**Introduction**

Disorders of consciousness (DOC), including vegetative state/unresponsive wakefulness syndrome (VS/UWS) (Lau-reys 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, over 40% of VS patients may be misdiagnosed by the behavioral scale used in clinic, such as the Coma Recovery Scale-Revised (CRS-R) (Giacino, Kalmar, & Whyte, 2004) which is not
sufficient for the detection of residual consciousness and prognosis of patients with DOC (W. Zheng et al., 2021).

With the development of neuroimaging technology and the diversification of post-processing analysis methods, many researchers have turned to neuroimaging and neuro-electrophysiological techniques to assess brain function and disease prognosis in DOC patients. Functional magnetic resonance imaging (fMRI), an imaging technique that can be used to acquire data from neuronal activities, (Z. Zhou et al., 2020; 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 MRI technique (Basser & Pierpaoli, 1996), which has dramatically improved our understanding of subcortical WM microstructural 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; Perlberg et al., 2009; Velly et al., 2018). 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; Z. S. 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 diffusion MRI (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 patients with DOC.

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

**Methods**

**Participants**

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 Tesla MRI scan. The assessments were performed at a fixed time in the morning when the patients were awake. The VS/MCS diagnosis was identical in the three evaluations. The MRI scan would be postponed if the patient’s consciousness level fluctuated across the three evaluations. 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 or alcohol/drug abuse; (5) no epilepsy or frequent spontaneous movements; (6) no large brain lesion or severe hydrocephalus. We screened thirty-three patients. Among whom 14 patients met the inclusion criteria and participated in
subsequent MRI scanning. Finally, 14 patients with severe brain injuries and 13 healthy volunteers were recruited in this study (see Figure S1 for details).

### Image acquisition

The MRI data were acquired on a Siemens Magnetom 7 Tesla 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/mm², 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/mm²) were also acquired. Whole-brain scanning was performed by using the sagittal T1-weighted 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".

### 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 correction of motion, susceptibility, and eddy current distortion with the FSL’s eddy and topup tools (Anderson, Skare, & Ashburner, 2003).

### Tract-based spatial statistics

Tract-based spatial statistics (TBSS) (Smith et al., 2006) analysis of the diffusion data between patients with DOC and healthy controls was performed as described in our previous study (Tan et al., 2019). A detailed description can be found in the Supplementary materials.

### 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.

### Statistical analysis

IBM SPSS Statistics 22.0 statistical package (SPSS Inc., Chicago, IL) was used to compare demographic differences not only between DOC patients and healthy controls, and also between patients in MCS and VS/UWS. 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. Besides, as the CRS-R total score is not a linear measure, we converted it to the CRS-R index which has a much more linear relation to the level of consciousness (Annen et al., 2019). Partial correlation analysis was conducted to investigate associations between the WM structure metrics and CRS-R index. 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 age, sex, and the duration of DOC status were utilized as covariates. Group connectometry in DSI Studio (http://dsi-studio.labsolver.org) was used for the connectometry analysis.

### Results

### Demographic and clinical information

Fourteen patients with DOC (12 males; age range: 46.9 ± 16.4 years) were enrolled. Six patients were diagnosed with VS (4 males; age range: 48.3 ± 18.8 years), and eight patients were diagnosed with MCS (8 males; age range: 45.8 ± 15.7 years). Thirteen healthy controls were also assessed (12 males; age range: 40.7 ± 15.9 years). No significant difference was found in age between the DOC patients and healthy controls or between patients in MCS and VS/UWS.

| 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) | 8/6 | 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. *p-value was obtained using the two-sample two-tailed t-test
(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.

**Widespread WM disruption in patients with DOC**

Voxel-wise TBSS analysis results of FA and MD differences between the DOC patients and healthy controls are shown in Figure S2. Widespread FA reductions in the WM of DOC patients were observed compared with control subjects. Meanwhile, the same contrast also exhibits higher MD for the patients in almost the entire WM skeleton. Conversely, there were no WM regions that showed higher FA or lower MD in the patients with DOC relative to controls.

**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 cortico-thalamic pathway, bilateral reticulospinal tract, and left dentatorubro-thalamic tract (FDR = 0.000024) (Table 2; Fig. 1). In contrast, compared with healthy controls, DOC patients had significantly higher QA in two WM fibers: bilateral cingulum (FDR = 0.000094) (Table 2; Fig. 2).

**Connectometry analysis between patients in MCS and VS/UWS**

The connectometry analysis between patients with MCS and VS/UWS revealed that the QA values were higher in MCS patients (FDR = 0.000149) (Table 3; Fig. 3) in the corpus callosum, right inferior fronto-occipital fasciculus, left arcuate fasciculus, right cingulum, right uncinate fasciculus, bilateral cortico-pontine tract, bilateral cortico-spinal tract, right fornix, and right cerebellum. In contrast, middle cerebellar peduncle and superior cerebellar peduncle showed higher QA in VS/UWS patients compared to those in MCS (FDR = 0.031250) (Table 3).

**Correlation between diffusion connectometry and CRS-R indexes**

In patients with DOC, the connectometry analysis revealed that the QA values of the right inferior fronto-occipital fasciculus, bilateral cortico-pontine tract, corpus callosum, bilateral cortico-spinal tract, right uncinate fasciculus, middle cerebellar peduncle, right dentato-rubro-thalamic tract, right reticulo-spinal tract, right inferior longitudinal fasciculus, right cingulum, right cerebellum, right cortico-thalamic pathway and anterior commissure were positively correlated with the CRS-R indexes (FDR = 0.008386) (Table 4). In contrast, the QA values of the left arcuate fasciculus, left inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, left cingulum, anterior commissure, left corticostrial pathway, and left optic radiation were negatively associated with the CRS-R indexes. However, these negative correlations found in QA had the FDR > 0.05 (FDR = 0.054318) (Table 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...
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. 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. Finally, we observed that the QA of many tracts in the right hemisphere positively correlated with the CRS-R index, 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 reticulo-spinal 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 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, Sersow, 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). Many researchers have reported that impaired cortico-thalamo-cortical circuitry, especially between thalamus and postero medial, sensorimotor, and frontal cortices (Fernandez-Espejo et al., 2012; Weng et al., 2017), were associated with the level of individual consciousness in patients with DOC (W. Zheng et al., 2020; Z. S. Zheng et al., 2017). Based on these, our results provided the interpretation that this two-stage feedforward and feedback system of the cerebellum might play a complementary role to the impaired cortico-thalamo-cortical circuitry.

The correlation analysis between diffusion connectometry and CRS-R indexes also revealed that the QA values were positively correlated with the CRS-R indexes in many tracts of the right hemisphere. In contrast, the QA values in some tracts in the left hemisphere were negatively associated with the CRS-R indexes, however, the FDR was higher than 0.05 (FDR = 0.054318). The right hemisphere is dominant for awareness (nosognosia), spatial attention, emotional regulation, facial and voice expressions, visual recognition, and topographical orientation (Carota & Bogousslavsky, 2018). Also it was reported that regions of the right hemisphere including fronto-temporal regions were capable of sustaining a sense of self-awareness (Keenan, Rubio, Raclopi, Johnson, & Barnacz, 2005). Furthermore, previous study has shown that the concentration of norepinephrine in the right thalamus is higher than that in the left (Oke, Keller, Mefford, & Adams, 1978). And norepinephrine-dependent activities have the effect of awakening and maintaining attention through sensory perception, which is essential for shaping consciousness. This is more active in the right hemisphere (W. Zheng et al., 2021). Besides, the right dominance of prefrontal activation in DOC patients after stroke and the right laterality of the excitatory interactions in the process of consciousness organization indicated the priority contribution of the right hemisphere to consciousness, which was hampered in DOC patients (Moriya & Sakatani, 2018; Velichkovsky et al., 2018). These findings lead to proposal of two hypotheses: first and foremost, it is assumed that right-hemispheric damage in patients might lead to more serious disorders of consciousness. Secondly, though FDR > 0.05, the increased QA of some fibers in the left hemisphere might be the result of compensation after damage to the right hemisphere. It has been reported that higher QA in some WM tracts was mainly attributed to compensatory mechanisms and formation of small networks in Parkinson’s disease (Sanjari Moghadam, Dolatshahi, Salardini, & Aarabi, 2019). Along with disease progression, the compensatory mechanisms could alter the structural architecture of brain. Another argument is that the emergence of diverse clinical symptoms could partially make changes to these networks. However, since there has been no studies that directly investigated compensatory mechanisms in patients with DOC, further investigations need to be pursued.

Three 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. Besides, the impact of edema on white matter connectometry in DOC patients should be considered. Fiber tracking reconstruction of axonal pathways depend on intervoxel coherence in directional water diffusion, and focal intracellular or extracellular edema may lead to an apparent tract disruption even when the underlying axons are structurally intact. These conditions were considered and minimized in connectometry. The GOI reconstruction minimized the partial volume effect of free or restricted water (Yeh, Verstynen, Wang, Fernandez-Miranda, & Tseng, 2013).

Conclusions

In this study, non-invasive ultra-high field (7 Tesla) 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 indexes. 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.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s11682-022-00668-z.

Author contribution XT, XZ, and BL were responsible for the study design, literature search, and manuscript drafting. XT, ZZ, YY, and JG were responsible for data collection and statistical analysis. XT, RW, YY, 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.

Funding This work was supported by National Key Research and Development Program of China (2018YFA0701400), National Natural Science Foundation of China (81870817, 81701774, and 61771423), the Fundamental Research Funds for the Central Universities (226-2022-00136), Zhejiang Provincial Natural Science Foundation of China (LGF20H090004), Zhejiang Lab (2018EB0ZX01), Key-Area Research and Development Program of Guangdong Province (2018B033330001), Guangzhou Key R&D Program of China (202007030005), Scientific Research Foundation of Zhejiang University City College (J-202224), and MOE Frontier Center for Brain Science and Brain-machine Integration at Zhejiang University.

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.

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.

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

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: https://doi.org/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: https://doi.org/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: https://doi.org/10.1016/S1053-8119(03)00336-7

Ammen, J., Filippini, M. M., Bonin, E., Cassol, H., Aubinet, C., Carrierre, M., & Chatelle, C. (2019). Diagnostic accuracy of the CRS-R index in patients with disorders of consciousness. *Brain Inj*, 33(11), 1409–1412. doi: https://doi.org/10.1080/02699052.2019.1644376

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: https://doi.org/10.1006/jmrb.1996.0086

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

Bernet, J. L. (2006). Chronic disorders of consciousness. *Lancet*, 367(9517), 1181–1192. doi: https://doi.org/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: https://doi.org/10.1002/hbm.20672
Brain Imaging and Behavior (2022) 16:1983–1991

Carota, A., & Bogousslavsky, J. (2018). Minor Hemisphere Major Syndromes. *Front Neurol Neurosci*, 41, 1–13. doi: https://doi.org/10.1159/000475690

Catani, M., Dell’acqua, F., & de Thiebaut, M. (2013). A revised limbic system model for memory, emotion and behaviour. *Neurosci Biobehav Rev*, 37(8), 1724–1737. doi: https://doi.org/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: https://doi.org/10.1016/j.nicl.2013.12.005

Delano-Wood, L., Bangen, K. J., Sorg, S. F., Clark, A. L., Schiebser, 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: https://doi.org/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: https://doi.org/10.1016/j.neuroimage.2010.08.035

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), 353–343. doi: https://doi.org/10.1002/ana.23635

Galanaud, D., Perlberg, V., Gupta, R., Stevens, R. D., Sanchez, P., Tolland, 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: https://doi.org/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: https://doi.org/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: https://doi.org/10.1016/j.apmr.2004.02.033

Jenkinson, M., Beckmann, C. F., Woolrich, M. W., & Smith, S. M. (2012).Fsl. NeuroImage, 62(2), 782–790. doi: https://doi.org/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. *BMC Med*, 8, 68. doi: https://doi.org/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: https://doi.org/10.1038/srep38866

Luyt, C. E., Galanaud, D., Perlberg, 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: https://doi.org/10.1097/ALN.0b013e318275148c

Marien, P., Ackermann, H., Adamszek, 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: https://doi.org/10.1007/s12311-013-0540-5

Mojtabah 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 Impulsive Control Disorders. *Front Neurol*, 9, 163. doi: https://doi.org/10.3389/fneur.2018.001163

Moira, M., & Sakatani, K. (2018). Relation Between Asymmetry of Prefrontal Activity and Autonomic Nervous System in Post-stroke Patients with a Disorder of Consciousness. *Adv Exp Med Biol*, 1072, 53–58. doi: https://doi.org/10.1007/978-3-319-91287-5_9

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

Oke, A., Keller, R., Mefford, I., & Adams, R. N. (1978). Lateralization of norepinephrine in human thalamus. *Science*, 200(4348), 1411–1413. doi: https://doi.org/10.1126/science.663623

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 Connectivity In Major Depressive Disorder. *Depress Anxiety*, 33(1), 56–65. doi: https://doi.org/10.1002/da.22445

Perlberg, V., Puybasset, L., Tolland, 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: https://doi.org/10.1002/hbm.20817

Romascano, D., Meskaldji, D. E., Bonnier, G., Simioni, S., Rotzinger, D., Lin, Y. C., & Granzier, 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: https://doi.org/10.1002/hbm.22698

Sanjari Moghaddam, H., Dolatshabi, M., Salardini, E., & Aarabi, M. H. (2019). Association of olfactory dysfunction with brain microstructure in prodromal Parkinson disease. *Neuroradiology*, 61(2), 283–291. doi: https://doi.org/10.1007/s00234-018-3629-2

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: https://doi.org/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: https://doi.org/10.1176/jnpn.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), 188–198e185. doi: https://doi.org/10.1016/j.neuron.2019.12.032

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., & Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*, 31(4), 1487–1505. doi: https://doi.org/10.1016/j.neuroimage.2006.02.024

Springer
