Global Functional Disconnections in Post-anoxic Coma Patient

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Key words: consciousness disorders, brain connectivity networks, resting state, functional MRI

SUMMARY – *Disorders of consciousness have been related to different disconnection patterns as assessed by neuroimaging tools such as PET or fMRI. In this report, we use resting-state functional MRI acquisition and a functional connectivity analysis by graph of brain networks, to investigate the global residual connection pattern in a patient with consciousness disorders following post-anoxic injury. We then compare this pattern with those of a group of twenty controls. We observed that the patient's graph presents multiple disconnections in primary areas and in high-order associative areas. This pattern is consistent with a vegetative state, as reported by other groups. Further, the informations conveyed by this approach are consistent with those provided by PET, fMRI and EP. This new approach presents a very strong potential for diagnosis for consciousness disorder patients since it is applicable very early after the insult.*

With the increase of coma patients admitted to critical care departments following cardio-respiratory arrest, there is a need for an early clinical assessment tool devoted to global functional brain damage evaluation. In these patients, neuroimaging tools such as PET and task-related fMRI have shown different patterns of functional disconnections depending on level of consciousness [1-4]. A global disconnection syndrome between higher-order association cortices and primary cortical areas is observed in vegetative state (VS) patients while the preservation of large-scale cortical networks associated with language and visual processing is noted in minimally conscious state patients [3,4]. Furthermore, the thalamocortical connectivity was found to be restored in a few patients who recover consciousness after being in a chronic VS [5]. Finally, the medial parietal cortex (precuneus) seems to be the brain region whose activity best differentiates between consciousness disorders patients [2].

Recent resting-state functional connectivity approaches have identified a particular set of areas (including the precuneus, the mesiofrontal cortex and the thalamus), the "default mode network" (DMN) which is hypothesised to be related to self-consciousness [6]. This DMN has been studied in non-communicative brain-damaged patients (coma, VS, MCS and locked-in syndrome [7-9]) and a relation was found between the amount of connectivity in the DMN and the degree of clinical consciousness impairment [9].

In 2006, Achard et al. [10] have proposed to explore the resting brain in terms of graphs of functional connectivity. This has the advantage of considering globally all the functional correlations within the brain. Human brains can be described as complex networks whose topological organization is characterized by highly

Paper presented at the XIX Symposium Neuroradiologicum, 2010.

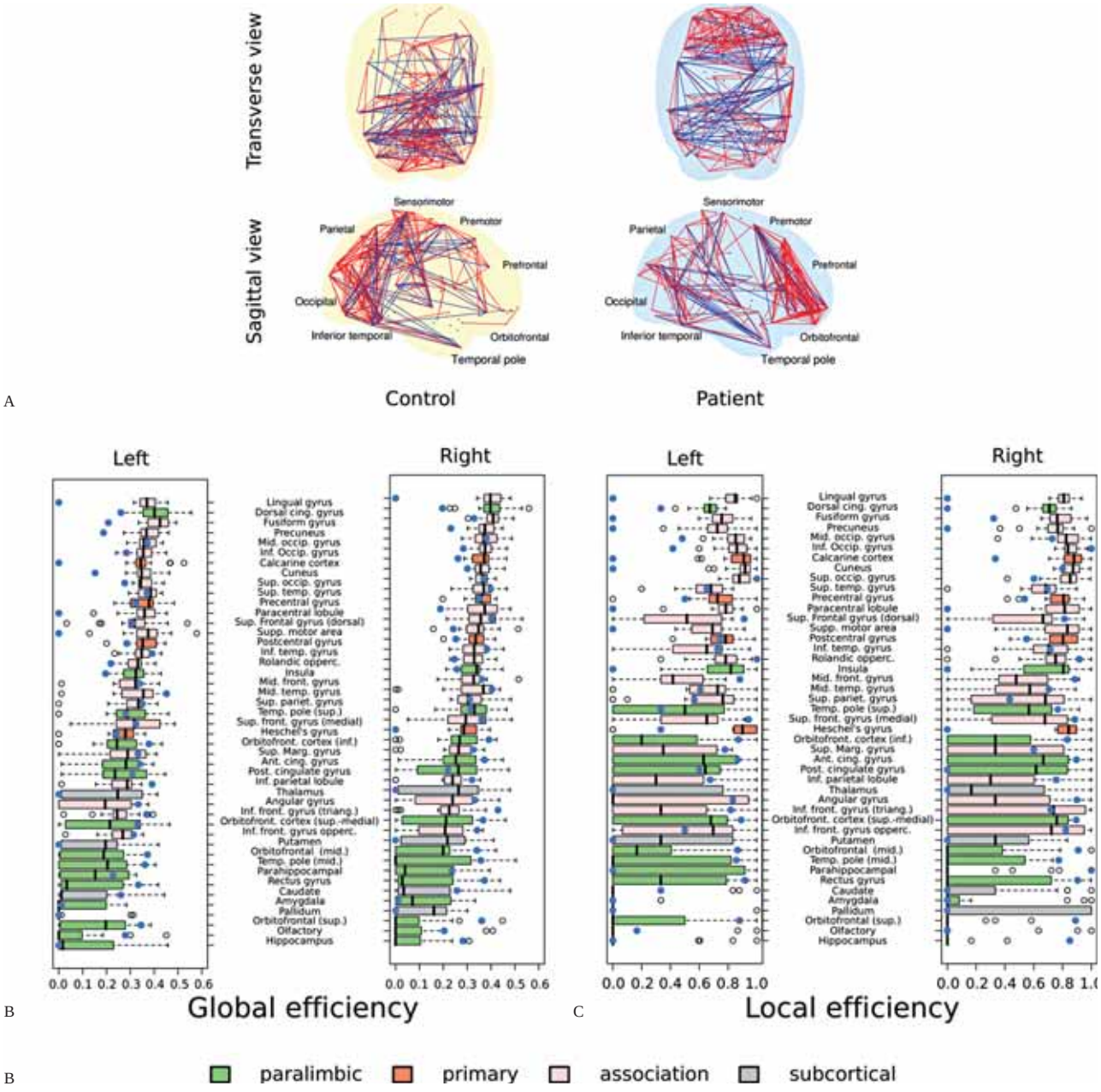

Figure 1 A Functional connectivity graphs for one typical control and the two patients with disorders of consciousness following anoxic injuries. Graphs are constructed by thresholding (at 0.8) the wavelet correlation matrix corresponding to the frequency band 0.02-0.04 Hz (connections between nodes separated by a Euclidean distance >7.5 cm (<7.5cm) are blue (red)). Global efficiency (B) and local efficiency (C) in the 90 regions of the AAL template. The nodal efficiency in the control group is represented as a rectangular boxplot whose limits represent 50% of the controls and dashed limits 95% of the controls. Efficiencies are represented as points in blue for patient 1.

connected cortical nodes that have numerous short- and long-distance connections [11]. In recent studies, alterations of these functional brain networks have been found in pathologies such as Alzheimer's disease [12].

Here, we describe one patient, with previous normal cerebral functioning, that experienced cerebral anoxic injury. We constructed a graph of the whole brain from resting-state fMRI in order to evaluate the remaining functional connectivity. We compared this graph to the ones of twenty controls in the same range of age, who were scanned in the same experimental conditions as the patient.

A 36-year-old man with a medical history of mild extrinsic asthma was admitted for anoxic coma after out-of-hospital cardiac arrest. He had been suffering from bronchitis with fever for a few days when he suddenly lost consciousness and was found in cardiac arrest by a lay bystander. Although emergency care givers resuscitated him within minutes, on admission, in the absence of any sedation, the patient was in a profound coma (absence of reactivity to any stimulus, GCS<3). Yet vegetative functions remained present: spontaneous ventilation was present, although insufficient to maintain haematosis for more than a few minutes, the heart rate and blood pressure were in the normal range. After two days of supportive care, intermittent diffuse myoclonus occurred at each resonant stimulation. Neither benzodiazepines, nor barbiturates or levotonine relieved them. Many consecutive EEGs recorded burst suppression pattern. The Wessex Head Injury Matrix [13] scored the degree of consciousness in this patient at zero at ten days. Three months later, the patient had still not recovered any consciousness and/or communication. He was still quadriplegic but had recovered continuous spontaneous ventilation, consistent with vegetative state. No drug influencing consciousness was given and myoclonia persisted. The 18-FDG PET scan revealed a large hypometabolism bilaterally in centro-parietal and occipital cortices, a preserved metabolic activity in frontal and temporal cortices and in central nuclei. There was an hypometabolism bilaterally in the thalamus and in the precuneus. Functional MRI was carried out using passive bilateral somesthesic and auditory stimulations, showing a lack of BOLD response in the primary sensory area, a normal response in the left auditory areas and a weaker response in the right auditory areas. Evoked potentials were performed with somesthesic, visual and auditory stimulations. Visual and auditory evoked potentials were altered and somesthesic evoked potentials were absent. Seven months after admission without any improvement in his state, the patient died after care withholding following a pulmonary embolism.

For functional connectivity analysis, a 20-minute-long BOLD-sensitive EPI sequence in the resting state was acquired for 20 controls and at 3 days after the injury for the patient. Main MR parameters were : 1.5 Tesla scanner (Avanto, Siemens, Erlangen, Germany), TR=3 s, TE=50 ms, isotropic voxel size = 4×4×4 mm, 405 images, and 32 axial slices covering the entire cortex. Written informed consent was obtained by next of kin for the patient and by the 20 healthy volunteers. The protocol was approved by the local ethics committee.

The graphs of functional connectivity network in all subjects were constructed in the following manner: [10]

Regional mean time series were estimated in each region of the Anatomical Automatic Labelling (AAL) template [14].

The pairwise inter-regional correlations between wavelet coefficients corresponding to 0.02-0.04 Hz was computed and tested for statistical significance between the patient and the control group.

The connectivity graphs were then explored by retaining the absolute correlations of statistical significance using multiple hypothesis test at 5%, and we retained those greater than a given threshold chosen such that every graph has the same number of connections.

Two topological properties of the graph were computed using the global and local efficiencies of each region. High global efficiency (GE) corresponds to highly connected regions to other distant regions. High local efficiency (LE) corresponds to the ability to easily compensate for a loss of the region.

After selection of the 300 edges with highest correlations, the corresponding graphs obtained for the patient and for one typical control subject (Figure 1A) give a global overview of all the functional connections. For the patient, there is a major disconnection of the frontal lobe with the other lobes. Notably, the fronto-parietal connections, part of the DMN network, are absent for the patient. It also presents a large local connectivity pattern within the prefrontal lobe.

The global and local efficiencies were computed for the group of controls and compared to the values obtained for the patient (Figure 1B and C) with random effect analysis based on statistical tests for z-values (Table 1).

Significantly lower GE and LE were found in primary areas (orange) in calcarine sulcus (CAL) bilaterally and in the right Heschl gyrus (HES); in associative areas (light pink) in occipital areas (LING bilateral, FFG bilateral, MOG and IOG left in LE, CUN left), in parietal areas (PCUN bilateral, PCL bilateral) and in frontal area (SMA bilateral); in paralimbic areas (green) (INS bilateral in LE, DCG bilateral). Significantly higher LE was found in right ORBsup. Note that deep grey nuclei (in grey) present null efficiency values (THA, PUT,

Table 1 Regions were LE or GE from the patient was significantly different from the group of controls. For each region, the p-value associated to the z-values was computed. After applying a multiple test using the False Discovery Rate, a significant decrease or increase in LE or GE is marked by three asterisks. Two asterisks (respectively one asterisk) corresponds to p-value < 0.01 (respectively <0.02), uncorrected for multiple comparisons.

		L/R	*GE z-value*	*GE pval*	*LE z-value*	*LE pval*
Parietal	Precuneus	L	–3.17	7.10–4 **	–4.32	7.10–6 ***
	Precuneus	R	–3.33	4.10–4 ***	–5.31	5.10–8 ***
Temporal	Heschl's gyrus	R	–3.41	4.10–4 ***	–2.19	0.014 *
Frontal	Orbitofrontal cortex (superior)	R	1.96	0.024	5.24	8.10–8 ***
	Supplementary motor area	L	–2.86	2.10–3 **	–2.48	6.10–3 **
	Supplementary motor area	R	–1.31	0.1	–3.1	1.10–3 **
Occipital	Lingual gyrus	L	–3.64	1.3.10–4 ***	–3.85	5.10–5 ***
	Lingual gyrus	R	–9.0	1.10–19 ***	–12.8	9.10–38 ***
	Middle occipital gyrus	L	0.15	0.44	–3.94	4.10–5 ***
	Calcarine cortex	L	–5.71	5.10–9 ***	–7.33	1.10–13 ***
	Calcarine cortex	R	–2.09	0.018 *	–6.34	1.10–10 ***
	Fusiform gyrus	L	–4	2.10–5 ***	–7.69	7.10–15 ***
	Fusiform gyrus	R	–1.56	0.06	–5.1	2.10–7 ***
	Cuneus	L	–4.52	3.10–6 ***	–9.48	1.10–21 ***
	Inferior occipital gyrus	L	–1.55	0.06	–4.66	1.10–6 ***
Limbic/ Paralimbic	Dorsal cingulate gyrus	L	–1.76	0.04	–2.76	3.10–3 **
	Dorsal cingulate gyrus	R	–2.5	5.10–3 **	–6.92	2.10–12 ***
Others	Insula	L	–1.85	0.03	–2.36	9.10–3 **
	Insula	R	–1.1	0.14	–2.41	8.10–3 **
	Paracentral lobule	L	–4.82	7.10–7 ***	–2.5	5.10–3 **
	Paracentral lobule	R	–2.1	0.018 *	–2.5	5.10–3 **

PAL) but are not out of the range defined by our group of control subjects.

Taken together, these measurements reveal disconnection patterns between primary areas and higher order areas, in visual and motor systems, and in the right auditory system. The functional connectivity within the left auditory system and the sensory system are not significantly altered.

The results obtained by the graph analysis provides results which are consistent with those obtained by other modalities [15]. In the visual system, there is a large hypometabolism bilaterally in the occipital cortices, and impaired visual EP. In the auditory system, PET showed a preserved metabolic activity in temporal cortices, BOLD a normal functional response in the left hemisphere and a reduced one in the right hemisphere. In the sensory system, PET revealed a hypometabolism and a lack of BOLD functional response but a reduced global efficiency in the graph although not significant.

The LE and GE of the precuneus are significantly decreased, this corresponds to a major loss of long-distance connections (pvalues of global efficiency = 7.10–4 left and 4.10–4 right), and also a loss of graph resilience (the ability to be replaced by its connected neighbours, pvalues of local efficiency = 7.10-6 left and 5.10-8 right).

This approach allows one to evaluate the overall remaining functional connections by constructing global connectivity graphs, extending the approaches focused on the DMN used by others [7,9]. In this patient, not only did we find a precuneus disconnection (as was also found in [9]) but also a global disconnection pattern between primary and associative areas,

consistent with a vegetative state [3]. Other associative areas were found to be disconnected (lingual gyrus, fusiform gyrus...) whose functionality cannot be easily evaluated by activation fMRI or EP.

The construction of global connectivity graphs allows us to also evidence the regions with enhanced connectivity, for this patient, local frontal connectivity was increased. Although not understood, this might be related to observations on fMRI simulated data[16] and on patients with Alzheimer disease [12].

This neuroimaging technique is to a large extent consistent with the other modalities used for this patient. The discrepancies could originate from impaired neuro-vascular coupling and need to be further investigated.

An additional major interest of the method is that the data for constructing a graph of functional connectivity can be acquired within days after admission in hospital, without the need of patient stimulation, the graph itself can be constructed off line in about one hour, so that it may be used as a complementary tool for the diagnosis and management of critical care patients with consciousness disorders.

Acknowledgements

This work was supported in part by "Reseaux National des Systemes Complexes" . SA work was supported in part by a BQR grant from Grenoble INP.

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