Functional and structural brain connectivity in disorders of consciousness

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Abstract

Brain connectivity, allowing information to be shared between distinct cortical areas and thus to be processed in an integrated way, has long been considered critical for consciousness. However, the relationship between functional intercortical interactions and the structural connections thought to underlie them is poorly understood. In the present work, we explore both functional (with an EEG-based metric: the median weighted symbolic mutual information in the theta band) and structural (with a brain MRI-based metric: fractional anisotropy) connectivities in a cohort of 78 patients affected with a disorder of consciousness. Both metrics could distinguish patients in a vegetative state from patients in minimally conscious state. Crucially, we discovered a significant positive correlation between functional and structural connectivities. Furthermore, we showed that this structure-function relationship is more specifically observed when considering structural connectivity within the intra- and inter-hemispheric long-distance cortico-cortical bundles involved in the Global Neuronal Workspace (GNW) theory of consciousness, thus supporting predictions of this model. Altogether, these results support the interest of multimodal assessments of brain connectivity in refining the diagnostic evaluation of patients with disorders of consciousness.

Keywords: Consciousness, disorders of consciousness, functional connectivity, structural connectivity, global neuronal workspace.

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Published in *Brain Structure and Function*: Altmayer, V., Sangare, A., Calligaris, C. *et al.* Functional and structural brain connectivity in disorders of consciousness. *Brain Struct Funct* (2024) doi:10.1007/s00429-024-02839-8

Abbreviations:

ABI: Acute Brain Injury
AUC: Area Under the Curve
CRS-R: Coma Recovery Scale-Revised
DoC: Disorders of Consciousness
DTI: Diffusion Tensor Imaging
FA: Fractional Anisotropy
fMRI: functional Magnetic Resonance Imaging
GNW: Global Neuronal Workspace
ICU: Intensive Care Unit
MCS: Minimally Conscious State
$mWSMI_0$: median Weighted Symbolic Mutual Information in the theta EEG-band
sd: standard deviation
VS/UWS: Vegetative State / Unresponsive Wakefulness Syndrom

Introduction

Despite significant progress in the study of consciousness over the past three decades, driven notably by advances in neuroimaging and neurophysiological techniques, the neural correlates of consciousness, i.e. of the ability to process, reason and report on external or internal information in the presence of a preserved arousal(Naccache 2018), are still a matter of debate. Indeed, various theoretical models have been proposed to account for the mechanisms of conscious access.(Dehaene et al. 2011; Seth and Bayne 2022) Nevertheless, most of these models tend to agree on the critical role of brain connectivity, allowing information to be broadcasted and shared between distant brain regions, and thus to be processed in an integrated way.(Tononi and Edelman 1998; Dehaene and Changeux 2011; Seth and Bayne 2022) Brain connectivity relies on a complex anatomical network and can be studied using both functional and structural markers. Functional connectivity, classically explored using functional magnetic resonance imaging (fMRI) or EEG, refers to the functional coupling of brain regions' activity across time. Results from various studies point to the critical role of functional connectivity between heteromodal associative cortices in conscious access, particularly between the prefrontal and parietal associative cortices.(Del Cul et al. 2007; Bartolomei and Naccache 2011; Jordan et al. 2013; Silva et al. 2015; Warnaby et al. 2016; Ranft et al. 2016; Huang et al. 2018; Demertzi et al. 2019; Mashour et al. 2020) On the other hand, structural connectivity markers allow to explore the integrity of anatomical bundles. Using diffusion tensor imaging (DTI), several studies have reported impairments of consciousness in the case of white matter lesions, i.e., neuronal connections damage(de Schotten et al. 2005; Reuter et al. 2007, 2009; Weng et al. 2017; Berkovitch et al. 2017; Has Silemek et al. 2021), and more specifically in the case of anatomical lesions affecting long-distance cortico-cortical associative bundles.(de Schotten et al. 2005; Reuter et al. 2009; Weng et al. 2017; Berkovitch et al. 2017)

Overall, these results appear to be primarily consistent with the Global Neuronal Workspace (GNW) theory, for which the long-distance propagation of processed information is a key element. Indeed, according to the GNW model, conscious access requires the coherent functional activation of different multimodal associative cortices. These cortices are hypothesized to be recruited by long-distance neuronal connections, in particular by the prefronto-posterior bundles, that allow the diffusion and efficient sharing of information between the different regions involved, thus enabling the integrated conscious processing of this information.(Dehaene 2001; Dehaene and Changeux 2011; Dehaene et al. 2014; Mashour et al. 2020) However, the structure-function relationship hypothesis proposed by this model remains to be tested. More generally, while it is commonly accepted that functional brain connectivity is shaped by anatomical structural connectivity, the exact relationship between structure and function may vary substantially and is not as straightforward as one might expect. Indeed, regions with little anatomical connectivity may show strong functional connectivity, thus necessarily connecting in an indirect way at the anatomical level.(Honey et al. 2009; Damoiseaux and Greicius 2009; Chu et al. 2015; Suárez et al. 2020) Studies focusing on the relationship between the structural networks critical for consciousness and the long-distance functional connectivity thought to underlie it are scarce. In one single study, Bodart and colleagues were able to show, in 24 subjects with altered consciousness, a correlation between global cerebral white matter integrity (fractional anisotropy) and a functional EEG marker of duration and complexity of the neural response (perturbational complexity index) to a transcranial magnetic stimulus.(Bodart et al. 2018) Although interesting, these results remain incomplete as they are unspecific and do not allow precise structural correlates of the functional marker of consciousness.

In this study, we aimed to clarify the relationship between the functional connectivity supporting conscious access and the structural network thought to underlie it, with respect to the GNW hypothesis. To do so, we explored functional and structural connectivity in patients with disorders of consciousness (DoC), clinically diagnosed either in a minimally conscious state (MCS) or in a vegetative state, also known as unresponsive wakefulness syndrome (VS/UWS). MCS and VS/UWS are characterized by preserved clinical signs of wakefulness, with or without slight clinical signs suggestive of conscious access,

respectively.(Giacino 2004) Functional connectivity was measured using the mWSMI$_\theta$ (median weighted symbolic mutual information in the theta EEG band), a scalp EEG marker shown to be one of the most robust and precise for indexing states of consciousness in healthy subjects(Imperatori et al. 2019; Bourdillon et al. 2020) as well as in DoC patients.(King et al. 2013; Sitt et al. 2014; Corazzol et al. 2017; Engemann et al. 2018) Moreover, prior research(King et al. 2013) has indicated that mWSMIθ predominantly reflects connectivity between medium-to-long distance cortico-cortical connections, which are hypothesized to exert a causal influence on the functional architecture of the GNW. Structural connectivity was assessed by the fractional anisotropy (FA) of deep white matter bundles, an indirect measure of their integrity(Basser and Pierpaoli 1996), shown to be strongly correlated with the functional prognosis of patients with impaired consciousness.(Galanaud et al. 2012; Luyt et al. 2012; Velly et al. 2018; Enciso-Olivera et al. 2021) After ensuring the relevance of the selected connectivity markers (mWSMI$_\theta$ and FA) to index the patients' state of consciousness, we explored the relationship between functional and structural connectivity at different brain levels. We first explored the correlation between these two aspects of connectivity at a global brain level. Secondly, following the predictions of the GNW model, we used a theory-based approach to test the hypothesis that global functional connectivity would show a stronger correlation with structural connectivity within a group of white matter tracts selected for their postulated role in the GNW.(de Schotten et al. 2005; Dehaene and Changeux 2011; Berkovitch et al. 2017; Mashour et al. 2020) The white matter tracts were categorized a priori as part of the GNW network when involved in long-distance connectivity between associative cortical areas(Mori et al. 2008), both inter-hemispherically with the corpus callosum (CC), and intra-hemispherically with the superior longitudinal (SLF), inferior longitudinal and fronto-occipital (ILF-IFOF), superior fronto-occipital (SFOF), uncinate (UNC), and cingulate (Cing, extra-hippocampal) fasciculi. Finally, to complete the results of the first approach and to avoid overlooking a potentially important role for consciousness of one of the tracts not selected a priori as part of the GNW network, we conducted a data-driven exploration of the relationship between global functional connectivity and the structural connectivity within each of the deep white matter bundles of the brain.

Materials and Methods

Patients

Patients suffering from DoC were prospectively enrolled between 2009 and 2019 in the Neurological Intensive Care Unit (ICU) of Pitié-Salpêtrière Hospital in Paris (France), where they were admitted for an expert assessment of consciousness and neuroprognosis. As part of the routine evaluation, patients were eligible for a multimodal high-density EEG recording and a multimodal brain MRI acquisition including DTI. In addition, several formalized clinical assessments of patients were carried out during their ICU stay, using the Coma Recovery Scale-Revised (CRS-R)(Giacino et al. 2004; Schnakers et al. 2008), from which patients' clinical state of consciousness was determined. Clinical CRS-R evaluations were performed by trained clinicians, at least 24 hours after sedation cessation. For this study, only the CRS-R performed on the same day as the EEG recording was considered. All patients clinically diagnosed in MCS or VS/UWS and having benefited from both an evaluation of functional connectivity by EEG, and an evaluation of structural connectivity by DTI were enrolled in the study unless the delay between EEG and MRI acquisitions was superior to 30 days, to guarantee the relevance of their comparative and combined analysis.
This study was approved by the institutional review board of the Pitié-Salpêtrière University Hospital (PSL – 2023 – R – CONS-CONNECT), in agreement with the French data protection authority (MR004).

Functional connectivity assessment: mWSMI$_\theta$

Functional connectivity was explored by measuring the *median weighted mutual symbolic information* in the theta (θ) EEG frequency band, or mWSMI$_\theta$, a mathematical index developed by King *et al*.(King et al. 2013) to measure medium-to-long distance cortico-cortical connectivity. A detailed description of this biomarker, ranging from 0.08 to

0.1 in healthy subjects(King et al. 2013; Sitt et al. 2014), is available in Online Resource 1.

The $mWSMI_{\theta}$ was computed on high-density EEG recordings obtained with a 256-electrodes geodesic sensor net (Electrical Geodesics Inc, EGI, Oregon, USA). As for the reference CRS-R clinical evaluations carried out on the same day, EEG recordings were recorded at least 24 hours after the cessation of any sedation to allow a reliable assessment of functional connectivity. Other drugs that could potentially influence the EEG, such as myorelaxants or anti-epileptic drugs, were maintained when needed. EEG recordings were performed by trained clinicians and the quality and nature of the ongoing electrical activity were verified before starting the recording. Patients that showed seizures or any identifiable abnormal activity were not recorded. To fit with the reference article describing $mWSMI_{\theta}$(King et al. 2013), EEG recordings were performed during the 'local-global' auditory protocol designed to elicit event-related potentials that help assess patients' state of consciousness.(Bekinschtein et al. 2009) Full experimental design and preprocessing are described in Online Resource 1.

Structural connectivity assessment: Fractional Anisotropy

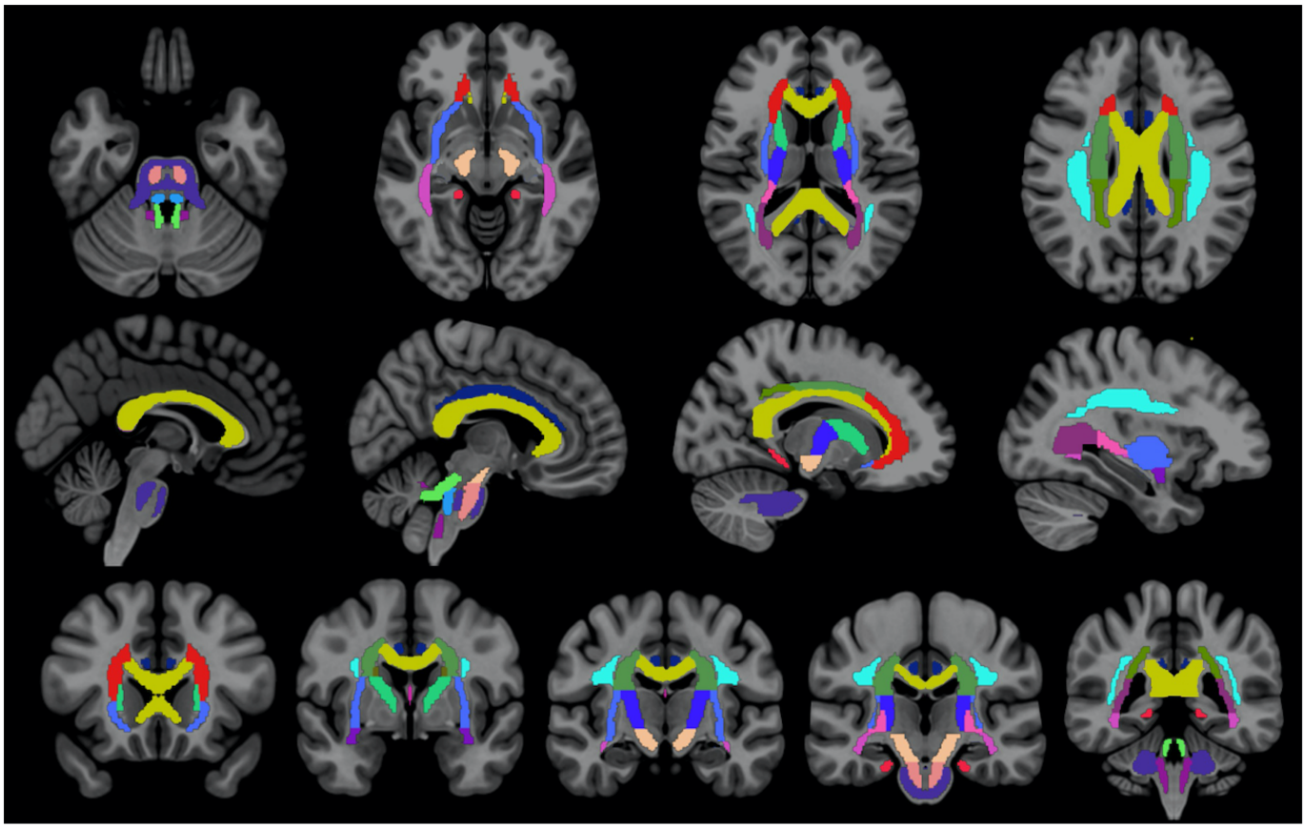
Structural connectivity was explored by measuring *fractional anisotropy* (FA), a commonly used DTI parameter assessing the level of diffusion restriction of water molecules in a given tissue, normalized between zero (isotropic diffusion = unrestricted) and one (anisotropic diffusion = restricted to one single direction). In the brain's white matter tracts, where water molecules are highly constrained in the direction of the axonal fibres, FA can thus be used as an approximation of fibres' integrity, with a FA close to one in healthy fibres, while lowered in the event of fibre damage, disrupting the directed diffusion of water molecules.(Basser and Pierpaoli 1996)

FA was obtained from the DTI sequence acquired as part of the clinical routine multimodal brain MRI performed in patients as soon as their clinical condition allowed it. During the MRI acquisition, patients were accompanied by a physician, sedated and mechanically ventilated if necessary, and vital signs were continuously monitored. Magnetic resonance images were acquired on 1.5 or 3 Tesla magnetic resonance machines (General Electric Healthcare, Velizy, France). Full scanning parameters are available in Online Resource 1.

DTI images were preprocessed using a validated method(Van Der Eerden et al. 2014; Puybasset et al. 2022) based on brainQuant Software (www.braintale.eu; research version 2.0), described in Online Resource 1. After eddy-current and motion corrections, FA maps were registered to the deep white matter ICBM-DTI-81 atlas defined in the MNI space (Mori et al. 2008), describing 56 deep white matter bundles that were gathered into 21 regions of interest for this study (Figure 1, Online Resource 1). This registration used a nonlinear approach, allowing to account for individual brain deformations related to the acute brain injury. FA values could thus be extracted at several topographical levels:

- The 'global FA' was calculated as the mean FA per voxel within all white matter ROIs
- The 'GNW FA' was calculated as the mean FA per voxel within a group of deep white matter bundles selected a priori for their involvement in the GNW network by three DoC experts (L.N, JD.S, and B.R) blinded to clinical, EEG and MRI data, based on the reference literature on the topic.(Wakana et al. 2004; Mori et al. 2008; Dehaene and Changeux 2011; Mashour et al. 2020) The selected tracts were those involved in long-distance cortico-cortical connectivity both at the intra-hemispheric (SLF, ILF-IFOF, SFOF, UNC, and Cing) and inter-hemispheric levels (CC) (Fig. 1). Conversely, the mean FA per voxel within the group of unselected tracts also calculated as the 'non-GNW FA'.
- The mean FA per voxel was calculated for each of the 21 predefined white matter tracts

The above processing and all subsequent MRI data analyses were performed by investigators blinded to clinical information.



Abbreviations	White Matter tracts
Brainstem	
CST	Corticospinal tract
mLEM	Medial lemniscus
ICP	Inferior cerebellar peduncle
MCP	Middle cerebellar peduncle
SCP	Superior cerebellar peduncle
Projection fibers	
ACR	Anterior corona radiata
SCR	Superior corona radiata
PCR	Posterior corona radiata
ALIC	Anterior limb of internal capsule
PLIC	Posterior limb of internal capsule
RLIC	Retrolenticular part of the internal capsule
CP	Cerebral peduncle
PTR	Posterior thalamic radiation

Abbreviations	White Matter tracts
Commissural fibers	
CC	Corpus callosum
Associative fibers	
SLF	Superior longitudinal fasciculus
SFOF	Superior fronto-occipital fasciculus
UNC	Uncinate fasciculus
ILF-IFOF	Inferior longitudinal fasciculus – Inferior fronto-occipital fasciculus
EC	External capsule
Cing	Cingulum
Cing_h	Cingulum (hippocampus)

Fig. 1 Anatomical distribution of the 21 deep white matter tracts of interest

Automatically segmented white matter ROIs for measurement of fractional anisotropy (*adapted from Mori et al.*(Mori et al. 2008)) are displayed on a standardized MNI template of a healthy brain. The red frame indicates the white matter tracts selected a priori as critical for consciousness according to the Global Neuronal Workspace theory.

Statistical analyses

All statistical analyses were performed using R software (4.1.2 version, https://cran.r-project.org/). We used an alpha risk of 0.05 to determine the significance of all tests.

Between-group differences for continuous variables were tested using two-tailed Mann-Whitney *U*-test, and the effect size was reported using the rank-biserial correlation *r* coefficient for significant results. Intergroup differences for categorical variables were tested using the Chi-square ($\chi 2$) test.

Two-way parametric ANOVAs were used to study how the ability of each studied connectivity parameter to distinguish between clinical status was robust to variability in aetiology or in delay since acute brain injury (ABI). Post hoc comparisons were made using the Tukey test.

Direct logistic regression models were used to explore the diagnostic performance of the different connectivity markers and of their combination to predict the state of consciousness of patients (i.e.: MCS versus VS/UWS). Goodness-of-fit of the models are reported using $\chi 2$ statistics, and models' performance using the AUC, sensitivity and specificity based on repeated stratified k-fold cross-validations with 10 iterations and 5 folds.

Between-models diagnostic performances were compared using Chi-square ($\chi 2$) tests comparing their deviance in the case of nested models (reporting the residual deviance), i.e., when comparing a model with a single predictor ($mWSMI_\theta$ or FA) with another model containing this predictor and another one; and using Vuong's z-test in the case of non-nested models (reporting z statistic).(Vuong 1989)

Positive correlations between functional connectivity and structural connectivity were explored using one-sided Spearman's rho (ρ) coefficients. We partialled out potential confounding effects of demographic variables: age, gender, aetiology (using four dummy variables) and ABI-EEG, ABI-MRI and EEG-MRI delays. When exploring multiple correlations, a Benjamini-Hochberg statistical correction was applied. The hypotheses that the correlation between functional connectivity and structural connectivity is higher when studied within the GNW network than when studied outside or when studied at a global brain level were tested using a unilateral Meng's z-test.(Diedenhofen and Musch 2015)

Results

Patients

One hundred and eight DoC patients in MCS or VS/UWS had both high-density EEG recording and DTI acquisition. Among them, 25 patients were excluded due to a delay superior to 30 days between MRI and EEG. Of the remaining 83 patients, five other patients were excluded due to technical issues during the regional FA extraction procedure. Finally, 78 patients (41 MCS and 37 VS/UWS) were included in the present study. Demographics are described in Table 1. Men were more represented than women (68% men, $\chi 2 = 10.05$, $P = 0.002$). Aetiologies of the alteration of consciousness corresponded to those classically encountered in DoC and were evenly distributed between the two groups except for cerebral anoxia, more frequent in VS/UWS patients, and for traumatic brain injury, more frequent in MCS patients (Table 1).

Clinical state of consciousness and brain connectivity

We first checked that both global functional ($mWSMI_\theta$) and structural (FA) connectivity markers, considered each in isolation, could discriminate MCS versus VS/UWS patients.

EEG-based functional connectivity is higher in MCS than in VS/UWS patients

Patients in MCS showed higher values of $mWSMI_\theta$ than patients in VS/UWS (mean ± sd = 0.0788 ± 0.0033 versus 0.07790 ± 0.0028; $U = 959.00$; $P = 0.045$; $r = 0.26$). A logistic regression confirmed that $mWSMI_\theta$ predicted the clinical status of patients ($\chi 2(76) = 4.02$; $P = 0.045$; $AUC = 0.631$, specificity = 0.68, sensitivity = 0.41).

We then tested how the ability of $mWSMI_\theta$ to distinguish between clinical status was robust to variability in delays since initial ABI (ABI-EEG delay) or in ABI aetiologies, respectively. First, patients were separated into three groups depending on whether their EEG acquisition was recorded after an acute (< 25 days), intermediate (25-50 days), or chronic (> 50 days) delay. The 2x3 ANOVA across clinical status and ABI-EEG delay found a main effect of the

Table 1: Demographic and clinical characteristics of patients

	Total (***n*** **= 78)**	**VS/UWS** (***n*** **= 37)**	**MCS** (***n*** **= 41)**	**Group comparison**
Gender (women)	25 (32%)	9 (24%)	16 (39%)	$\chi 2 = 1.93$; $P = 0.165$
Age (years)	43.7 (18.1)	44.2 (17.6)	43.3 (18.8)	$U = 737.00$; $P = 0.835$
ABI – EEG delay (days)	103.8 (297.9)	103.3 (270.2)	104.3 (324.1)	$U = 772.50$; $P = 0.893$
- Acute	21 (27%)	11 (14%)	10 (13%)	$\chi 2 = 0.28$; $P = 0.596$
- Intermediate	32 (41%)	13 (17%)	19 (24%)	$\chi 2 = 1.01$; $P = 0.315$
- Chronic	25 (32%)	13 (17%)	12 (15%)	$\chi 2 = 0.31$; $P = 0.579$
ABI – MRI delay (days)	104.2 (298.1)	104.0 (270.3)	104.3 (324.5)	$U = 767.00$; $P = 0.936$
- Acute	21 (27%)	13 (17%)	8 (10%)	$\chi 2 = 2.41$; $P = 0.120$
- Intermediate	31 (40%)	11 (14%)	20 (26%)	$\chi 2 = 2.95$; $P = 0.086$
- Chronic	26 (33%)	13 (17%)	13 (17%)	$\chi 2 = 0.10$; $P = 0.748$
EEG – MRI delay	0.9 (10.1)	1.1 (8.8)	0.8 (11.2)	$U = 699.50$; $P = 0.561$
ABI aetiology				
- Anoxia	40 (51%)	25 (68%)	15 (37%)	$\chi 2 = 7.47$; $P = 0.006$
- Traumatic brain injury	16 (21%)	4 (11%)	12 (29%)	$\chi 2 = 4.06$; $P = 0.044$
- Stroke	10 (13%)	2 (5%)	8 (20%)	$\chi 2 = 3.46$; $P = 0.063$
- Others	12 (15%)	6 (16%)	6 (15%)	$\chi 2 = 0.12$; $P = 0.731$

Results are expressed as mean (standard deviation) or number (%)
Significant differences between the two groups are shown in bold

clinical status ($F(1,72) = 4.66$; $P = 0.034$). No significant effect of the ABI-EEG delay ($F(2,72) = 0.52$; $P = 0.596$) nor significant interaction ($F(2,72) = 1.52$; $P = 0.225$) were found. A descriptive plot of this ANOVA is provided in Fig. S3A. Secondly, we performed a 2x4 ANOVA across clinical status and ABI aetiology (anoxia, TBI, stroke, or other aetiologies), which did not show a significant effect of the clinical status ($F(1,70) = 0.50$; $P = 0.483$), nor of ABI aetiology ($F(3,70) = 2.18$; $P = 0.098$), nor of their interaction ($F(3,70) = 0.35$; $P = 0.787$). The descriptive plot (Fig. S3B) of this ANOVA suggested that the absence of a significant main effect may be related to a lack of sensitivity in the 'Other aetiologies' group when compared to anoxia, TBI, or stroke.

MRI-based global structural connectivity is higher in MCS than in VS/UWS patients

Patients in MCS showed higher values of global FA than patients in VS/UWS (mean ± sd = 0.83 ± 0.10 versus 0.70 ± 0.15; $U = 1168.50$; $P < 0.001$; $r = 0.54$). Integrity of global structural connectivity predicted clinical status ($\chi 2(76) = 19.47$; $P < 0.001$, specificity = 0.79, sensitivity = 0.58) with an *AUC* of 0.768. This discriminative performance was higher than that of the $mWSMI_{\theta}$ ($z = 01.92$; $P = 0.027$). We then tested how the discriminative performance of FA in distinguishing between clinical status was robust to variability in delays since initial ABI (ABI-EEG delay) or in ABI aetiologies, respectively. We found a main effect of the clinical status ($F(1,72) = 23.05$; $P < 0.001$) with a significant post-hoc contrast ($t = 4.80$; $P_{tukey} < 0.001$). We also found a main effect of the ABI-MRI delay ($F(2,72) = 4.36$; $P = 0.016$), with a lower global FA in patients evaluated chronically than in those evaluated acutely ($t = 2.82$; $P_{tukey} = 0.017$), while contrasts in FA between patients evaluated after an intermediate delay and those evaluated acutely ($t = 0.92$; $P_{tukey} = 0.631$) or chronically ($t = -2.11$; $P_{tukey} = 0.095$) were not significant. There was no interaction between clinical status and ABI-MRI delay ($F(2,72) = 0.01$; $P = 0.988$). Finally, we also conducted an ANOVA across clinical state of consciousness and ABI aetiology, finding a main effect of the clinical status ($F(1,70) = 9.98$; $P = 0.002$), with no significant effect of the aetiology ($F(3,70) = 2.17$; $P = 0.100$) and no significant interaction ($F(3,70) = 0.95$; $P = 0.421$). Descriptive plots of both ANOVAs are provided in figure S3C and S3D.

Brain connectivity and level of consciousness: the relationship between structure and function

Global functional and structural connectivities are positively correlated

As predicted, a significant positive correlation was observed between $mWSMI_\theta$ and global FA ($\rho = 0.24$; $P = 0.024$; 95% CI [0.01, 0.46]; Fig. 2). When combined in a logistic regression model, $mWSMI_\theta$ and global FA predicted patient's clinical status (MCS versus VS/UWS; $\chi 2(75) = 20.64$; $P < 0.001$, specificity = 0.76, sensitivity = 0.62) with an *AUC* of 0.770. This performance was significantly higher than the regression model including $mWSMI_\theta$ only (residual deviance = 16.62; $p < 0.001$), and superior without reaching significance (residual deviance = 1.17; $p = 0.280$) to the regression model including global FA only.

Structure-function correlation is stronger within the Global Neural Workspace

We then analysed structural connectivity at a more fine-grained level, by exploring FA within the group of white matter tracts selected a priori as part of the GNW network. Crucially, a significant positive correlation between $mWSMI_\theta$ and mean FA within the GNW bundles ($\rho = 0.30$; $P = 0.005$; 95% CI [0.08, 0.51]), which was significantly greater than the correlation coefficient between $mWSMI_\theta$ and global FA ($z = 2.37$; $P = 0.009$), as well as greater ($z = 2.36$; $P = 0.009$) than the correlation between $mWSMI_\theta$ and mean FA outside the GNW ($\rho = 0.23$; $P = 0.025$; 95% CI [0.01, 0.47]).

When combined in a logistic regression model, GNW FA and $mWSMI_\theta$ discriminated MCS and VS/UWS patients ($\chi 2(75) = 20.99$; $P < 0.001$, specificity = 0.78, sensitivity = 0.62) with a higher performance (*AUC* = 0.775) than that of the model based on global FA and $mWSMI_\theta$, however without reaching statistical difference ($z = 0.31$; $P = 0.378$). Of note, the model based on GNW FA only also discriminated MCS and VS/UWS patients ($\chi 2(76) = 20.22$; $P < 0.001$, specificity = 0.80, sensitivity = 0.60), again with a higher performance (*AUC* = 0.773) than the model based on global FA only, although without significant difference ($z = 0.58$; $P = 0.280$).

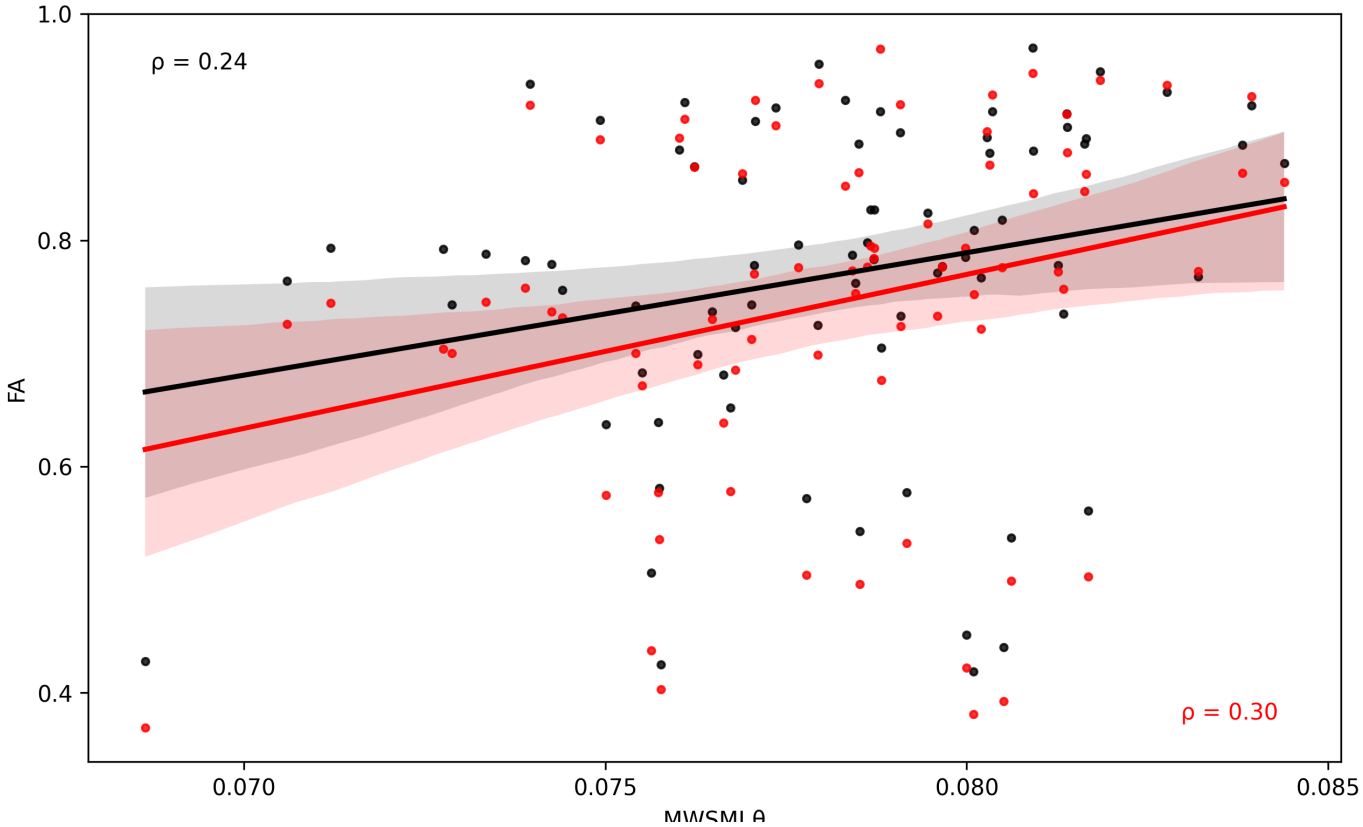


Fig. 2 Correlation between global functional connectivity ($mWSMI_\theta$) and structural connectivity (FA) at a global scale (black) or within the Global.
Shaded zones indicate the 95% confidence level intervals of the regression lines.

Structure-function correlation is stronger in long distance associative deep white matter bundles

Finally, to ensure the validity of our theory-based approach and to prevent disregarding a potentially important role of non-GNW white matter tracts in consciousness, we analysed the correlations between $mWSMI_{\theta}$ and FA within each deep white matter tract of interest. After Benjamini-Hochberg correction for multiple correlations, we observed a positive correlation between the global $mWSMI_{\theta}$ and FA within all tracts belonging to the GNW (SLF, UNC, ILF-IFOF, cingulum, corpus callosum) apart from the SFOF, and additionally between global $mWSMI_{\theta}$ and FA within the posterior corona radiata and within the cerebral peduncles (Table 2).

Table 2: Correlations between $mWSMI_{\theta}$ and FA within each of the 21 deep white matter tracts of interest

Discussion

In this study, we explored two different measures of brain connectivity, one functional and the other structural, in the context of DoC. We first confirmed the interest of assessing both medium-to-long distance functional connectivity and deep brain white matter structural connectivity for the diagnosis of patients' level of consciousness, for which they seem to provide complementary information. We then explored the relationship between these two types of connectivity, and showed a modest positive correlation between functional and structural connectivities. Finally, we highlighted that this correlation is stronger when considering structural connectivity within the intra- and inter-hemispheric long-distance cortico-cortical bundles involved in the Global Neuronal Workspace (GNW) theory of consciousness, thus supporting predictions of this model.

Brain connectivity as a diagnostic tool for disorders of consciousness

Global medium-to-long distance functional connectivity indexes states of consciousness

According to several theoretical models, conscious access requires the efficient broadcasting of information between several brain areas.(Tononi and Edelman 1998; Dehaene and Changeux 2011; Seth and Bayne 2022) In particular, the GNW theory assumes that conscious access to information relies on the global and stable diffusion of this information, allowing its simultaneous processing by different cortical areas distant from each other.(Dehaene et al. 1998; Dehaene 2001; Mashour et al. 2020) In line with this prediction, we showed in this work that $mWSMI_{\theta}$, a functional connectivity index derived from scalp EEG and estimating the global amount of information shared by distant brain areas, is higher in minimally conscious state (MCS) patients than in vegetative state (VS) patients. $mWSMI_{\theta}$ thus indexed the clinical status of patients, and this regardless of the delay between brain injury and clinical and EEG assessments. These results confirmed previous studies establishing $mWSMI_{\theta}$ as a marker of consciousness that can be helpful in clinical practice.(King et al. 2013; Sitt et al. 2014; Corazzol et al. 2017; Engemann et al. 2018; Imperatori et al. 2019; Comanducci et al. 2020; Bourdillon et al. 2020) However, it is important to note that the ability of $mWSMI_{\theta}$ to distinguish between clinical status was not robust to variability in aetiologies. Our data suggest that this diagnostic tool may be more informative for the most common aetiologies of disorders of consciousness (i.e. anoxia, TBI, stroke) than in more infrequent ones, as supported by previous research. (King et al. 2013) Hence, future research exploring the diagnostic value of $mWSMI_{\theta}$ separately for distinct aetiologies might be useful to refine its application and enable more personalized diagnostic and prognostic procedures.

Global structural connectivity indexes states of consciousness

If the sharing of information between distant brain areas is necessary for that information to be processed consciously, then the integrity of the anatomical structures allowing the cerebral diffusion of information should also be critical for conscious access. However, the relation between brain structural connectivity and the prediction of consciousness remains poorly investigated.(Fernández-Espejo et al. 2011, 2012; Weng et al. 2017) In this work, we were able to show

for the first time that the global integrity of the brain's main deep white matter tracts, measured by the global FA, allows to discriminate patients in MCS from those in VS, in whom it is more affected. Interestingly, global FA was more reduced when assessed after a chronic (> 50 days) than after an acute (< 25 days) delay, probably due to the continuation of white matter degeneration processes long after the brain injury.(Conforti et al. 2014) Nevertheless, global FA remained capable of indexing the clinical status of patients regardless of the delay of acquisition since the brain injury. Finally, FA was also able to index the clinical status of patients independently of DoC aetiology.

Although the links between global cerebral FA and long-term prognosis of patients have already been well characterized in several aetiologies of DoC(Newcombe et al. 2011; Galanaud et al. 2012; Luyt et al. 2012; Velly et al. 2018; Edlow et al. 2021), our results represent, to our knowledge, the first demonstration of the value of global cerebral FA exploration to support clinicians' assessments of patients' consciousness. These results are substantiated by another work by Fernández-Espejo and colleagues, who showed the interest of another DTI marker of cerebral white matter integrity, mean diffusivity, in differentiating 15 MCS patients from 10 VS/UWS patients.(Fernández-Espejo et al. 2011)

Relation between structural and functional connectivity: supporting the GNW theory of consciousness

Global structural and functional connectivities are positively correlated

Although it is classically assumed that functional connectivity is directly dependent on the structural architecture of the brain, many studies have shown that the relationship between functional and structural connectivity is not as direct as could be expected.(Damoiseaux and Greicius 2009; Chu et al. 2015) We therefore sought to explore the relationship between these two types of connectivity, in the context of consciousness disorders. We were able to show the existence of a positive although weak correlation between $mWSMI_{\theta}$ and global FA, demonstrating that medium-to-long distance information sharing at least partly relies on the integrity of the large invariant deep white matter bundles of the brain. However, the low correlation coefficient ($r = 0.24$) reflects only partial congruence between these two types of connectivity, in agreement with the previously cited studies.(Damoiseaux and Greicius 2009; Chu et al. 2015) Functional and structural connectivity could therefore potentially provide complementary information, both relevant for an accurate diagnosis of patients' level of consciousness. The combination of $mWSMI_{\theta}$ and global FA in the predictive model showed promising discriminative performance for patients' conscious states, outperforming the model based solely on $mWSMI_{\theta}$. However, the comparison with the model based solely on global FA did not yield statistically significant differences, suggesting that further investigation may be warranted to fully assess the added value of combining these predictors.

Theory-driven approach: function-structure association is stronger in the Global Neuronal Workspace

To further explore the anatomical correlates of medium-to-long distance functional connectivity as assessed by $mWSMI_{\theta}$, known to index levels of consciousness, we then investigated the links between $mWSMI_{\theta}$ and FA within deep white matter bundles, assessed at different scales. Our approach was to first test the GNW theory, according to which information sharing between different brain areas, allowing conscious access, is supported by a network of medium-to-long distance anatomical connections between cortical areas, and in particular between prefrontal regions and other associative areas. We thus explored the link between the $mWSMI_{\theta}$, and the mean FA within a network consisting of white matter bundles selected for their presumed role in the GNW. $mWSMI_{\theta}$ indeed showed a significant positive correlation with GNW FA, and this correlation proved to be significantly stronger than the correlation between $mWSMI_{\theta}$ and global FA, and than the correlation between $mWSMI_{\theta}$ and FA within the group of non-GNW bundles. These results represent the first demonstration of the critical importance of the integrity of the deep brain white matter fasciculi involved in the GNW

for the global cerebral diffusion of information, which in turn is critical for conscious access. Moreover, the prediction models using the GNW FA, alone or in combination with $mWSMI_{\theta}$, performed better in distinguishing MCS and VS/UWS patients than models based on global FA, although statistical superiority could not be shown. Altogether, our results thus provide strong support for the GNW theory, by reinforcing the hypothesis that cortico-cortical medium-to-long distance bundles play a key role in conscious processing, as suggested by previous studies.(Annen et al. 2016; Berkovitch et al. 2017)

Data-driven approach: critical role of long-distance associative bundles for functional connectivity

In order to verify, without a priori expectations, the links between structural connectivity in each of the studied bundles and global functional connectivity, our second step was to explore, in a data-driven approach, how $mWSMI_{\theta}$ related to FA within each of the 21 deep white matter tracts of interest. The bundles in which FA correlated with $mWSMI_{\theta}$ corresponded, with the exception of the superior fronto-occipital fasiculi (SFOF), to those previously selected as belonging to the GNW: superior longitudinal (SLF), uncinate (UNC), inferior longitudinal and fronto-occipital (ILF-IFOF) fasciculi, cingulate (Cing), and corpus callosum (CC). In addition to these bundles suspected a priori, we also found a positive correlation between $mWSMI_{\theta}$ and FA within the posterior corona radiata (PCR), and between $mWSMI_{\theta}$ and FA within the cerebral peduncles (CP). These results confirm the involvement of the main long-distance associative bundles (SLF, UNC, ILF-IFOF, cingulate), and of the corpus callosum, essential for inter-hemispheric exchanges, in brain-wide information exchanges (Urbanski et al. 2008).

Moreover, the correlation of their integrity with $mWSMI_{\theta}$, known for indexing levels of consciousness, suggests the involvement of these fasciculi in access to conscious content. These results are consistent with previous studies, which have shown a link between the structural damage of these bundles and disorders of consciousness, evaluated through different approaches. Indeed, the structural integrity of the CC, cingulum, and IFOF has been correlated with the severity of DoC after head trauma(Fernández-Espejo et al. 2012); or with the threshold of conscious access to a visual stimulus in psychotic patients.(Berkovitch et al. 2017) Damage to the IFOF, SLF or ILF can also be responsible for impaired conscious access to visual stimuli.(de Schotten et al. 2005; Bartolomeo et al. 2007; Urbanski et al. 2008; Reuter et al. 2009) Uncinate fasciculi, suspected to be involved in the GNW(Dehaene and Changeux 2011), were also related to consciousness levels in a study reporting a positive correlation between uncinate fasciculi integrity and the CRS-R scale in head trauma patients.(Wang et al. 2018)

However, although expected based on the GNW hypothesis, we did not identify a relationship between global functional connectivity and SFOF integrity. This could be explained by the SFOF being a bundle whose anatomic boundaries remain imperfectly described.(Catani et al. 2002; de Schotten et al. 2005) Indeed, the atlas used to individualize each bundle specifies in its description that the SFOF could correspond to a portion of the anterior thalamic radiations rather than to an associative bundle.(Mori et al. 2008) The inclusion of this bundle in future studies of the GNW should therefore be reconsidered. Finally, $mWSMI_{\theta}$ also unexpectedly correlated with the integrity of the PCR and of the CP. The involvement of the PCR might be explained by the coexistence within the corona radiata of projection fibres, of callosal fibres, but also of associative fibres, the latter being particularly present within the posterior corona radiata, where fibres from the ILF-IFOF converge.(Wakana et al. 2004) As for the involvement of the CP, these results suggest that, although $mWSMI_{\theta}$ is designed to capture cortical information exchange, it may also depend on the integrity of the ascending reticular activating system, critical to maintain arousal in brain-lesioned patients(Enciso-Olivera et al. 2021; Parra-Morales et al. 2019), which might be injured in the case of mesencephalum lesions, for which FA within the CP was the only available index. Indeed, a link between FA decrease within the CP and poor outcome in disorders of consciousness has been previously described.(Luyt et al. 2012)

Limitations and perspectives

While our results support the GNW theory and highlight the value of exploring FA within the GNW and $mWSMI_{\theta}$ in DoC patients, some methodological limitations of the project should nevertheless be mentioned.

First, the diagnostic performance of $mWSMI_{\theta}$ was lower in this study (AUC 0.632) than in previous works exploring the discrimination of VS/UWS and MCS patients (0.73 and 0.74 in (King et al. 2013; Sitt et al. 2014), respectively). Although we did search for potential confounding effects of aetiology or delay since ABI in the relationship between, none of these were clearly identified, suggesting a need for further investigation $mWSMI_{\theta}$'s diagnostic performances in distinct populations in future studies. However, $mWSMI_{\theta}$ is a validated tool for the assessment of levels of consciousness in disorders of consciousness, and we cannot exclude that some of the patients misclassified by the $mWSMI_{\theta}$ logistic regression model might be related to an initial clinical misdiagnosis. In these cases, $mWSMI_{\theta}$ would serve as a valuable tool to alert clinicians to the need for reassessment of these patients.

Secondly, it is not possible to formally exclude that some values of the two markers used might have been over- or under-estimated. Indeed, like all paraclinical markers, FA and $mWSMI_{\theta}$ are sensitive to acquisition conditions, but also to variations related to the specific characteristics of each patient. For example, FA measurement may be biased toward an increase or decrease in some patients presenting with hydrocephalus(Scheel et al. 2012) or cerebral oedema(Assaf and Pasternak 2008; Kimura-Ohba et al. 2016), conditions often reversible but that may have been present during the MRI acquisition of patients from our cohort. FA also tends to be lowered in various brain pathological conditions such as inflammatory, vascular, or demyelinating leukopathies.(Assaf and Pasternak 2008) Such pathological conditions could potentially distort the interpretation of FA in some patients, especially if they preceded the brain injury responsible for the consciousness disorder. On the other hand, functional connectivity indices are by definition dynamic, and therefore fluctuate over time, under the influence of various parameters.(Comanducci et al. 2020) Although the risk of underestimating the level of functional connectivity due to deep sedation had been minimized by stopping all sedatives for at least 24 hours before EEG acquisition, some other drugs that can have a significant impact on the state of consciousness or on the EEG waveform (anti-epileptics, some antibiotics, myorelaxants...) were sometimes required, and could potentially have lowered the $mWSMI_{\theta}$. Additionally, as consciousness disorders in the ICU are by definition fluctuating states(Rohaut et al. 2019), we cannot exclude that some EEG recordings took place at a time when the participants' level of vigilance was unrepresentatively low. Nevertheless, EEG and clinical assessments were performed on the same day one after the other, thus reducing the risk of a decorrelation between $mWSMI_{\theta}$ and clinical status in our study. The fluctuation of clinical manifestations of level of consciousness and their functional correlates would, however, justify repeating clinical and paraclinical assessments to increase their reliability. For this purpose, the EEG presents important advantages in terms of accessibility, as it can be repeated many times at patients' bedside. While the cohort presented in this project was recorded using a high-density EEG headset with 256 electrodes, a recent work has shown the reliability of $mWSMI_{\theta}$ when analysed with clinical routine headsets with far fewer electrodes (minimum eight), opening possibilities for routine care applications.(Engemann et al. 2018) Finally, the limitations outlined here regarding FA or $mWSMI_{\theta}$ acquisition are also exportable to the clinical examination. Indeed, clinical assessment also needs to be repeated to increase its reliability(Schnakers et al. 2009; Rohaut et al. 2019), and also has certain limitations, especially in patients with motor deficiencies in whom a reliable assessment of consciousness is difficult and could therefore be helped by structural and functional connectivity information.(Smith and Delargy 2005; Kondziella et al. 2016; Claassen et al. 2019; Rohaut et al. 2019) The clinical and paraclinical approaches thus seem to be complementary, and should therefore be used in association by clinicians.(Comanducci et al. 2020; Kondziella et al. 2020; Giacino et al. 2018)

Finally, this project explored structural connectivity at the GNW level, but did not include a regional or a cortico-cortical distance thresholded analysis of $mWSMI_{\theta}$, which could further improve our results and prediction

performance. Indeed, the GNW was assumed to be the support of functional information exchange at a global brain scale. Nonetheless, some works suggest that alterations in $mWSMI_{\theta}$ in patients with impaired consciousness could predominate in centroposterior brain regions(King et al. 2013; Sitt et al. 2014), consistent with the characterization of the mesoparietal and posterior cingulate regions as important nodes in the consciousness network and in long distance prefronto-posterior connections.(Vogt and Laureys 2005; Alkire et al. 2008; Dehaene and Changeux 2011; Laureys and Schiff 2012) Future analyses of the link between FA within the GNW and $mWSMI_{\theta}$ in these centroposterior regions could therefore provide further insight into the neural correlates of consciousness, and potentially help to refine the characterization of patients in whom it is impaired.

Conclusion

In this work, we have been able to show the existence of a positive correlation between measures of functional and structural connectivity indexing states of consciousness, which is more significant when studied within the bundles involved in the GNW network, thus supporting this theory of consciousness. Furthermore, our results also established the clinical interest of exploring anatomical connectivity, indexed by FA, in DoC patients, and confirmed the interest of evaluating medium-to-long distance functional brain connectivity, indexed by $mWSMI_{\theta}$. Altogether, these results suggest the interest of a combined assessment of functional and structural connectivity within the GNW as part of multimodal approaches aiming to refine the diagnostic and prognostic evaluation of patients with disorders of consciousness.

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Statements and Declarations

Acknowledgments

This work was supported by Sorbonne University, the James S. McDonnell Foundation, Fondation pour la Recherche Médicale 2015, Union Nationale pour les Intérêts de la Médecine, Académie des Sciences-Lamonica Prize 2016 (L.N.) and PerMed grant (JD.S.). The research leading to these results has received funding from the Investissements d'avenir ANR-10-IAIHU-06 program.

Competing interests

Financial interests: L.P. is co-founder of BrainTale. V.P. is co-founder and employee of BrainTale. The other authors report no competing interests.

Non-financial interests: None

Author Contributions

L.N., B.R., V.A., JD.S. and L.P. contributed to the conception and design of the study

B.R., A.S., and C.C., contributed to behavioral and EEG data collection

V.P. contributed to MRI data collection.

V.A. performed the data analyses.

V.A. B.R., L.N., JD.S. and V.P. contributed to drafting a significant portion of the text

Data availability

The authors confirm that the data supporting the findings of this study will be available on an online data repository upon publication, apart from any potentially identifying data (i.e., sex, age, date of birth, and subject identifier).

Ethics approval

This study was approved by the institutional review board of the Pitié-Salpêtrière University Hospital (PSL – 2023 – R – CONS-CONNECT), in agreement with the French data protection authority (MR004).

Consent to participate

This research study was conducted retrospectively from data obtained for clinical purposes. All participants, or their relatives if they did not recover from their disorder of consciousness, received information of the possible use of their health data collected as part of routine care, and did not object.

Table 1: Demographic and clinical characteristics of patients

	Total (*n* = 78)	**VS/UWS (*n* = 37)**	**MCS (*n* = 41)**	**Group comparison**
Gender (women)	25 (32%)	9 (24%)	16 (39%)	$\chi 2 = 1.93$; $P = 0.165$
Age (years)	43.7 (18.1)	44.2 (17.6)	43.3 (18.8)	$U = 737.00$; $P = 0.835$
ABI – EEG delay (days)	103.8 (297.9)	103.3 (270.2)	104.3 (324.1)	$U = 772.50$; $P = 0.893$
- Acute	21 (27%)	11 (14%)	10 (13%)	$\chi 2 = 0.28$; $P = 0.596$
- Intermediate	32 (41%)	13 (17%)	19 (24%)	$\chi 2 = 1.01$; $P = 0.315$
- Chronic	25 (32%)	13 (17%)	12 (15%)	$\chi 2 = 0.31$; $P = 0.579$
ABI – MRI delay (days)	104.2 (298.1)	104.0 (270.3)	104.3 (324.5)	$U = 767.00$; $P = 0.936$
- Acute	21 (27%)	13 (17%)	8 (10%)	$\chi 2 = 2.41$; $P = 0.120$
- Intermediate	31 (40%)	11 (14%)	20 (26%)	$\chi 2 = 2.95$; $P = 0.086$
- Chronic	26 (33%)	13 (17%)	13 (17%)	$\chi 2 = 0.10$; $P = 0.748$
EEG – MRI delay	0.9 (10.1)	1.1 (8.8)	0.8 (11.2)	$U = 699.50$; $P = 0.561$
ABI aetiology				
- Anoxia	40 (51%)	25 (68%)	15 (37%)	$\chi 2 = 7.47$; $P = 0.006$
- Traumatic brain injury	16 (21%)	4 (11%)	12 (29%)	$\chi 2 = 4.06$; $P = 0.044$
- Stroke	10 (13%)	2 (5%)	8 (20%)	$\chi 2 = 3.46$; $P = 0.063$
- Others	12 (15%)	6 (16%)	6 (15%)	$\chi 2 = 0.12$; $P = 0.731$

Results are expressed as mean (standard deviation) or number (%)
Significant differences between the two groups are shown in bold

Table 2: Correlations between $mWSMI_{\theta}$ and FA within each of the 21 deep white matter tracts of interest

	Spearman's rho	95% CI	*P* value
Corticospinal tract (CST)	0.19	[-0.06, 0.43]	0.051
Medial lemniscus (mLEM)	0.08	[-0.16, 0.32]	0.268
Inferior cerebellar peduncle (ICP)	0.16	[-0.09, 0.38]	0.094
Middle cerebellar peduncle (MCP)	0.19	[-0.03, 0.43]	0.052
Superior cerebellar peduncle (SCP)	0.13	[-0.13, 0.35]	0.137
Anterior corona radiata (ACR)	0.23	[-0.01, 0.47]	0.027
Superior corona radiata (SCR)	0.24	[-0.05, 0.41]	0.065
Posterior corona radiata (PCR)	0.28	[0.05, 0.50]	**0.007**
Anterior limb of internal capsule (ALIC)	0.20	[-0.05, 0.42]	0.049
Posterior limb of internal capsule (PLIC)	0.21	[-0.04, 0.43]	0.041
Retrolenticular part of internal capsule (RLIC)	0.20	[-0.04, 0.45]	0.049
Cerebral peduncle (CP)	0.25	[0.03, 0.48]	**0.017**
Posterior thalamic radiation (PTR)	0.18	[-0.08, 0.42]	0.065
Superior longitudinal fasciculus (SLF)	0.26	[0.02, 0.50]	**0.015**
Superior fronto-occipital fasciculus (SFOF)	0.10	[-0.12, 0.34]	0.207
Uncinate fasciculus (UNC)	0.34	[0.13, 0.53]	**< 0.001**
Inferior longitudinal fasciculus – Inferior fronto-occipital fasciculus (ILF-IFOF)	0.25	[0.01, 0.48]	**0.016**
Cingulum (Cing)	0.25	[0.03, 0.47]	**0.016**
Cingulum-hippocampus (Cing_h)	0.13	[-0.13, 0.39]	0.138
External capsule (EC)	0.24	[0.00, 0.47]	0.021
Corpus callosum (CC)	0.30	[0.07, 0.51]	**0.004**

Significant correlations after Benjamini-Hochberg correction for multiple correlations are shown in bold.
95% CI: 95% confidence interval based on 1000 boostrap replicates

Supplementary Methods

Supplementary Method 1: median Weighted Symbolic Mutual Information Theta ($mWSMI_\theta$)

$mWSMI_\theta$ computation

$mWSMI_\theta$ is a robust and precise EEG marker for the assessment of medium-to-long distance functional connectivity.(King et al. 2013; Sitt et al. 2014) It corresponds to the median value, among all pairs of EEG electrodes, of the weighted mutual symbolic information, a measure of the amount of mutual information shared between two points of the scalp. EEG signals from each electrode are transformed into a series of discrete symbols defined by the ordering of three consecutive time samples separated by a temporal interval τ (Figure S1A). This symbolic transform then allows the study of non-random joint fluctuations between two EEG signals, by calculating the probability matrix of occurrence of each pair of symbols, thus quantifying the nonlinear functional coupling between the two signals (Fig. S1B). The more the probability that two symbols appear together in the two EEG signals increases, the more the mutual symbolic information shared between these two signals is important. Importantly, zero weights are applied to the probability matrix for pairs of identical or opposite signals, as these pairs are likely to come from the same cerebral source for identical symbols, or from both sides of the same dipole for opposite symbols (Fig. S1C). This signal processing also makes it possible to focus the analysis on medium-to-long distance functional connectivity, since the information reflecting short-distance connectivity contains a greater proportion of pairs of identical or opposite symbols, and will therefore tend towards 0 after weights are applied. Finally, different values of the temporal separation parameter τ can be used, thus varying the corresponding analyzed signal frequency (e.g., 4–10 Hz or 8–20 Hz for τ = 32 or 16ms respectively). In this work, we use a value of 32ms, corresponding to an analysis frequency between 4 and 10 Hz, sensitized to events in the physiological theta band (θ = 4-8Hz), thus defining $mWSMI_\theta$. This choice is motivated by the results of the reference article describing the $mWSMI_\theta$, which observed that this θ frequency was the most effective in discriminating between MCS and VS/UWS patients.(King et al. 2013)

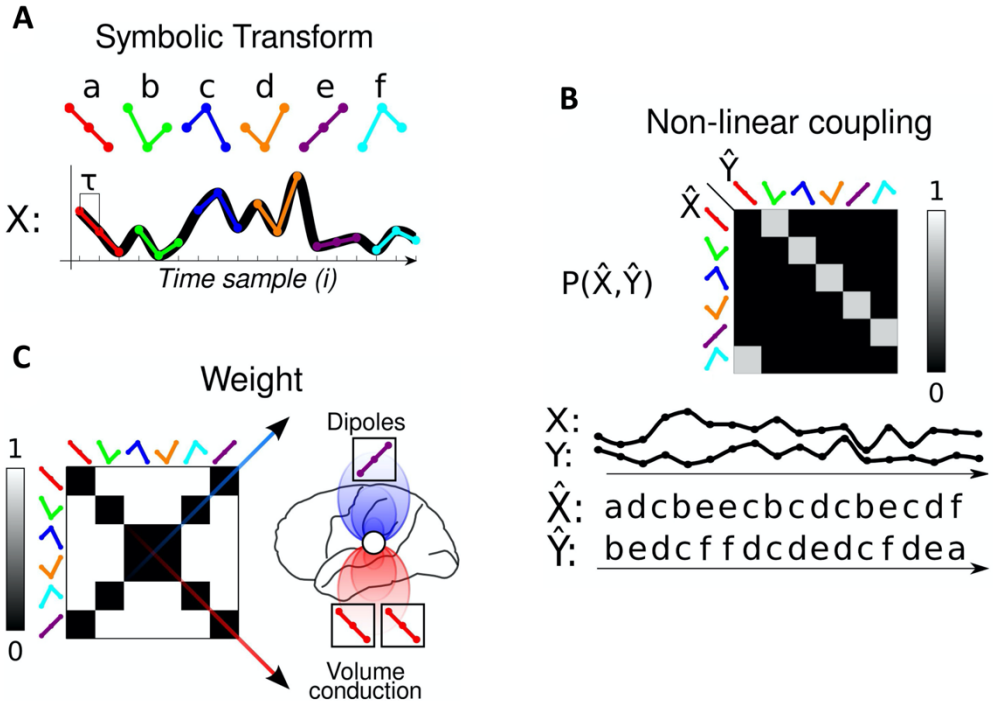

Figure S1: Weighted Symbolic Mutual Information

A: The transformation of continuous signals (X) into sequences ($\hat{X}$) of discrete symbols (A, B, ..., F) enables an easy and robust estimation of the mutual information shared between two signals. The τ parameter refers to the temporal separation of the three time points constituting a symbol.

B: By computing the joint probability of each pair of symbols, we can estimate the symbolic mutual information (SMI) shared across two signals.

C: To compute weighted symbolic mutual information (wSMI), the SMI is weighted to disregard conjunctions of identical or opposite-sign symbols, which could potentially arise from common-source artefacts.

(*Figure kindly provided by King et al.(King et al. 2013))*

EEG recordings and preprocessing

EEG recordings were captured using a high-density headset with 256-electrodes geodesic sensor net (Electrical Geodesics Inc, EGI, Oregon, USA) referenced to the vertex, with a sampling frequency of 250 Hz. EEG signals were band-pass filtered for frequencies between 0.2 to 45 Hz. To stick to $mWSMI_{\theta}$'s initial description(King et al. 2013), the EEG signal used to compute $mWSMI_{\theta}$ corresponded to a period of 800ms during which the patient was administered a "local-global" auditory protocol, carried out as a routine care evaluation of patients' state of consciousness.(Bekinschtein et al. 2009) Different sets of this paradigm were carried out (at least 8), and the active periods of 800ms of each of the tests were then grouped for this project, as its purpose is to evaluate the functional cerebral connectivity in ongoing brain activity in a general way, with no interest for the different conditions of the "local-global" paradigm. Each trial was baseline-corrected over the first window 200ms before the onset of the first auditory stimulus (from 200ms to 0ms). Trials in which voltages exceeded ±150 μV were rejected, as for trials in which the eye movement voltage exceeded ±80 μV. Electrodes with a rejection rate greater than 20% across trials were discarded and interpolated with neighbouring non-artefacted electrodes. Trials with more than 20% corrected electrodes were rejected. All these processing steps were performed using the Waveform Tools Package provided by EGI.

Finally, EEG recordings of each patient were corrected using a spatial Laplacian transform, also known as Current Source Density estimate.(Kayser and Tenke 2006) This transformation schematically consists in subtracting from the activity of each electrode the activity of its neighbouring electrodes, with the main advantage of increasing the spatial resolution and minimizing the influence of distant sources.

Supplementary Method 2: Fractional Anisotropy (FA)

Scanning parameters

Magnetic resonance images were acquired on 1.5 or 3 Tesla magnetic resonance machines (General Electric Healthcare, Velizy, France) with quadratic or multi-channel head coils. The precise parameters of each sequence, such as echo time (TE) and repetition time (TR), were adjusted to the individual specifications of each manufacturer and scanner. The following sequences were acquired: sagittal localization T1 sequence, axial T2/FLAIR (Fluid Attenuated Inversion Recovery), axial T2, axial T2*, 3D T1, and DTI.

The DTI acquisition was acquired in an axial plane perpendicular to the main magnetic field B0, with a series acquired with the application of a gradient (B) of a value of 1000 mT/m applied in 11 to 50 directions, as well as a series acquired without the diffusion gradient (low-B image). Different DTI acquisition parameters were used depending on the time period during which the patient was included:

- 1.5 T (12 directions): 3-mm thickness, no gap, 11 directions, matrix 96 × 96, FOV = 28 cm, TR = 10,000ms, TE = 87ms
- 1.5 T (23 directions): 5-mm thickness, no gap, 23 directions, matrix 96 × 96, FOV = 28 cm, TR = 8,000ms, TE = 80ms
- 3 T (12 directions): 3-mm thickness, no gap, 12 directions, matrix 96 × 96, FOV = 28 cm, TR = 12,000ms, TE = 81.9ms

- 3 T (50 directions): 2.5 mm thickness, no gap, 50 directions, matrix 128 × 128, FOV = 28 cm, TR = 14,000ms, TE = 84.5ms

DTI images preprocessing

An operator examined the quality of all DTI images to exclude low-quality data from final analysis, verifying protocol compliance (scanner model, coil, number of diffusion gradient directions, echo time, repetition time and voxel size) and absence of motion artefacts (maximal displacement under 5 mm, ratio of signal loss detections under 5%).

DTI were then preprocessed using brainQuant Software (http://www.braintale.eu; research version 2.0), implementing preprocessing steps from the FMRIB Software Library (FSL, https://fsl.fmrib.ox.ac.uk/fsl; version 5.0.6). DTI images were first corrected for head motion and eddy-current-induced distortions using linear registration(Haselgrove and Moore 1996; Jenkinson et al. 2002), before segmentation into brain and non-brain volumes using the brain extraction tool.(Smith 2002)

A diffusion tensor model was then used for each voxel of each subject's brain, allowing the extraction of two diffusion parameters, the FA and the mean diffusivity, used to construct two parametric maps. The FA map of each subject was normalized in the Montreal Neurological Institute's standard 1×1×1mm3 space (MNI-152) using both linear and nonlinear transformations. FA maps were then registered to the deep white matter ICBM-DTI-81 atlas defined in the MNI space (Mori et al. 2008), describing 56 deep white matter bundles, that were gathered into 21 regions of interest for this study (Figure 1, Figure S2). This registration used a nonlinear approach, allowing to account for individual brain deformations related to the acute brain injury. Additionally, the use of an atlas focused on deep white matter bundles enhanced the robustness of the registration approach for our measures in comparison to a whole-brain approach. The quality of this processing step was checked by verifying several parameters: entropy of the spatial distribution of the main diffusion direction(Farzinfar et al. 2013), residuals of the diffusion tensor model remaining within the range of those of healthy subjects, and visual inspection of the quality of the coregistration between FA map and ICBM-DTI-81 atlas. FA values were then averaged within each white matter bundle of interest, before being normalized to account for intersequence variability. Normalization consisted of scaling each patient’s FA by the mean FA calculated from a normative control group that underwent the same imaging sequence.

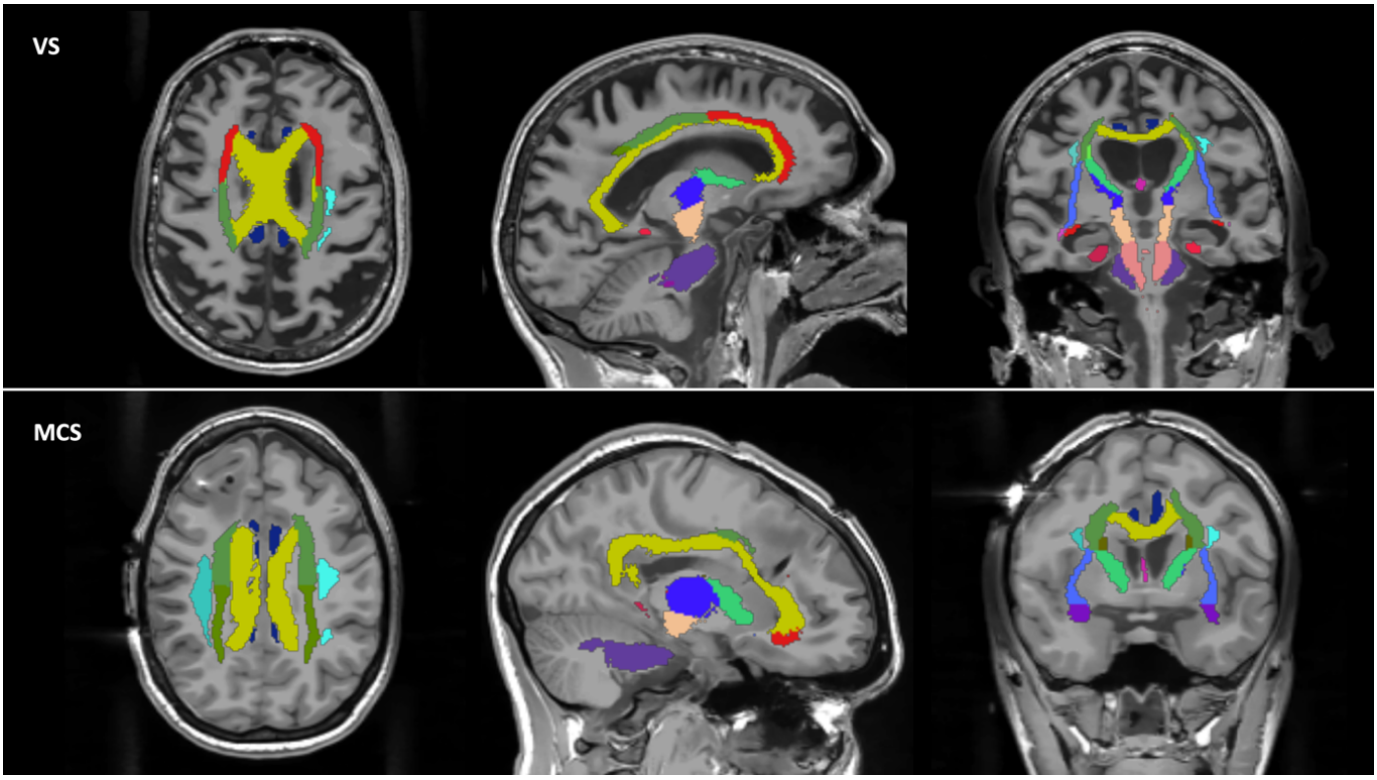

Figure S2: Examples of the ICBM-DTI-81 atlas in patients

The deep white matter ICBM-DTI-81 atlas (Mori et al. 2008) is displayed on brain slices of a patient diagnosed in a vegetative state / unresponsive wakefulness syndrom (VS/UWS) secondary to anoxia; and of a patient diagnosed in a minimally conscious state (MCS) after traumatic brain injury.

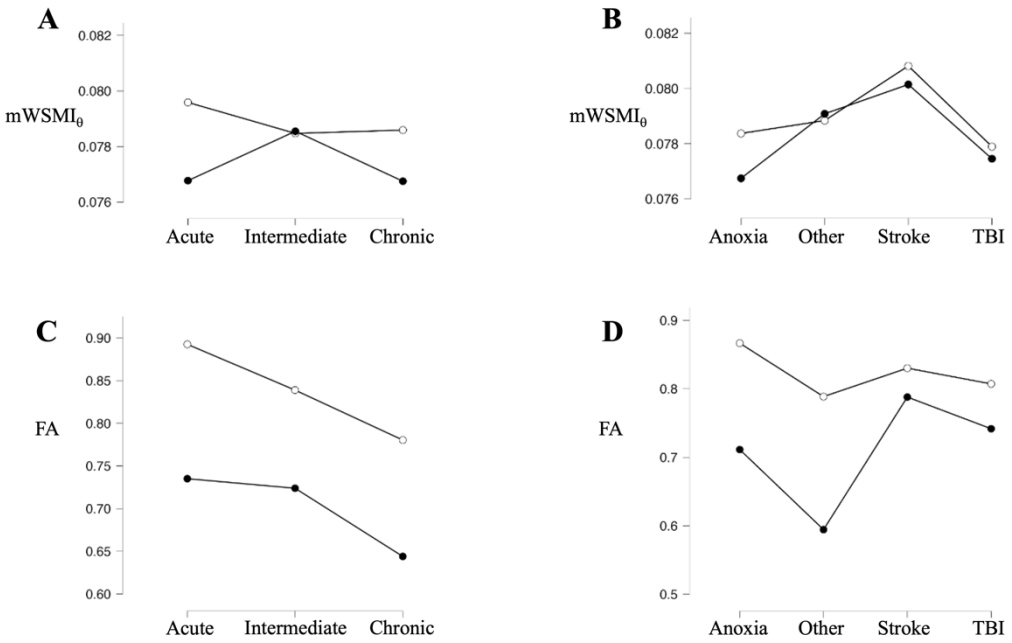

Figure S3: Descriptive plots of the ANOVAS exploring the robustness of each connectivity parameter to variability in aetiology or in delay since acute brain injury (ABI).

The top row shows descriptive plots of ANOVAs exploring how the ability of $mWSMI_{\theta}$ to distinguish between clinical status is robust to variability in delays since initial ABI (ABI-EEG delay) (**A**) or in ABI aetiologies (**B**).

The top row shows descriptive plots of ANOVAs exploring how the ability of FA_{θ} to distinguish between clinical status is robust to variability in delays since initial ABI (ABI-MRI delay) (**C**) or in ABI aetiologies (**D**).

Supplementary Methods' References

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