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Modulation of the default-mode network and the attentional network by self-referential processes in patients with disorder of consciousness

Verónica Mäki-Marttunen [a,b,*], Mariana Castro [a,b], Lisandro Olmos [a], Ramón Leiguarda [a,b,c], Mirta Villarreal [a,b,c]

[a] Institute for Neurological Research, F.L.E.N.I., Montañeses 2325, 1428 Buenos Aires, Argentina
[b] CONICET, Buenos Aires, Argentina
[c] Departamento de Física, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Argentina

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ABSTRACT

Disorders of consciousness (DOC) are related to an altered capacity of the brain to successfully integrate and segregate information. Alterations in brain functional networks structure have been found in fMRI studies, which could account for the incapability of the brain to efficiently manage internally and externally generated information. Here we assess the modulation of neural activity in areas of the networks related to active introspective or extrospective processing in 9 patients with DOC and 17 controls using fMRI. In addition, we assess the functional connectivity between those areas in resting state. Patients were experimentally studied in an early phase after the event of brain injury (3 ± 1 months after the event) and subsequently in a second session 4 ± 1 months after the first session. The results showed that the concerted modulation of the default mode network (DMN) and attentional network (AN) in response to the active involvement in the task improved with the level of consciousness, reflecting an integral recovery of the brain in its ability to be engaged in cognitive processes. In addition, functional connectivity decreased between the DMN and AN with recovery. Our results help to further understand the neural underpins of the disorders of consciousness.

1. Introduction

Primary consciousness implies a multimodal reportable process involving perceptual and motor events which are present in mammals with a developed thalamo-cortical system (Zeman, 2006). High-level consciousness, distinctive of humans, implicates references to the content of consciousness for semantic interpretation. It includes the sense of the self and the capacity to explicitly build up past and future scenery (Seth et al., 2005; Mantini and Vanduffel, 2013; Dehaene and Changeux, 2011). Including these two levels in a succinct definition, consciousness is a state of wakefulness with awareness of the environment and the self (Laureys et al., 2007).

Several theories of consciousness posit that high-level consciousness is a global, dynamic process in the brain rather than a localized phenomenon (Dehaene et al., 2003; Tononi and Edelman, 1998; Seth et al., 2006). It implies a balance between integration and segregation of information (Edelman, 2003; Seth et al., 2006; Tononi, 2008), which warrants the proper distinction between different mental states and, at the same time, their conscious experience as a unity, maintaining constancy of an internal framework across perceptual situations. At a neural networks level, dynamic interactions among neural populations generate the complexity of consciousness, allowing for the integration of specialized brain functions (Seth et al., 2006; Baars, 2005). This interaction between the long-range cerebral systems that serve external and self-directed cognition sustains the phenomenological complexity of awareness in humans (Mesulam, 1990; He et al., 2007; Demertzi et al., 2013).

Consciousness is reduced during certain natural (dreamless sleep) or pathological (epileptic seizures, coma) states. Therefore, a great amount of research has been conducted on these conditions, particularly in patients with disorders of consciousness (DOC), not only for its relevance to understand consciousness but also for the potential medical value to improve clinical management and rehabilitation of the patients. DOC is typically the result of traumatic lesions that cause focal or diffuse neural damage, and encompasses a wide spectrum of clinical conditions with different levels in the content of conscious awareness. DOCs range from the coma state (CS) and vegetative state (VS, also referred to as unresponsive wakefulness syndrome, UWS) to minimally

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[*] Corresponding author at: Institute for Neurological Research, F.L.E.N.I., 2nd subsoil, Montañeses 2325, 1428 Buenos Aires, Argentina
E-mail address: makimarttunen.veronica@gmail.com (V. Mäki-Marttunen).

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consciousness state (MCS) and locked-in syndrome (LIS) (see Owen (2008), Young (2009) and Laureys et al. (2004) for review). Briefly, patients in UWS preserve alternating periods of eye opening and eye closure but are unaware of themselves and the environment (Laureys et al., 2010). They do not follow instructions nor present any form of communication or any purposeful movement (Ashwal et al., 1994). Patients in MCS are unable to reliably communicate but show reproducible albeit fluctuating behavioral evidence of awareness. They can fixate their eyes on persons or objects in front of them, follow simple instructions and utter some words, and they may respond by smiling or crying and may show purposeful gestures (Giacino et al., 2002). Patients in LIS are fully conscious but paralyzed of all four limbs and most facial muscles due to deafferentiation, and are usually able to communicate by means of small movements of the eyes or eyelids (Plum and Posner, 1966; Smith and Delargy, 2005).

Many studies using imaging techniques have assessed the neural characteristics that convey a potential relation with the emergence from coma to conscious state, such as brain metabolism (Laureys et al., 1999a; Laureys et al., 2003; Phillips et al., 2011) or structural connectivity (Fernández-Espejo et al., 2011). Following the finding that the coherence of low-frequency fluctuations of blood-oxygen-level-dependent (BOLD) signal may carry important information about brain function (Friston, 2011), much work has been carried out in this field in patients with DOC. Resting state (RS) functional connectivity assessed with functional magnetic resonance imaging (fMRI) is defined in terms of the inter-regional synchrony of spontaneous low-frequency fluctuations (Damoiseaux et al., 2006; see Deco and Corbetta (2011), for review). Brain regions showing such synchronous activity constitute a network, and multiple large-scale spatially distributed networks can be detected at rest in healthy subjects (see Van Den Heuvel and Hulshoff Pol (2010), for review). Patients with DOC have an altered spontaneous functional connectivity (Cauda et al., 2009; Ovadia-Caro et al., 2012; Soddu et al., 2011; Demertzi et al., 2014; Mäki-Marttunen et al., 2013, Qin et al., 2015).

The default mode network (DMN) is the RS network that received the greatest attention. This network is composed of the ventral medial prefrontal area, anterior and posterior cingulated cortices as well as the precuneus, the inferior parietal cortices/angular gyri and the middle temporal lobe. The DMN shows increased activity when healthy subjects are at rest in a state of unrestricted mental content (Greicius et al., 2003; Gusnard and Raichle, 2001). Additionally, the DMN is involved in the processing of the self, such as autobiographic memory recall (Spreng et al., 2009; Spreng and Grady, 2010; Andreasen et al., 1995; Schacter et al., 2007), self-centered thoughts (McKiernan et al., 2006; Mason et al., 2007; Goldberg et al., 2006), prospective personal projection (Spreng and Grady, 2010) and self-reference (Whitfield-Gabrieli et al., 2011; D'Argembeau et al., 2005; Gusnard et al., 2001). In the last years, resting state fMRI studies showed that DOC patients have a disrupted metabolism and functional connectivity between posterior cingulated cortex, precuneus and part of the ventromedial prefrontal area in the DMN (Laureys et al., 1999b; Soddu et al., 2012; Norton et al., 2012; Vanhaudenhuyse et al., 2009; Cauda et al., 2009).

Opposite to the unrestricted mental state of rest, consistent general directed behavior depends on the ability to sustain attention over time. Functional connectivity studies in healthy subjects have identified a fronto-parietal attentional network (AN), which includes among other structures the frontal eye fields, inferior precentral sulcus, middle temporal motion complex and superior parietal lobule. The AN is engaged during attentionally demanding tasks such as cognitive selection of sensory information and responses (Corbetta and Shulman, 2002). DMN and AN have mainly an opposing functionality and it was found that during spontaneous activity they also present an anticorrelated behavior. (Fox and Raichle, 2007; Fransson, 2006; Gusnard and Raichle, 2001; Vanhaudenhuyse et al., 2011; Dixon et al., 2014). The default-mode interference hypothesis suggests that an efficient switching between the DMN and AN networks is associated with a better performance in an attention-demanding task in healthy people, and a failure of this mechanism may be related to poor performance in attention-demanding tasks (Weissman et al., 2006; Sonuga-Barke and Castellanos, 2007). Thus, the integration-segregation duality necessary for consciousness and complex cognition is expressed as dynamic patterns of regional brain interaction and network coupling (Mesulam, 1998; Spreng et al., 2013; Boly et al., 2011; Fair et al., 2007). Therefore, it is of relevance to examine the AN in DOC patients and its interplay with the DMN.

Several studies show that brain activity is modulated in response to different tasks in DOC patients. In some studies, the activity was evaluated during passive stimulation (auditory, visual, somatosensory or nociceptive). In others, they explicitly requested the patient to perform a task in order to properly assess processing, recruitment and modulation in the underlying neural systems (Bardin et al., 2012; Bekinschtein et al., 2011; Cruse et al., 2012; Goldfine et al., 2011; Owen et al., 2006, Huang et al., 2014; Monti et al., 2015). In some of such studies, the activity of the frontal component of the DMN during self-related processing has been reported to correlate with recovery from DOC (Huang et al., 2014), and the patients with more severe DOC fail to deactivate it during a passive task (Crone et al., 2011). Taken together, the spontaneous as well as the task-related functions supported by the DMN are disrupted in DOC, therefore indicating a reduction in self-referential appraisal and ongoing conscious cognition in these patients (Heine et al., 2012). On the contrary, little attention has been paid to the integrity of the AN in DOC patients, and less to its dynamics with the DMN.

Here, we use fMRI to examine the state of integration of different networks in DOC patients. We assess the neural response of DMN and AN areas led by active involvement of the patients in an alternating internal and external attention task without resting blocks. We use an fMRI auditory paradigm in which subjects are delivered blocks of questions about themselves or questions about general knowledge and are explicitly instructed to answer them. We use a novel approach to assess the integral modulation caused by the external stimuli on the activity of the brain networks correlated or uncorrelated with self-referential processing. We hypothesize that the intro or extrospective attentional states cause a differential modulation in DMN and AN (Johnson et al., 2002), and that it is more pronounced in patients with higher level of consciousness, while patients with a severe disorder present an absence of such modulation. Furthermore, we evaluate the relation between network activity and functional connectivity. We predict a relation between the connectivity within the DMN (and between the DMN and the AN) and the ability of the paradigm to modulate the activity in areas of self-processing in DOC patients. Moreover, we expect that the disruption of connectivity within and between the DMN and the AN may help to anticipate the clinical outcome of the patients.

2. Methods

2.1. Subjects

Seventeen healthy subjects aged 25 ± 5 year old (8 men, 9 women), with no history of neurological or psychiatric problems, participated in this study as a control group. The Edinburgh Handedness Inventory was used to assess handedness (Oldfield, 1971), resulting in thirteen right-handed and four left-handed

Table 1
Clinical characteristics of DOC patients. UWS: unresponsive wakefulness syndrome; MCS: minimally consciousness state; C: conscious; EMCS: emergence from MCS (an intermediate state between MCS and C); TBI: traumatic brain injury; BA: brain abscess; M: male; F: female. CRS-R subscores: auditive, visual, motor, verbal/oromotor, communication and arousal.

Patient	Age/gender	Etiology of injury	Time between accident and first scan (days)	Clinical assessment at first scan	CRS-R score at first scan	Time between first and second scan (days)	Clinical assessment at second scan	CRS-R score at second scan
P1	34/m	TBI	72	UWS	4 (0/0/2/1/0/1)	147	UWS	5 (0/0/2/1/0/2)
P2	18/m	TBI	116	MCS	11 (3/2/2/2/0/2)	132	C	22 (4/5/5/3/2/3)
P3	44/f	TBI	50	MCS	18 (na)	110	C	23
P4	17/m	BA		UWS	10 (3/1/2/1/2/1)	185	MCS	12 (3/1/5/2/0/1)
P5	26/f	TBI	102	UWS	13 (3/2/5/1/0/2)	66	MCS	17 (3/5/6/1/1/1)
P6	26/f	TBI	113	EMCS	18 (na)	120	C	22
P7	29/m	TBI	122	MCS	14 (2/4/5/1/0/2)	118	MCS	17 (4/4/6/1/0/2)
P8	41/m	TBI	120	UWS	10 (2/3/2/1/0/2)	173	UWS	11 (3/3/2/1/0/2)
P9	34/m	TBI	165	UWS	12 (3/3/3/1/1/1)	140	C	23

subjects. Eleven patients with DOC were scanned (age range, 17–44 years, 7 men, 4 women). The severity of DOC for each patient was clinically assessed using the Revised Coma Recovery Scale (CRS-R, Giacino et al., 2004): score ranges from 0 (meaning deep coma state) to 23 (full recovery). The patients were scanned a first time between 2 and 6 months after major acute brain injury, and a second time between 3 and 6 months after the first scan (Table 1). Two patients were subsequently excluded because of unacceptable degrees of head and body movements (exceeding 4 standard deviations). Data from the task runs of the first experimental session of three patients (P1, P2 and P3) were left out due to the presence of artifacts. Therefore, we included in the analysis: the task data of 6 patients from the first experimental session, of 9 patients from the second experimental session, and the RS data of 9 patients from each session. Patients were assessed weekly with the CRS-R test; the values reported in Table 1 correspond to the measurement at the time of the scan session. Auditory evoked potentials were acquired previous to the fMRI session to control for preserved auditory functions. The experimental protocol was approved by the Institutional Review Board of the Institute of Neurological Research FLENI. Informed consent was directly obtained from healthy participants and from the next kin of each of the patients.

2.2. *Task*

Each fMRI session consisted on three scans: the first two were auditory tasks, and the third one was a resting state paradigm (REST). During the task scans, subjects were delivered through earphones two sets of questions: one concerning knowledge and reflection on the domain of own abilities, traits and attitudes (SELF condition; for example: “Are you shy?”, “Do you like gossip?”), and the other about general, factual knowledge (NON-SELF, for example: “Blue and yellow make green?”, “A half is more than a quarter?”). They were instructed to mentally answer “Yes” or “No”. Patients were given the instruction twice. The questions were recorded in clear male voice in Spanish by one person of the lab group. Half of the NON-SELF questions were true and the other half false, and they were asked in semi-random order in order to keep the subjects alert.

Questions were presented every 4 s in blocks of 30 questions. The questions were on average 2 s in duration, thus leaving approximately 2 s to respond. Each task-run lasted 8 min and contained two blocks of each task condition, with conditions being alternated throughout the scan; i.e. ABAB. A total of 120 questions of each type were used. The same blocks of questions were delivered to every subject. The REST run lasted 7 min and the subjects were lying in the scanner without any stimulation.

2.3. *MRI data acquisition*

The fMRI measurements were carried out on a 3T Signa HDxt GE scanner using an 8-channel head coil. Change in BOLD T2* signal was measured using an interleaved gradient-echo EPI sequence. Thirty contiguous slices were obtained in the AC-PC plane with the following parameters: 2 s repetition time (TR), flip angle: 90°, echo time: 30 ms (TE), 24 cm field of view, 64×64 pixel matrix, and $3.75 \times 3.75 \times 4.0$ mm voxel dimensions. 240 whole brain volumes were obtained per task runs and 210 for the REST, including 4 dummy scans to allow for T1 saturation effects that were discarded from the analysis. High resolution T1-weighted 3D fast SPGR-IR were also acquired.

Table 2
Regions of interest used for the analysis of modulation and functional connectivity. ROIs in cells with grey background belong to the SELF-related network, and with white background belong to the NON-SELF-related network.

ROI	Peak coordinate (*x y z*)	Size (voxels)	P value[a]
MedFG	10 50 32	2049	< 0.001
Precuneus	−8 −58 32	1251	< 0.001
lMTG	−56 −68 25	953	< 0.001
rMTG	48 −56 24	735	< 0.001
iPS	−46 2 30	187	0.004
IFG	−44 28 20	166	0.05
ITG	−44 −52 −18	360	0.001

[a] Cluster level, FWE corrected in a small volume.

2.4. fMRI analysis

2.4.1. Image processing

The imaging data was analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (MathWorks Inc., Natick, MA). Images were subjected to temporal alignment and the time series of volumes were corrected for movement using a six-parameter automated algorithm. The results of this step were carefully inspected across scans and the volumes with excessive movement were excluded from the analysis. The remaining realigned volumes were spatially normalized to fit to the template created using the Montreal Neurological Institute reference brain based on Talairach and Tournoux's stereotaxic coordinate system. We confirmed successful normalization by visual inspection. The spatially normalized volumes consisting of $2 \times 2 \times 2\ \text{mm}^3$ voxels were smoothed with a 8-mm FWHM isotropic Gaussian kernel.

Statistical analysis was performed on a single subject basis using the general linear model for a blocked design. The signal changes that were associated to the blocks of SELF and NON-SELF questions were modeled by convolving a boxcar function with the canonical hemodynamic response function to create regressors of interest. The following individual linear contrasts were applied: (SELF > NON-SELF) and (NON-SELF > SELF). The design matrix also included correction for head movements as regressors of no interest. In order to evaluate the main effects of SELF/NON-SELF conditions a 2nd-stage group analysis was carried out on healthy subjects, treating subjects as a random variable. One-sample t-tests on differences in the magnitude of each condition-related response were performed.

In order to correct for heart-bit and respiration spurious effects we extracted cerebro-spinal fluid (CBF) and white matter average signals in each subject. For patients, individual normalized and corregistered T1 images were segmented into grey matter, white matter and CBF masks and the EPI signal was extracted within each mask. For control subjects, a template of white matter and CBF was employed as mask. These extracted signals were used to correct BOLD signals (see below).

2.4.2. Task modulation

Since patients had different traumatic damages and were scanned at different levels of consciousness we did not treat them as random variables. We implemented a different approach consisting in the analysis of the modulation exerted by the task epochs on the activity of areas related to the SELF and the NON-SELF processing in each patient, and their comparison with the mean modulation of these networks in the control group. This analysis was carried out under the hypothesis that if a brain network is involved in the SELF task then it should show a pattern of activity modulated by the design, and therefore have a high correlation with it.

For this analysis, we extracted the mean activity of patients' task scan data in the zone of active clusters derived from SELF > NON-SELF and NON-SELF > SELF contrasts of control group that match the DMN and AN networks as reported in previous resting state and similar task-related studies (Johnson et al., 2002; Graham et al., 2003; Kelley et al., 2002; Johnson et al., 2005; Ino et al., 2011). For this purpose, we created spheres (18 mm of radius) around the coordinates of the areas reported in Graham et al. (2003), and made a small volume correction analysis on the contrasts in the control group. As a result, we conserved those clusters that have voxels above a threshold of $p < 0.05$ FWE corrected within the spheres. We used the following regions of interest (ROIs) from SELF condition: medial frontal gyrus (MedFG), precuneus (PC), posterior cingulated cortex, right middle/superior temporal gyrus (rMTG) and left middle/superior temporal gyrus (lMTG). Medial parietal and frontal, as well as posterior middle temporal regions are identified as the primary areas of the DMN (Fox and Raichle, 2007). From NON-SELF condition the main areas identified were left inferior precentral sulcus (iPS), left inferior frontal gyrus (IFG) and left middle temporal motion complex in the posterior inferior temporal gyrus (ITG). Those areas from the attentional network (Spreng et al., 2013) have been shown to participate in attentional tasks involving semantic processing (Graham et al., 2003; Vigneau et al., 2006; Binder et al., 2009). Details of the peak coordinates and sizes of the clusters are reported in Table 2. We extracted the mean temporal activity of each ROI per scan by averaging the fMRI time-series corresponding to all voxels within the ROI. We then regressed out the six movement parameters and the average signals of white matter and CBF, from each ROI signal. Next, we calculated the linear correlation coefficient (ρ_{model}, as in Greicius and Menon (2004)) between this signal and the modeled task waveform (i.e. the boxcar waveform corresponding to SELF-NON-SELF conditions convolved with the canonical hemodynamic response function). Therefore, for each ROI, scan and subject we obtained a correlation parameter ranging between -1 (inverse correlation) and 1 (direct correlation). This value accounts for the degree to which an area's activity is coupled with the SELF task. For statistical analysis we averaged the values of the two task scans.

In this way, the different degrees of correlation of each ROI with the model allowed to establish a pattern of response to the external task, or moreover, an interrelated brain response. Then, calculating this pattern in the patients and comparing it with the control group we obtained more integrated information of their brain response to the paradigm than by looking at the activity of separated areas. In order to compare patients with healthy subjects we calculated the average ρ_{model} per ROI among the healthy subjects and evaluated how far each patient's coefficient was from the normal mean. The calculus of distance for each patient was

$$\sum_{i=1:A} \rho^{Ci}_{\text{model}} - \rho^{i}_{\text{model}}$$

where ρ^{Ci}_{model} is the average of ρ_{model} of control group, ρ^{i}_{model} is the correlation coefficient of the patient and A is the number of ROIs considered. The sum indicates that the final distance calculated is the addition of the individual ROIs distances over the A ROIs. A positive distance indicates that controls' fit with the model is higher than DOC patients; a zero distance indicates that the patients reached the level of controls; finally, a positive distance indicates that the patients' signal fit better with the model than controls. For statistical analysis on the distances we performed a repeated measures ANOVA with Network (DMN, AN) as within-subject factor and CRS-R score and number of subject as covariates. For the DMN the ROIs considered were MedFG, PC, lMTG and rMTG. For the AN, the ROIs included were aIPS, IFG and ITG. After significant main and interaction effects, post-hoc tests were performed. We report significant Pearson and Spearman correlation coefficients between the variables of interest and the CRS-R score.

In order to confirm that the results from the previous analysis were due to the external stimuli instead of spontaneous fluctuation, we performed the same analysis with the REST scan. That is, we evaluated the correlation between the same ROIs and the SELF > NON-SELF model curve, but this time we extracted the fMRI temporal signal from the resting state scan.

2.4.3. *Functional connectivity*

For the functional connectivity analysis, a linear trend removal and band pass filtering between 0.01 and 0.08 Hz was applied to the preprocessed (slice timing, realign, normalization and smooth procedures) images acquired during the scans. A seed-based approach was used to calculate the connectivity between all pairs of ROIs described in the previous section. We first regressed out the six movement parameters and the average signals of white matter and CBF, from each ROI signal. Second, for each condition (SELF, NON-SELF) and REST scan, the minimum partial correlation (Nie et al., 2015) between the temporal series of each pair of areas ($\rho_{\text{connectivity}}$) was obtained, correcting for the temporal series of the other areas. Thus, there were connectivity values between ROIs within the DMN, within the AN, and between DMN and AN. A correlation matrix was obtained for each subject in each condition and REST.

Again, distance measures were computed by calculating the average $\rho_{\text{connectivity}}$ value of each pair of areas in the control group and evaluating how far each patient's coefficient was from the controls' mean. Then we obtained the distance for the intra DMN, the intra AN and the inter DMN-AN by adding the distances of the pairs of areas falling in each category. For statistical analysis of the distances, we performed a repeated measures ANOVA with Network connectivity (intra DMN, intra AN, and inter DMN-AN) as within-subject factor and CRS-R score and subject as covariates. After significant main and interaction effects, post-hoc tests were performed. We report significant Pearson and Spearman correlation coefficients between the variables of interest and the CRS-R score. We were interested in the intra and inter-relation of the two networks and the differences between healthy and DOC groups. In order to assess this statistically, we performed a repeated measure ANOVA. Within-subjects factor was Network connectivity (levels: intra DMN, inter DMN-AN, and intra AN), and between-subject factor was Group (level: control, DOC).

Post-hoc paired t-tests were performed and the significance level was set as $p = 0.05$ (Bonferroni corrected). The statistical tests were performed in Origin Pro 8 and IBM SPSS Statistics 20.

3. Results

3.1. *Networks of activation*

In healthy subjects the SELF compared to the NON-SELF condition (SELF > NON-SELF) presented a stronger activation in anterior cingulate/medial frontal gyri and superior frontal gyrus, posterior cingulate/precuneus, bilateral middle temporal gyri extending into inferior parietal lobule, bilateral inferior orbital gyrus and caudate (Fig. 1 left). These areas resemble the DMN. Conversely, the contrast NON-SELF > SELF showed increased activity in a left lateralized network involving inferior frontal gyrus, inferior precentral sulcus, inferior parietal lobule and inferior temporal gyrus, areas belonging to the attentional network (Fig. 1 right).

In the patients, these patterns of activation were not as consistent, as some patients showed incomplete or nonexistent DMN or AN networks corresponding to the SELF > NON-SELF or NON-SELF > SELF contrasts, respectively (Figs. S1 and S2).

3.2. *Task modulation*

Next, we inspected the modulation exerted by the paradigm on fMRI activity in the patients with DOC. In Fig. 2 (top), we plot the correlation values between the areas and the paradigm in the

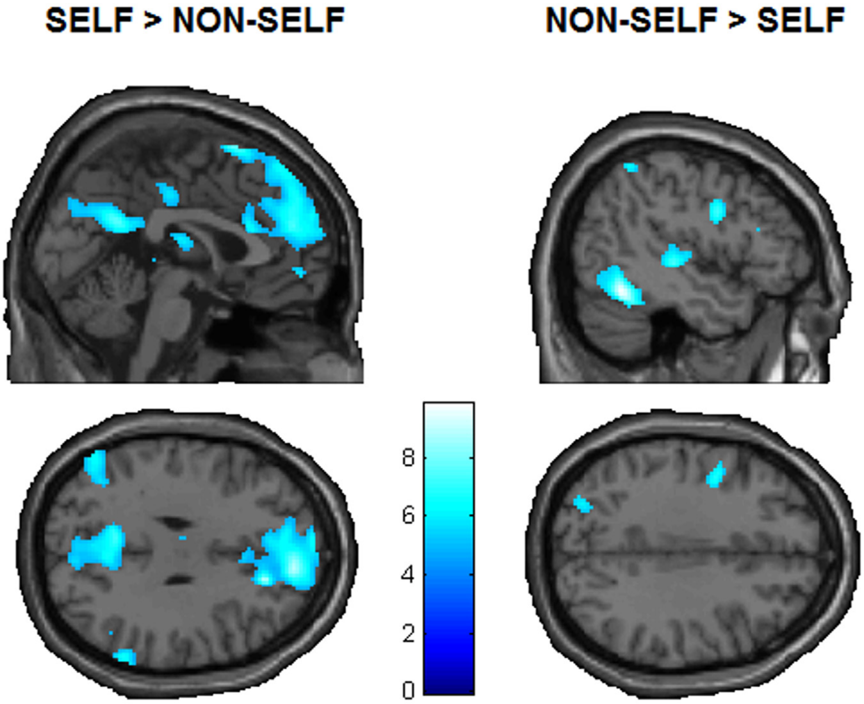

Fig. 1. One-sample *t*-tests on healthy subjects. Differences in the magnitude of each condition-related response ($p < 0.001$ for visualization uncorrected). Sagital planes: $x = 0$ (left) and $x = -46$ (right). Axial planes: $z = 30$ (left) and $z = 34$ (right). The colorbar indicates the T value.

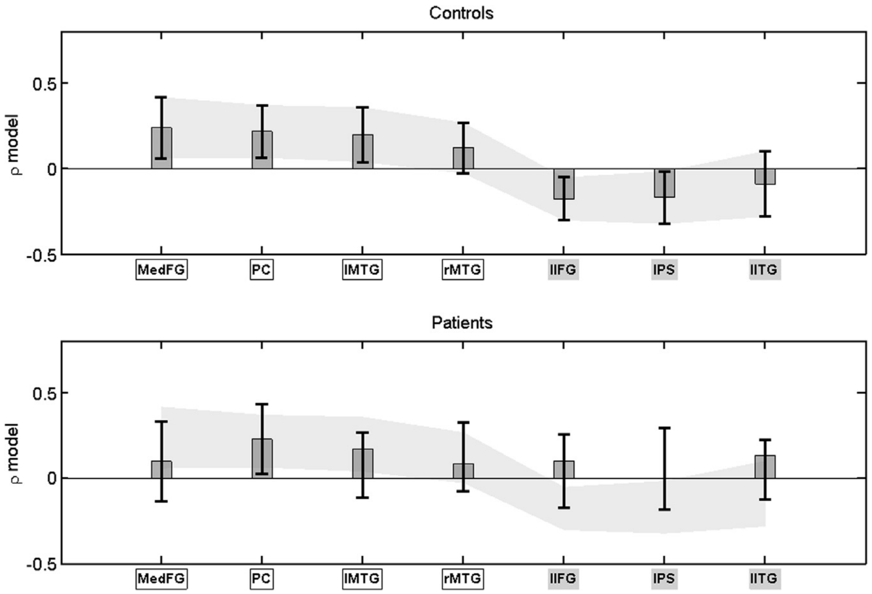

Fig. 2. Correlation values (ρ_{model}) between the time-course of the DMN and AN areas and the SELF > NON-SELF model. Top: Control group. Mean ρ_{model} values (bars); error bars and grey area indicate standard deviation. Bottom: Patient group. Bars indicate mean values of the patient group; grey area is determined by controls' mean ± standard deviation. Labels of areas in white boxes belong to the SELF network; labels of areas in grey boxes belong to the NON-SELF network. It can be observed that the mean for DOC group lies below or in the bottom of the control region for SELF > NON-SELF areas, indicating low correlation of DMN areas with the SELF condition, and above the control region for NON-SELF > SELF areas, indicating low anti-correlation of AN areas with the SELF condition. The DOC group presents large variability on the interval of ρ_{model} values determined by the control group, as well as more de-correlated brain activity with the tasks.

control group. The areas comprised in the DMN were positively correlated with the model, while areas in the AN were negatively correlated. In Fig. 2 (top), the mean values of ρ_{model} (heights of the bars) form a pattern of correlations that we considered for the control group. A relatively small deviation of the sample around the mean values can be observed. The patients, on the contrary, showed a very variable pattern, with a general smaller value as compared to controls (Fig. 2 bottom).

Then we inspected the distance between patients and controls, that is, the differences between the average pattern of controls and the correlation pattern of individual patients. The ANOVA shows that the distance on the ρ_{model} for the DMN was significantly different from the distance for the AN (main effect of network: $F=26.33$, $p<0.001$; post-hoc *T* test: $p<0.001$; mean ρ_{model} DMN: 0.19; mean ρ_{model} AN: -0.66). In addition, there was a decreasing distance for the DMN as a function of CRS-R score, where patients with higher scores presented reduced distance to controls (interaction network by CRS-R: $F=20.66$, $p=0.001$; $r_{Pearson}=-0.51$, $p=0.049$; $r_{Spearman}=-0.54$, $p=0.03$; Fig. 3). No trend as a function of the CRS-R score was observed for the AN.

To disentangle whether the decreasing in the distance with recovery was due to a self-referential modulation and not just to language comprehension recovery, we studied the brain modulation in the areas of the DMN and the AN together. That is, we plotted the subtraction of the modulation in the DMN minus the modulation in the AN. As both conditions included a language comprehension task, if there was a modulation due to self -referential process we would find a DMN–AN increasing difference with the CRS-R score. Fig. 4 shows that, effectively, there is a linear increase as a function of the CRS-R score, indicating an integral self-modulation of the brain with increasing level of consciousness.

In order to strengthen the results of brain modulation due to the task, we performed the same correlation analysis with the REST scan. We argued that if the modulation found with the model was due to spontaneous fluctuation and not because of the external stimuli, then we would find a similar result during the REST run. Fig. S3 shows the results of the control group ρ_{model} pattern, the patients' distributions, and the distance plots as a function of the CRS-R score. As expected, no correlation was found in this case, which reinforces the sense that an integrated modulation of the DMN was obtained in the data from the sessions due to the external stimuli, and this response was the more similar to healthy subjects the higher the consciousness level was.

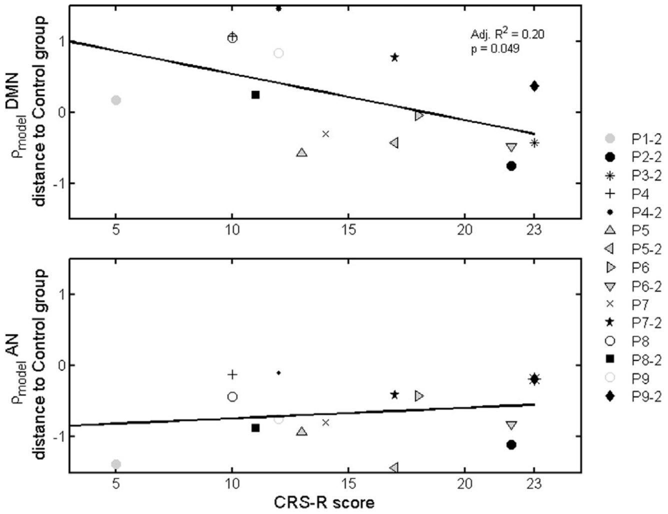

Fig. 3. ρ_{model} distance. Distance between the mean DMN ρ_{model} (or AN ρ_{model}), of healthy subjects and individual patient's DMN ρ_{model} (top; or AN ρ_{model}, bottom) as a function of the patient's CRS-R score. The straight lines represent the linear fit of the regression model. Each dot corresponds to a different patient and session, as indicated in the figure legend; the second session is indicated by a number 2 after the patient's ID. The patients present an integral task response in SELF-related areas that is closer to mean control response as they recover from DOC.

3.3. *Functional connectivity*

The functional connectivity analysis applied on control group during REST showed a particular pattern of correlations within and between DMN and AN (Fig. 5, top). As expected, intra connectivity values were higher than inter-network connectivity values with

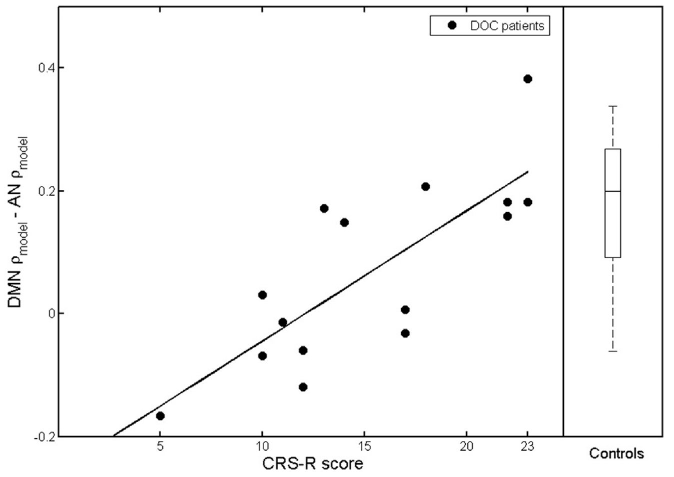

Fig. 4. Difference between DMN and AN ρ_{model} as a function of CRS-R score for patients (major plot). Straight line is the linear fit of the data (Adj $R^2=0.58$, $p=0.001$). Subplot to the right corresponds to the control mean differences in the corresponding ρ_{model} (DMN-AN).

means for intra DMN: 0.30 ± 0.18, inter DMN-AN: 0.02 ± 0.13, and intra AN: 0.37 ± 0.25.

The distribution of patients' correlation values ($\rho_{connectivity}$) is presented in Fig. 5, bottom. As in the modulation analysis, patients showed a wide-spread distribution. For the DMN and AN intra-network connectivity the general mean (bars) lied in the inferior part of the controls' distribution (grey area). Conversely, for the inter DMN-AN connectivity the patients' mean lied in the superior part (DMN: 0.22 ± 0.25, inter DMN-AN: 0.09 ± 0.22, and intra AN: 0.22 ± 0.26).

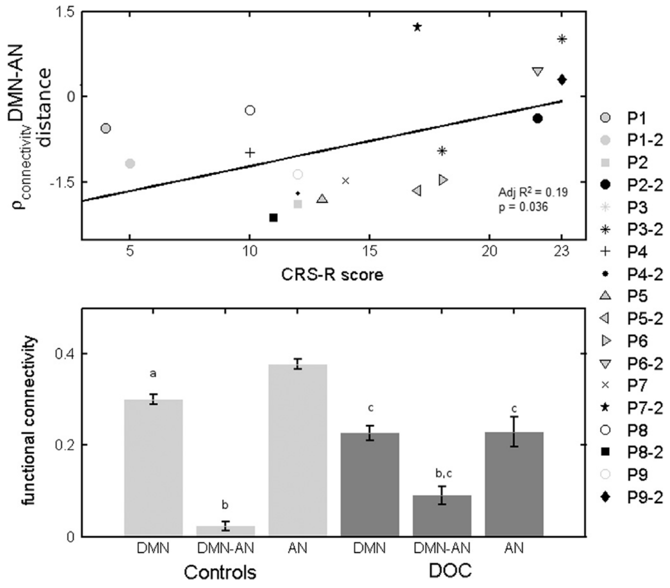

Fig. 6. $\rho_{connectivity}$ distance in resting state. Top: dots represent the individual patients' distance from the control mean of $\rho_{connectivity}$ between DMN-AN. The straight line is the linear fit of the regression model. Bottom: average functional connectivity in Control and DOC groups for the different network connectivity. Error bars indicate mean standard error. a: Significantly different than intra AN connectivity in Controls; b: significantly different than intra DMN and AN connectivity; c: significantly different than connectivity in control group. All significant values at a threshold level of $p=0.05$, Bonferroni corrected.

To assess the effect that recovery had on the intra and inter network connectivity, we performed an ANOVA on the distances for intra DMN, intra AN and inter DMN-AN connectivity including

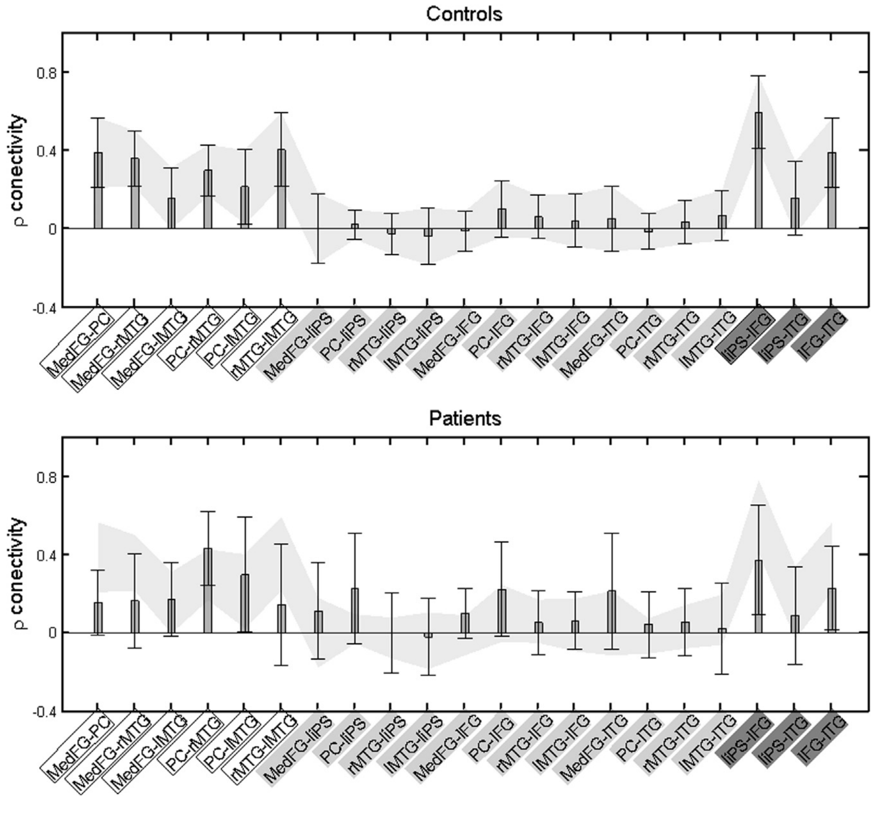

Fig. 5. Functional connectivity between DMN and AN areas during REST. Values of $\rho_{connectivity}$ in control group (top; bars: mean values; error bars: standard deviation) and patients (bottom; bars indicate mean of DOC group; grey area is determined by control's mean ± standard deviation). MedFG: Medial Frontal Gyrus; PC: Precuneus; rMTG: right Middle Temporal Gyrus; lMTG: left Middle Temporal Gyrus; iPS: inferior Precentral Sulcus; IFG: Inferior Frontal Gyrus; ITG: inferior temporal gyrus. Labels in white boxes: intra DMN; light grey boxes: inter DMN-AN; dark grey boxes: intra AN.

CRS-R score as a covariate. Inter DMN-AN distance was significantly different than intra DMN and intra AN (main effect of Network connectivity: F=10; p=0.002; post-hoc *T* test: $p \leq 0.001$). Notably, inter DMN-AN distance showed a significant decreasing (i.e., closer to zero) linear relation with CRS-R score (interaction Network by CRS-R: F=3.82, p=0.05; $r_{Pearson}=0.49$, p=0.036; $r_{Spearman}=0.41$, p=0.08; Fig. 6, top). Intra DMN and intra AN distances did not show a significant trend with CRS-R score.

The same analysis performed with the connectivity values from task runs gave results similar to REST (data not shown).

We then compared the intra and inter connectivity values across groups (Fig. 6, bottom). Inter-network connectivity was significantly lower than intra DMN and than intra AN (main effect of network: F=96.4, $p < 0.001$; post-hoc *T* test: $p < 0.001$). On the other hand, total connectivity was significantly higher in control than in DOC group (main group effect: F=10.31, p=0.003). Remarkably, intra DMN and intra AN connectivity were larger in control group compared to DOC while inter DMN-AN connectivity was larger in patients (interaction network connectivity by group: F=16.56, $p < 0.001$; post-hoc independent T tests: intra DMN, p=0.001; intra AN, $p < 0.001$; inter DMN-AN, p=0.006; Fig. 7). Furthermore, intra AN was larger than intra DMN in control ($p < 0.001$) but not in DOC group.

We then inspected the relation between activity and connectivity in DOC patients, in order to assess whether a disrupted connectivity in the DMN and AN was related to an abnormal correlation with the model, or, on the opposite, a normal connectivity could exist despite an abnormal correlation with the task. We found a trend from UWS to recovered states, where UWS state was related to high inter-networks connectivity and low networks' modulation by the task, while conscious state presented higher modulation and low interconnectivity (Fig. 8). Conscious patients presented therefore a similar pattern than controls, despite their modulation value was in the lower range determined by the control group. Interestingly, MCS state presented a profile between these two extremes: some patients in MCS presented higher modulation (similar to recovered patients) while others did not; however, this state was characterized by a high inter-network connectivity. Given the small sample of DOC patients employed in this study, these results and their interpretation must be taken as preliminary.

4. Discussion

In this study we investigated the fMRI modulation of the brain activity in DOC patients under external stimulation and during resting state. The study focused on brain networks participating in SELF and NON SELF processes in response to the external task, instead of opting for the conventional approach of looking at different areas separately. We were interested in SELF condition because it is extensively known to activate the DMN, whose integrity is disrupted in DOC state. In addition, we studied its counterpart, the attentional network, and the functional connectivity between them. The selection of these two networks was based on several studies reporting that correct antagonistic dynamics between their signals are associated to a better cognitive response. We observed a lack of alternating modulation between networks at lower level of consciousness, which was recovered at higher CRS. Such recovery was linear with respect to the level of consciousness (Fig. 4). Moreover, the difference in ρ_{model} between DMN and AN in patients evolved gradually with the improvement of the CRS, whereas the connectivity intra-networks showed a sharper behavior (Fig. 8).

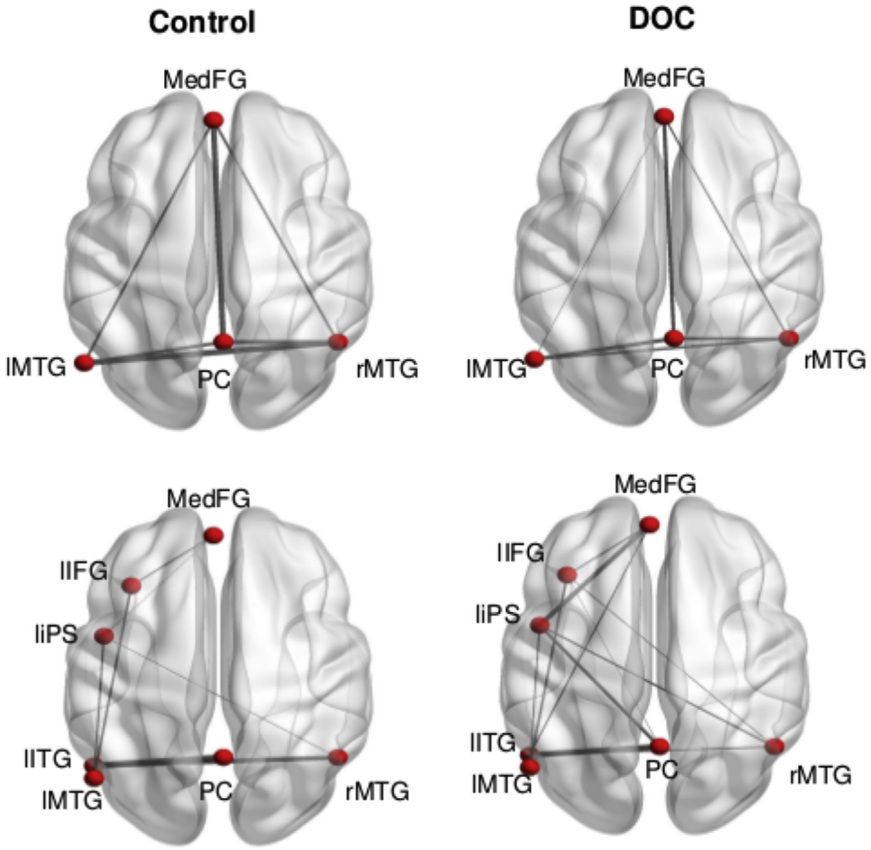

Fig. 7. Brain connectivity maps. Average connectivity in control (left column) and DOC group (right column) within the DMN (top row) and between the DMN and the AN (bottom row).

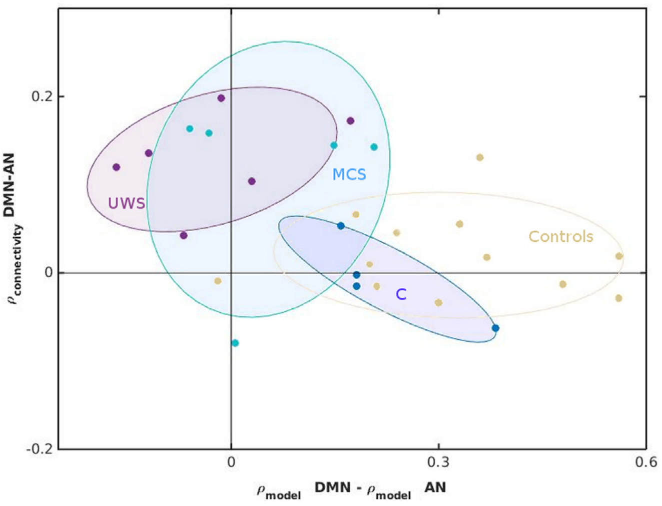

Fig. 8. Relation between the modulation of DMN and AN activity by the task, and the inter-network connectivity. Each dot corresponds to a different subject. Data from first and second acquisition of patients is included. The states are indicated with different colors and labels: UWS: unresponsive wakefulness syndrome; MCS: minimally conscious state; C: conscious recovered. The ellipses were drawn for illustrative purposes around the average of each group and the extension is proportional to the standard deviation.

4.1. *Modulation of the DMN and AN by external stimuli*

In healthy subjects the task recruited the areas of the DMN during the self-directed questions, as was already reported by Johnson et al. (2002). The areas of the AN recruited during the general questions correspond to the left-lateralized network reported for semantic processing and conceptual memory retrieval in several studies (Graham et al., 2003; Vigneau et al., 2006; Binder et al., 2009; Crone et al., 2011). In DOC patients, the patterns of brain activity were found to be more variable. Thus, we evaluated individually the modulation exerted by the task in different brain areas, and calculated its distance between each patient to the mean of healthy people. This measure surpasses the beta value estimates associated to the events because it catches the general dynamics of the activity due to a task involving different brain processes (Greicius and Menon, 2004).

The analysis revealed a decreasing distance of DOC ρ_{model} to the mean ρ_{model} of the control group, with increasing CRS-R score. This result goes beyond the ones of Huang et al. (2014) (showing that MedFG presents increased activity in a self-reflection task with increased level of consciousness) since in our case the recovery of activity was observed including both DMN and AN networks and not only one isolated region. Our results highlight an integral effect regarding the modulation exerted by the task on the brain, and manifests that the effect of the recovery is not only frontal. Thus, the inclusion of the reported areas of the DMN and the AN allowed to obtain a general picture of the modulation of the brain areas due to the pertain tasks, taking into account not only their individual behavior but also their potential integration as members of interacting networks.

Previous work suggested that the activity of areas of the DMN and their functional connectivity during an external task can be employed as markers of consciousness (Vanhaudenhuyse et al., 2009, Huang et al., 2014). Here, we showed that a more general pattern of cognitive processing, including both DMN and AN, during an attentional task may offer substantial information about the state of disorder of consciousness. This is in line with the idea that cognitive processes involving neural interaction might better contribute to the assessment of higher cognitive capabilities in patients with DOC (Coleman et al., 2009, Crone et al., 2011, Demertzi et al., 2013, Qin et al., 2015).

In summary, our results show that the involvement of the DMN and AN in an active task in patients with DOC present a linear recovery with behavioral CRS-R measure of consciousness.

4.2. *Functional connectivity*

The pattern of functional connectivity in healthy controls showed high correlation within DMN and AN networks and low correlation between networks, which reflects the functional differentiation of the networks as reported elsewhere (Spreng et al., 2013). In DOC patients, however, the pattern was less evident, hinting a lack of functional specificity not only within networks (i.e., between the areas of the same network), as stated by previous works, but also between networks, as suggested by the significant correlation of the distance between patients and controls with the CRS-R score in the inter DMN-AN connectivity (Fig. 6). Taken together, the result implicates a lack of information segregation. A similar phenomenon has been reported in one patient in vegetative state by Boly et al. (2009), who observed that in this patient the connectivity within the DMN was diminished while the anticorrelation between the precuneus and the "task-positive" network (equivalent to the AN) disappeared. In a previous work with PET, Thibaut et al. (2012) found a linear increase of metabolic activity in DMN and AN networks with level of consciousness. The increase in DMN and AN metabolism parallels the increase in functional connectivity within the DMN and within the AN that we found here. Taken together, the results suggest that the connectivity between intrinsic and extrinsic networks assessed by fMRI may have an important diagnostic value. Further studies of this phenomenon will help to better understand the interplay between the DMN and AN networks at the functional connectivity level.

In a previous work with the same group of patients we observed a disruption in the effective connectivity at the brain level at rest (Mäki-Marttunen et al., 2013). This could be reflected by the more homogeneous connectivity between networks as we found here, where in consequence information cannot be successfully segregated.

In summary, an increased coupling between the SELF and NON-SELF systems and a decreased coupling within systems is evident in DOC patients.

4.3. *Modulation of self-directed activity and functional connectivity*

We investigated a possible relation between the connectivity intra DMN, intra AN, and inter DMN-AN, and the ability of the paradigm to modulate the areas of self-processing. In patients we found that a decrease in ρ_{model} DMN minus ρ_{model} AN is related to a decrease in the functional connectivity between these networks. Particularly we found a non-linear trend between them. While a gradual increase in ρ_{model} DMN minus ρ_{model} AN is observed throughout all the diagnosis up to healthy subjects, the inter DMN-AN connectivity remains high in UWS and MCS, but is low in recovered patients and controls, showing a disrupted behavior. Our findings suggest that inter-networks connectivity (spontaneous or induced by a task) might help to understand the pathophysiology of DOC patients. Further work on this field will extend these results.

A disruption in intra and inter DMN and AN connectivity was observed in healthy subjects during propofol-induced anesthesia (Boveroux et al., 2010). In addition, an altered functional connectivity between DMN and AN networks has been found in several neuropathological states (Broyd et al., 2009 and cites therein). For instance, the DMN and AN are abnormally anticorrelated in schizophrenic patients. Conversely, in patients with autism spectrum disorder (ASD) the anticorrelation between these networks is diminished, in addition to an abnormally decreased correlation within the DMN but not in the AN. Strikingly, a similar phenomenon was observed here in the DOC patients. Kennedy and Courchesne (2008) suggest that "this imbalance may either bias or reflect a bias of the autistic individual away from social and emotional processing, but toward a particular non-social and non-emotional cognitive processing style". The different nature of the etiology of the ASD, DOC and anesthesia states makes the comparison difficult; however, the common factors are an altered intra DMN and inter DMN-AN functional connectivity and a withdrawal from the environment.

According to the Default Mode Interference Hypothesis (Sonuga-Barke and Castellanos, 2007) we found that, at the functional connectivity level, there is a clear lack of differentiation in the connectivity between and within these networks, thus a possible interplay between them might not be feasible in patients with severe DOC.

4.4. Prospective analysis

In the present work we analyzed patients in DOC state in two stages: a first time, closer to the traumatic accident, and a second time, 3–6 months later. The purpose was to investigate possible brain variables that allow to predict future recovery. Here we have not found any measure associated to brain modulation or functional connectivity that allowed for predicting the DOC state at the second scan session. Probably, one limitation in this prospective analysis would be the limited number of patients, and the reduced number of patients in the different states, making it difficult to compare the recovered subgroups against the non-recovered subgroups. Future longitudinal studies may allow digging deeper into brain attributes that convey predictive value of recovery.

4.5. Technical issues

Several works suggest that the anti-correlation between the DMN and AN might in fact depend on the preprocessing of the data. The correction with overall signal components (for example, global signal regression) may influence the emergence of anticorrelations (Murphy et al., 2009; Chai et al., 2012). Here, we did not follow this procedure and found a near-zero correlation between areas of the networks in healthy subjects (Fig. 5), which agrees with Murphy et al. (2009), suggesting that the networks are not functionally interacting but segregated.

An important limitation is the actual difficulty in the interpretation of fMRI activity data obtained from patients in DOC because this activity could be simply driven by brain unspecific response to stimulation. In fact, it is almost impossible to know how engaged are the patients with the task. Even when we found a recovery of the DMN and AN activity related with the improvement of consciousness and consequently of language capacity, the subtraction between these networks (Fig. 4) showed a linear increment with the CRS, which might not be explained only with language improvement. Besides, even when the activity were due to unspecific response to stimulation, it may be expected to find activation in primary sensory brain areas; nevertheless, we found activity in DMN and AN networks which include association cortices.

Another important limitation of the study is the reduced number of patients that could be recruited and included in the analysis. However, we had two acquisitions from each patient in different stages of their evolution, obtaining information not only of the activity and connectivity properties of the brain in each state but also of the evolution.

4.6. Future directions

Further studies on the interplay between the identified brain networks in DOC patients may help to understand their functioning. For instance, in this work we neither assess the involvement of the so-called fronto-parietal control network (FPN) nor the salience network (Seeley et al., 2007). Probably both tasks that we employed here involved some of the areas integrating them (Spreng et al., 2009, 2013), but these networks are difficult to be properly functionally assessed in patients with DOC. For example, impairment of self-awareness after TBI results from a breakdown of functional interactions between nodes within the FPN (Ham et al., 2013), whereas structural integrity of the AN seems necessary for the efficient regulation of the activity in the DMN (Bonnelle et al., 2012).

5. Conclusions

In the present study, we assessed the question of whether functional connectivity and modulation of activity in areas belonging to the DMN and AN networks are balanced in DOC patients. For this purpose, we investigated the modulation of the temporal activity during the performance of a task involving only self-referential and sustained attention processes. We subsequently looked at the functional connectivity between those areas during resting state. We found that disorders of consciousness presented a disrupted relationship between the two networks during the task and that this disruption was gradually recovered with consciousness. At rest, DOC patients also showed an altered pattern of functional connectivity within the DMN and between the DMN and the AN, although the trend of the connectivity with recovery was different than that of the induced activity. In the frame of the default-mode interference hypothesis, which posits that an efficient switching between the default-mode and attentional networks is required for peak cognitive performance, our findings suggest that more than one area of the networks have to be taken into account in order to evaluate the interference hypothesis in illness. Moreover, although further work in this field will extend these results, the present work helps to understand the pathophysiology of DOC patients.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2016.01.022.

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