Hum Brain Mapp, 30*(8), 2393-2400. doi: 10.1002/hbm.20672

Catani, M., Dell'acqua, F., & Thiebaut de Schotten, M. (2013). A revised limbic system model for memory, emotion and behaviour. *Neurosci Biobehav Rev, 37*(8), 1724-1737. doi: 10.1016/j.neubiorev.2013.07.001

Crone, J. S., Soddu, A., Holler, Y., Vanhaudenhuyse, A., Schurz, M., Bergmann, J., . . . Kronbichler, M. (2014). Altered network properties of the fronto-parietal network and the thalamus in impaired consciousness. *Neuroimage Clin, 4*, 240-248. doi: 10.1016/j.nicl.2013.12.005

Delano-Wood, L., Bangen, K. J., Sorg, S. F., Clark, A. L., Schiehser, D. M., Luc, N., . . . Bigler, E. D. (2015). Brainstem white matter integrity is related to loss of consciousness and postconcussive symptomatology in veterans with chronic mild to moderate traumatic brain injury. *Brain Imaging Behav, 9*(3), 500-512. doi: 10.1007/s11682-015-9432-2

Fernandez-Espejo, D., Bekinschtein, T., Monti, M. M., Pickard, J. D., Junque, C., Coleman, M. R., & Owen, A. M. (2011). Diffusion weighted imaging distinguishes the vegetative state from the minimally conscious state. *Neuroimage, 54*(1), 103-112. doi: 10.1016/j.neuroimage.2010.08.035

Fernandez-Espejo, D., Junque, C., Bernabeu, M., Roig-Rovira, T., Vendrell, P., & Mercader, J. M. (2010). Reductions of thalamic volume and regional shape changes in the vegetative and the minimally conscious states. *J Neurotrauma, 27*(7), 1187-1193. doi: 10.1089/neu.2010.1297

Fernandez-Espejo, D., Soddu, A., Cruse, D., Palacios, E. M., Junque, C., Vanhaudenhuyse, A., . . . Owen, A. M. (2012). A role for the default mode network in the bases of disorders of consciousness. *Ann Neurol, 72*(3), 335-343. doi: 10.1002/ana.23635

Galanaud, D., Perlbarg, V., Gupta, R., Stevens, R. D., Sanchez, P., Tollard, E., . . . Recovery, C. (2012). Assessment of white matter injury and outcome in severe brain trauma: a prospective multicenter cohort. *Anesthesiology, 117*(6), 1300-1310. doi: 10.1097/ALN.0b013e3182755558

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., . . . Zasler, N. D. (2002). The minimally conscious state: definition and diagnostic criteria. *Neurology, 58*(3), 349-353. doi: 10.1212/wnl.58.3.349

Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys*

Med Rehabil, 85(12), 2020-2029. doi: 10.1016/j.apmr.2004.02.033
Guldenmund, P., Soddu, A., Baquero, K., Vanhaudenhuyse, A., Bruno, M. A., Gosseries, O., . . . Gomez, F. (2016). Structural brain injury in patients with disorders of consciousness: A voxel-based morphometry study. *Brain Inj, 30*(3), 343-352. doi: 10.3109/02699052.2015.1118765
Haaland, K. Y., & Harrington, D. L. (1989). Hemispheric control of the initial and corrective components of aiming movements. *Neuropsychologia, 27*(7), 961-969. doi: 10.1016/0028-3932(89)90071-7
Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *Neuroimage, 62*(2), 782-790. doi: 10.1016/j.neuroimage.2011.09.015
Jennett, B., & Plum, F. (1972). Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet, 1*(7753), 734-737. doi: 10.1016/s0140-6736(72)90242-5
Kimura, D. (1977). Acquisition of a motor skill after left-hemisphere damage. *Brain, 100*(3), 527-542. doi: 10.1093/brain/100.3.527
Koziol, L. F., Budding, D., Andreasen, N., D'Arrigo, S., Bulgheroni, S., Imamizu, H., . . . Yamazaki, T. (2014). Consensus paper: the cerebellum's role in movement and cognition. *Cerebellum, 13*(1), 151-177. doi: 10.1007/s12311-013-0511-x
Kwon, H. G., Hong, J. H., Hong, C. P., Lee, D. H., Ahn, S. H., & Jang, S. H. (2011). Dentatorubrothalamic tract in human brain: diffusion tensor tractography study. *Neuroradiology, 53*(10), 787-791. doi: 10.1007/s00234-011-0878-7
Laureys, S., Celesia, G. G., Cohadon, F., Lavrijsen, J., Leon-Carrion, J., Sannita, W. G., . . . European Task Force on Disorders of, C. (2010). Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. *BMC Med, 8*, 68. doi: 10.1186/1741-7015-8-68
Long, J., Xie, Q., Ma, Q., Urbin, M. A., Liu, L., Weng, L., . . . Huang, R. (2016). Distinct Interactions between Fronto-Parietal and Default Mode Networks in Impaired Consciousness. *Sci Rep, 6*, 38866. doi: 10.1038/srep38866
Lutkenhoff, E. S., Chiang, J., Tshibanda, L., Kamau, E., Kirsch, M., Pickard, J. D., . . . Monti, M. M. (2015). Thalamic and extrathalamic mechanisms of consciousness after severe brain injury. *Ann Neurol, 78*(1), 68-76. doi: 10.1002/ana.24423
Luyt, C. E., Galanaud, D., Perlbarg, V., Vanhaudenhuyse, A., Stevens, R. D., Gupta, R., . . . Recovery, C. (2012). Diffusion tensor imaging to predict long-term outcome after cardiac arrest: a bicentric pilot study. *Anesthesiology, 117*(6), 1311-1321. doi: 10.1097/ALN.0b013e318275148c
Marien, P., Ackermann, H., Adamaszek, M., Barwood, C. H., Beaton, A., Desmond, J., . . . Ziegler, W. (2014). Consensus paper: Language and the cerebellum: an ongoing enigma. *Cerebellum, 13*(3), 386-410. doi: 10.1007/s12311-013-0540-5
Mojtahed Zadeh, M., Ashraf-Ganjouei, A., Ghazi Sherbaf, F., Haghshomar, M., & Aarabi, M. H. (2018). White Matter Tract Alterations in Drug-Naive

Parkinson's Disease Patients With Impulse Control Disorders. *Front Neurol, 9*, 163. doi: 10.3389/fneur.2018.00163

Newcombe, V., Chatfield, D., Outtrim, J., Vowler, S., Manktelow, A., Cross, J., . . . Menon, D. (2011). Mapping traumatic axonal injury using diffusion tensor imaging: correlations with functional outcome. *PLoS One, 6*(5), e19214. doi: 10.1371/journal.pone.0019214

Olvet, D. M., Delaparte, L., Yeh, F. C., DeLorenzo, C., McGrath, P. J., Weissman, M. M., . . . Parsey, R. V. (2016). A Comprehensive Examination Of White Matter Tracts And Connectometry In Major Depressive Disorder. *Depress Anxiety, 33*(1), 56-65. doi: 10.1002/da.22445

Perlbarg, V., Puybasset, L., Tollard, E., Lehericy, S., Benali, H., & Galanaud, D. (2009). Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: a diffusion tensor imaging study using voxel-based approaches. *Hum Brain Mapp, 30*(12), 3924-3933. doi: 10.1002/hbm.20817

Romascano, D., Meskaldji, D. E., Bonnier, G., Simioni, S., Rotzinger, D., Lin, Y. C., . . . Granziera, C. (2015). Multicontrast connectometry: a new tool to assess cerebellum alterations in early relapsing-remitting multiple sclerosis. *Hum Brain Mapp, 36*(4), 1609-1619. doi: 10.1002/hbm.22698

Schilling, K. G., Gao, Y., Stepniewska, I., Janve, V., Landman, B. A., & Anderson, A. W. (2019). Histologically derived fiber response functions for diffusion MRI vary across white matter fibers-An ex vivo validation study in the squirrel monkey brain. *NMR Biomed, 32*(6), e4090. doi: 10.1002/nbm.4090

Schmahmann, J. D. (2004). Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J Neuropsychiatry Clin Neurosci, 16*(3), 367-378. doi: 10.1176/jnp.16.3.367

Sendhilnathan, N., Semework, M., Goldberg, M. E., & Ipata, A. E. (2020). Neural Correlates of Reinforcement Learning in Mid-lateral Cerebellum. *Neuron, 106*(1), 188-198 e185. doi: 10.1016/j.neuron.2019.12.032

Sobhani, S., Rahmani, F., Aarabi, M. H., & Sadr, A. V. (2019). Exploring white matter microstructure and olfaction dysfunction in early parkinson disease: diffusion MRI reveals new insight. *Brain Imaging Behav, 13*(1), 210-219. doi: 10.1007/s11682-017-9781-0

Stafford, C. A., Owen, A. M., & Fernandez-Espejo, D. (2019). The neural basis of external responsiveness in prolonged disorders of consciousness. *Neuroimage Clin, 22*, 101791. doi: 10.1016/j.nicl.2019.101791

Stoodley, C. J., & Schmahmann, J. D. (2010). Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex, 46*(7), 831-844. doi: 10.1016/j.cortex.2009.11.008

Tan, X., Zhou, Z., Gao, J., Meng, F., Yu, Y., Zhang, J., . . . Luo, B. (2019). Structural connectome alterations in patients with disorders of consciousness revealed by 7-tesla magnetic resonance imaging. *Neuroimage Clin, 22*, 101702. doi: 10.1016/j.nicl.2019.101702

Wang, L., Yang, Y., Chen, S., Ge, M., He, J., Yang, Z., . . . Wu, X. (2018). White

matter integrity correlates with residual consciousness in patients with severe brain injury. *Brain Imaging Behav, 12*(6), 1669-1677. doi: 10.1007/s11682-018-9832-1

Weng, L., Xie, Q., Zhao, L., Zhang, R., Ma, Q., Wang, J., . . . Huang, R. (2017). Abnormal structural connectivity between the basal ganglia, thalamus, and frontal cortex in patients with disorders of consciousness. *Cortex, 90*, 71-87. doi: 10.1016/j.cortex.2017.02.011

Wu, X., Zhang, J., Cui, Z., Tang, W., Shao, C., Hu, J., . . . He, Y. (2018). White Matter Deficits Underlying the Impaired Consciousness Level in Patients with Disorders of Consciousness. *Neurosci Bull, 34*(4), 668-678. doi: 10.1007/s12264-018-0253-3

Wyke, M. (1966). Postural arm drift associated with brain lesions in man. An experimental analysis. *Arch Neurol, 15*(3), 329-334. doi: 10.1001/archneur.1966.00470150107016

Wyke, M. (1967). Effect of brain lesions on the rapidity of arm movement. *Neurology, 17*(11), 1113-1120. doi: 10.1212/wnl.17.11.1113

Yeh, F. C., Badre, D., & Verstynen, T. (2016). Connectometry: A statistical approach harnessing the analytical potential of the local connectome. *Neuroimage, 125*, 162-171. doi: 10.1016/j.neuroimage.2015.10.053

Yeh, F. C., Tang, P. F., & Tseng, W. Y. (2013). Diffusion MRI connectometry automatically reveals affected fiber pathways in individuals with chronic stroke. *Neuroimage Clin, 2*, 912-921. doi: 10.1016/j.nicl.2013.06.014

Yeh, F. C., & Tseng, W. Y. (2011). NTU-90: a high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. *Neuroimage, 58*(1), 91-99. doi: 10.1016/j.neuroimage.2011.06.021

Yeh, F. C., Wedeen, V. J., & Tseng, W. Y. (2010). Generalized q-sampling imaging. *IEEE Trans Med Imaging, 29*(9), 1626-1635. doi: 10.1109/TMI.2010.2045126

Zheng, Z. S., Reggente, N., Lutkenhoff, E., Owen, A. M., & Monti, M. M. (2017). Disentangling disorders of consciousness: Insights from diffusion tensor imaging and machine learning. *Hum Brain Mapp, 38*(1), 431-443. doi: 10.1002/hbm.23370

Zhou, J., Liu, X., Song, W., Yang, Y., Zhao, Z., Ling, F., . . . Li, S. J. (2011). Specific and nonspecific thalamocortical functional connectivity in normal and vegetative states. *Conscious Cogn, 20*(2), 257-268. doi: 10.1016/j.concog.2010.08.003

Zhou, Z., Wang, J. B., Zang, Y. F., & Pan, G. (2017). PAIR Comparison between Two Within-Group Conditions of Resting-State fMRI Improves Classification Accuracy. *Front Neurosci, 11*, 740. doi: 10.3389/fnins.2017.00740

Figures

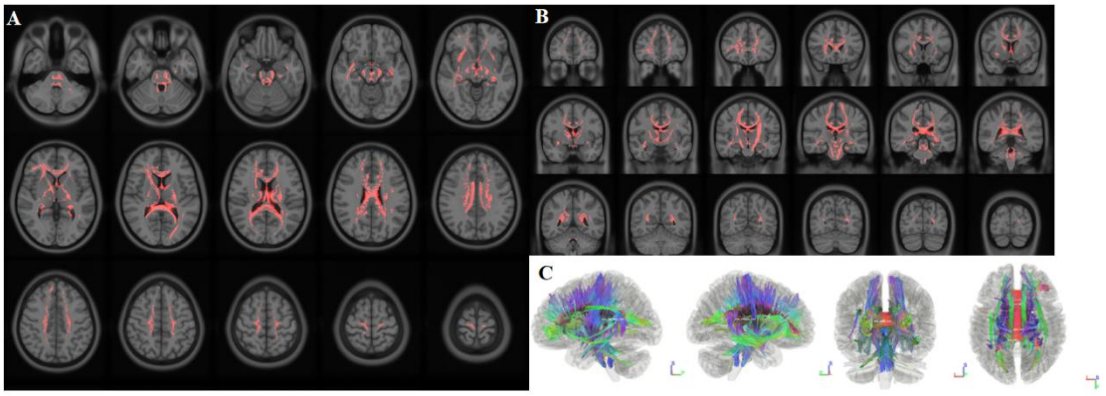


Figure 1 Tracks with QA increased in healthy controls compared with DOC patients

The connectometry analysis found corpus callosum, bilateral fornix, bilateral corticospinal tract, bilateral cingulum, right inferior fronto-occipital fasciculus, left corticopontine tract, right cortico-thalamic pathway, bilateral reticulospinal tract, left dentatorubro-thalamic tract showing QA increased in healthy controls compared with DOC patients (FDR = 0.000024). Axial (A) and Coronal (B) view (radiologic orientation) of the fibers that showed increased QA in healthy controls compared with DOC patients (red color). (C) Brain regions that showed increased QA. The color of the tract depends on the direction of the fibers (red: left-right, green: anterior-posterior, blue: superior-inferior).

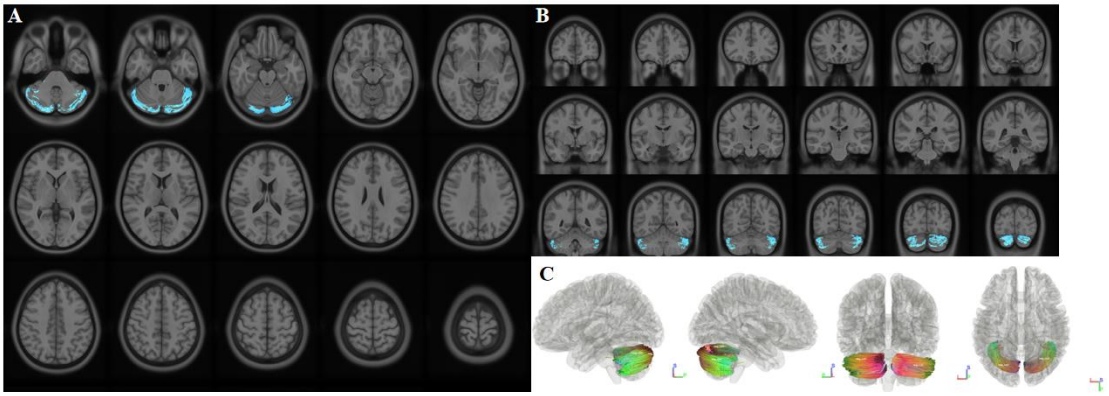
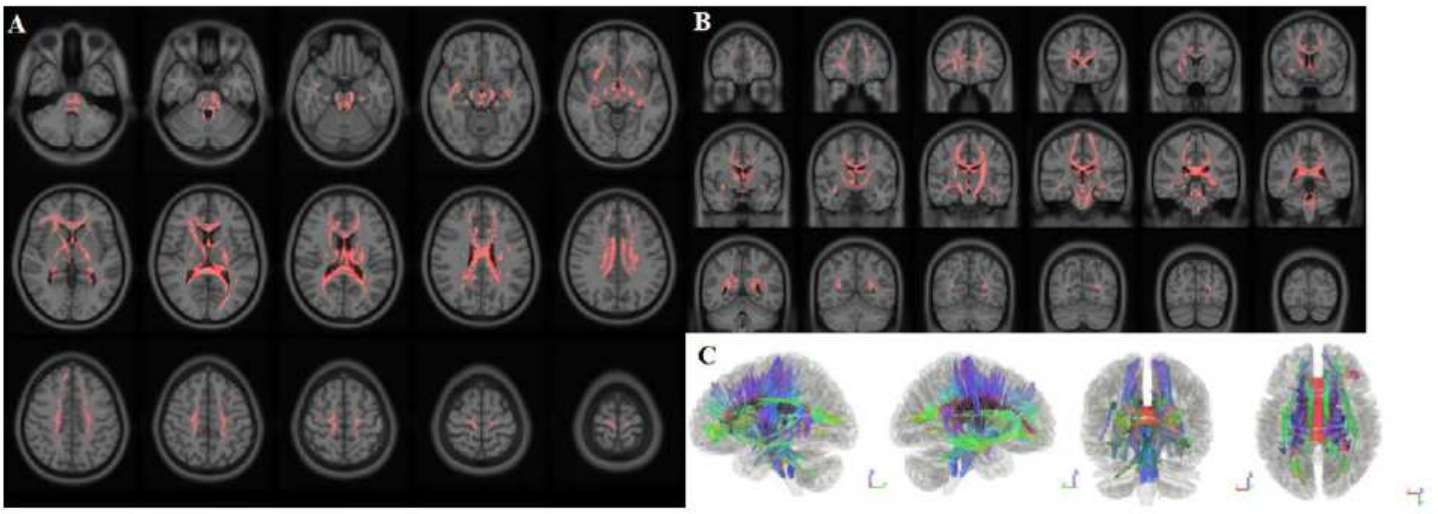


Figure 2 Tracks with QA increased in DOC patients compared with healthy controls

The connectometry analysis found left cerebellum and right cerebellum showing QA increased in DOC patients compared with healthy controls (FDR = 0.000094). Axial (A) and Coronal (B) view (radiologic orientation) of the fibers that showed increased QA in DOC patients compared with healthy controls (blue color). (C) Brain regions that showed increased QA. The color of the tract depends on the direction of the fibers (red: left-right, green: anterior-posterior, blue: superior-inferior).

Figures



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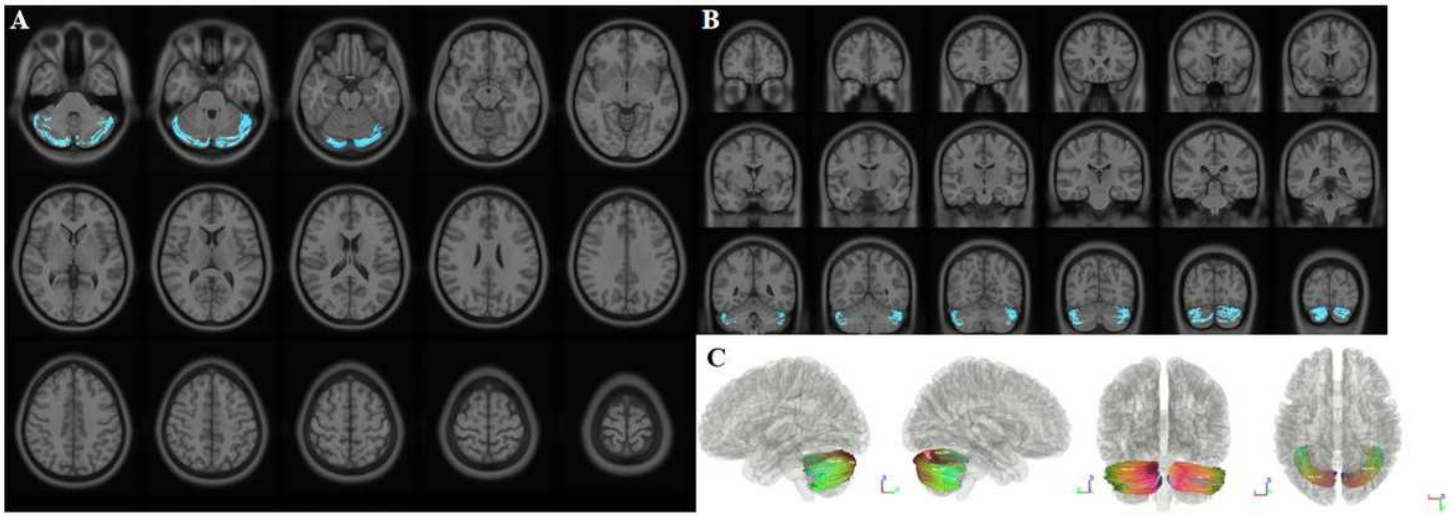

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