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Influence of the segmentation on the characterization of cerebral networks of structural damage for patients with disorders of consciousness

Darwin Martínez
Universidad Central, Bogota

Jamuna J. Mahalingam
University of Southern California

Andrea Soddu
The University of Western Ontario, asoddu@uwo.ca

Hugo Franco
Universidad Central, Bogota

Natasha Lepore
University of Southern California

See next page for additional authors

Authors

Darwin Martínez, Jamuna J. Mahalingam, Andrea Soddu, Hugo Franco, Natasha Lepore, Steven Laureys, and Francisco Gómez

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INFLUENCE OF THE SEGMENTATION ON THE CHARACTERIZATION OF CEREBRAL NETWORKS OF STRUCTURAL DAMAGE FOR PATIENTS WITH DISORDERS OF CONSCIOUSNESS

Darwin Martínez[a], Jamuna J. Mahalingam[b], Andrea Soddu[c], Hugo Franco[a], Natasha Lepore[b], Steven Laureys[d], Francisco Gómez[a]

[a]*Computer Science Department, Universidad Central, Colombia*
[b]*Radiology Department, University of Southern California, United States*
[c]*Physics and Astronomy Department, Western University, Canada*
[d]*Cyclotron Research Center, University of Liège, Belgium*

KEYWORDS: Disorders of consciousness, cerebral brain networks of structural damage, subcortical spatial relationships, image segmentation, subcortical structures

ABSTRACT

Disorders of consciousness (DOC) are a consequence of a variety of severe brain injuries. DOC commonly results in anatomical brain modifications, which can affect cortical and sub-cortical brain structures. Postmortem studies suggest that severity of brain damage correlates with level of impairment in DOC. In-vivo studies in neuroimaging mainly focus in alterations on single structures. Recent evidence suggests that rather than one, multiple brain regions can be simultaneously affected by this condition. In other words, DOC may be linked to an underlying cerebral network of structural damage. Recently, geometrical spatial relationships among key sub-cortical brain regions, such as left and right thalamus and brain stem, have been used for the characterization of this network. This approach is strongly supported on automatic segmentation processes, which aim to extract regions of interests without human intervention. Nevertheless, patients with DOC usually present massive structural brain changes. Therefore, segmentation methods may highly influence the characterization of the underlying cerebral network structure. In this work, we evaluate the level of characterization obtained by using the spatial relationships as descriptor of a sub-cortical cerebral network (left and right thalamus) in patients with DOC, when different segmentation approaches are used (FSL, Free-surfer and manual segmentation). Our results suggest that segmentation process may play a critical role for the construction of robust and reliable structural characterization of DOC conditions.

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INTRODUCTION

Coma may result of severe brain injuries, such as, stroke, anoxic brain damage, traumatic brain injury, among others.[1,2,3] This condition is characterized by the absence of brain arousal and awareness. It usually last no longer than three weeks, after which patients may evolve to an state of no detectable awareness, commonly known as vegetative state/unresponsive wakefulness syndrome (VS/UWS). From this state some patients may evolve to an state of fluctuating awareness and arousal, an condition known as minimally conscious state (MCS). These alterations of consciousness are known as disorders of consciousness (DOC). Currently, diagnosis of DOC conditions is mainly based on behavioural scales, such as the Coma Recovery Scale revised,[4] which aim to quantify the level of awareness and arousal observed in the patient, when different sensorial channels are stimulated. Unfortunately, diagnoses based on these scales may be largely influenced by the evaluator expertise, resulting on a high misdiagnosis rate.[5]

In the recent years, modern brain imaging methods, such as positron emission technology,[6] transcranialmagnetic stimulation[7] and magnetic resonance imaging[8] have been used to investigate different patterns of brain activity associated to the different levels of consciousness. These approaches provide valuable information about the existence of high-order functional networks, such as the so called Default Mode Network, which are probably related to the emergence of the consciousness phenomena.[8] Other subcortical regions as thalamus also has proved to play a important role for loss-of-consciousness. For instance, depressed metabolic activity in thalamus has been found to correlate with the level of consciousness, as measured behaviourally.[9] However, despite of the advances in the comprehension of the functional brain activity in DOC, much uncertainty remains about the structural damage underlying loss-of-consciousness. A proper understanding of the structural alternations mechanisms underlying these brain altered conditions is of paramount importance to improve diagnosis, prognosis and treatment strategies.[10]

From the structural point of view, patients with DOC have evidenced damages in subcortical structures. In particular, diffuse axonal injury and thalamic structural damages, as observed on post-mortem studies.[6] In the recent years, in-vivo studies using neuroimaging aimed to further investigated these structural alterations. A diffusion tensor imaging study suggested a reduction in the thalamic volume related to structural damage, which may be associated to impaired consciousness states.[11] Interestingly, this study also showed than rather than one multiple brain structures may be simultaneously affected by the DOC conditions.[11] A set of global indices of structural damage, computed on white matter and whole brain, was shown also to correlate with the level-of-consciousness.[12] These evidences together may suggest the existence of a cerebral structural network of damage underlying the DOC conditions, i.e., a set of regions which are simultaneously affected by the pathology.

In a recent work we characterized the cerebral network of structural damage associated to DOC by computing geometrical spatial relationships among key brain regions selected a-priori.[13] The proposed network encompassed left and right thalamus and brain stem.[14]

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The relationships studied include minimum, maximum and average distances between these structures. Results of this study suggest that characterization this characterization may provide important information about the pattern of structural damage on these patients. However, a critical aspect in this determination of the Regions-of-Interest (RoIs). In this case, RoI segmentation was based on brain atlases and spatial normalization strategies.[15,16,17] Nevertheless, these approaches may fail when applied on severely structural damaged brains, as in the patients with DOC.[18] In this work, we evaluate the impact of the use of different segmentation strategies for the characterization of a sub-cortical cerebral network of structural damage, encompassing left and right thalamus, for the discrimination of DOC patients and control subjects.

MATERIALS AND METHODS

SUBJECTS AND DATA ACQUISITION

Data from 67 subjects were used in this study : 20 Vegetative State/Unresponsive Wakefulness State (VS/UWS) and 30 Minimally Conscious State (MCS) (average age 45 years (SD 18), > 2 months after injury) and 17 healthy control subjects (average age 47 years (SD 16)). For each subject, a T1 structural magnetic resonance image (matrix size = 256 × 240 × 120, voxel size 1 × 1 × 1.2 mm^3, 3T Siemens medical Solution in Erlangen, Germany) was acquired. MRI data from patients were acquired at the Hospital University of Liège, Belgium.

All patients were clinically examined using the French version of the Coma Recovery Scale Revised (CRS- R).[19] Diagnosis was established based on these scores. Written informed consent to participate in the study was obtained from all patients or legal surrogates of the patients.

DATA SEGMENTATION

Left and right thalamus were selected for structural characterization. Three different methods were used for segmentation: 1) FSL-FIRST and FSL-FAST,[15] 2) Freesurfer,[16,17] and 3) manual expert segmentation. The first two approaches are based on atlas and deformable models. For automatic approaches, data from 23 subjects were excluded because of fails in segmentation, mainly due to large bleeding regions and low quality acquisitions. No images were discarded in the case of manual expert segmentation.

SPATIAL RELATIONSHIP MEASUREMENT

After region segmentation, the Euclidean distances between pairs of voxels located on each structure were computed. The minimum (d_{min}), average (d_{ave}) and maximum (d_{max}) of these distances were used as features to characterize the spatial relationship between thalami, as illustrates figure 1.

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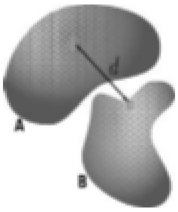
Figure 1. *Spatial relationship measurements. Three different measures of spatial relationships between regions A and B were computed: minimum (d_{min}), average (d_{ave}) and maximum (d_{max}).*



$$\mathbf{d}_{min} = \min \mathbf{d}(p_i, q_j)$$
$$\mathbf{d}_{ave} = \frac{1}{m \times n}\left(\sum_{i=1}^{m}\sum_{j=1}^{n} \mathbf{d}(p_i, q_j)\right)$$
$$\mathbf{d}_{max} = \max \mathbf{d}(p_i, q_j)$$
$$\mathbf{A} = \{p_i\}^m,\ p_i \in \mathbb{R}^3 \quad \mathbf{B} = \{q_j\}^n,\ q_j \in \mathbb{R}^3 \quad \mathbf{A} \cap \mathbf{B} = \emptyset$$
$$p_i = (x_i, y_i, z_i) \quad q_j = (x_j, y_j, z_j)$$
$$\mathbf{d}(p_i, q_j) = \sqrt{(x_j - x_i)^2 + (y_j - y_i)^2 + (z_j - z_i)^2}$$

STATISTICAL SIGNIFICANCE

Possible differences between controls and DOC patients in these spatial relationships were assessed through a Student's t-test. Cohen's d coefficients were computed to assess the level of discrimination obtained by using different segmentation approaches.

RESULTS

Figure 2 shows examples of segmentation for the three evaluated methods. Figures 2a 2b 2c show the segmented thalamus on controls subjects when used FreeSurfer, FSL and manual approaches, respectively. Similary, figures 2d 2e 2f show the thalamus obtained on DOC patients when the three segmentation methods are used. In general, the tested segmentation on control subjects were successful for the three methods. However, in bad acquisition conditions due to very low contrast or huge damaged areas, as in DOC patients, automatic processes failed. In these cases, algorithms abnormally finished or finished with non satisfactory results. In contrast, the manual expert labeling were made even with those image conditions.

Figure 2: *Thalami segmentation on Controls a) b) c) and patients with DOC d) e) f) using three different segmentation approaches: FreeSurfer, FSL and manual processes.*

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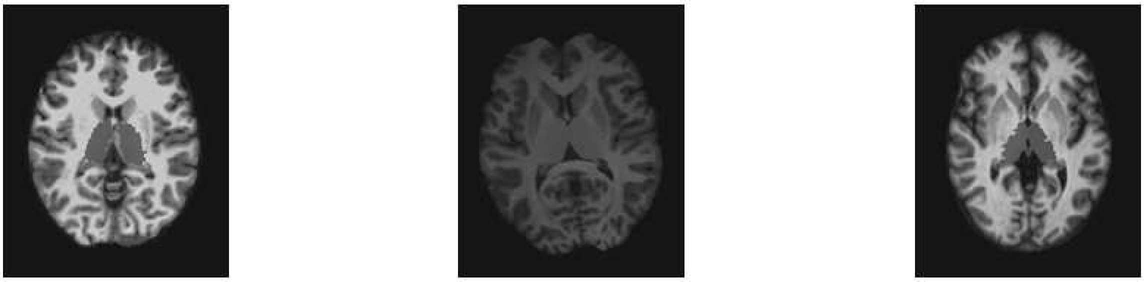
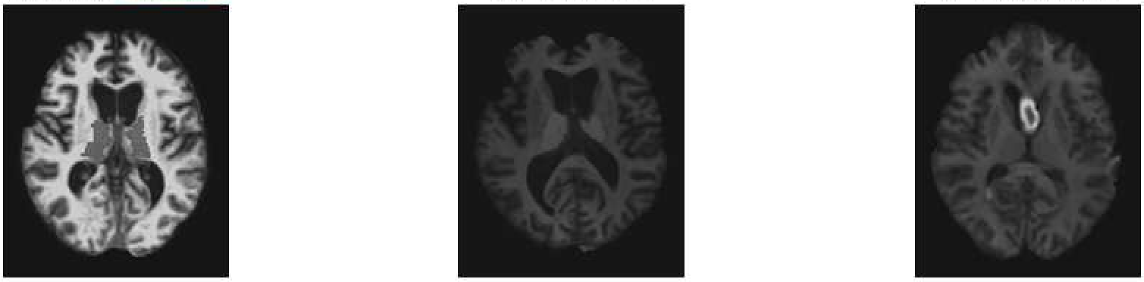


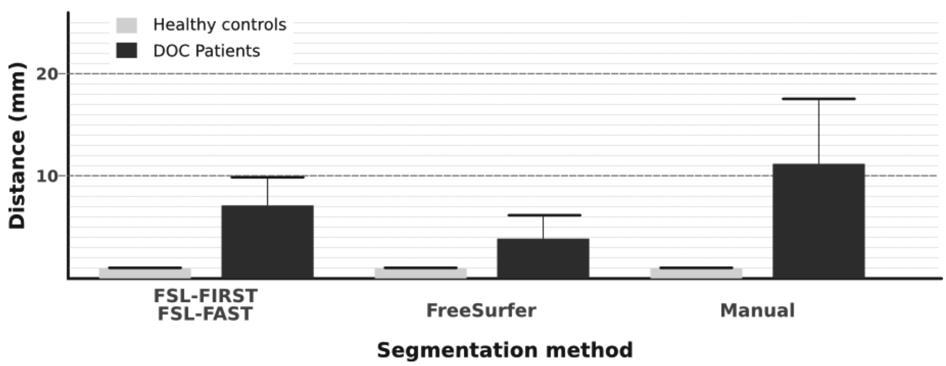
(a) Control-FreeSurfer (b) Control-FSL (c) Control-Manual



(d) DOC-FreeSurfer (e) DOC-FSL (f) DOC-Manual

Figure 3a shows the minimum distance between both thalami for the three segmentation approaches. Significant differences were observed for the three methods when comparing healthy controls and patients with DOC (p<.05 Bonferroni corrected). The manual segmentation resulted in a large separation between both thalami for DOC when comparing to healthy controls. Figure 3b shows the average distances computed between both thalami. Significant differences between controls and DOC were also observed for the three segmentation methods (p<.05 Bonferroni corrected). Figure 3c shows the maximum distances, no significant differences were observed in this case.

Figure 3: *Geometrical relationships (minimum, average and maximum) between between left and right thalamus for three segmentation approaches (FSL, Freesurfer and manual), Healthy controls (light blue), patients with DOC (violet).*



(a) Minimum distance

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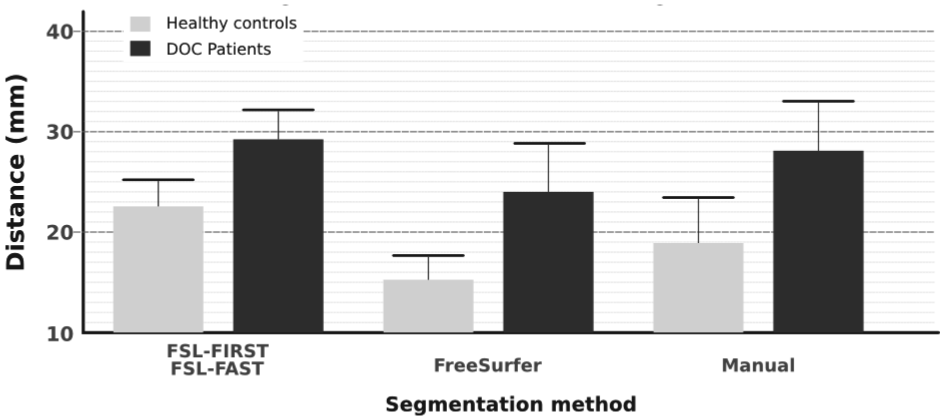
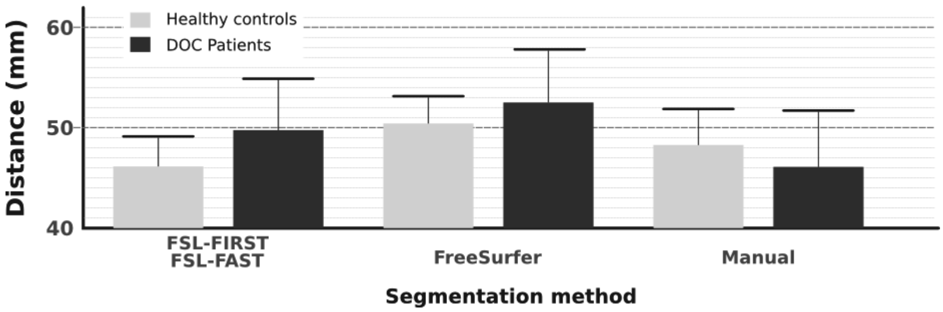


(b) Average distance



(c) Maximum distance

Table 1 reports the effect sizes for each measurement when different segmentation methods were used. Higher effect sizes were observed for automatic segmentation approaches compared to manual segmentation. The minimum distances obtained by using FSL segmentation method resulted in the higher effect size. Manual segmentation provided the lower effect sizes of the three evaluated segmentation approaches.

Table 1: *Cohen's effect size for the minimum, average and maximum distances for each segmentation process.*

		Segmentation method		
Effect size	Relationship	FSL	FreeSurfer	Manual
	Minimum Distance	3.1	2.5	0.9
	Average Distance	1.9	2.4	0.5
	Maximum Distance	2.3	2.0	0.5

CONCLUSIONS

Our results indicate that segmentation processes may influence the spatial relationships estimations for the studied sub-cortical cerebral network. A discriminative capacity between controls and patients with DOC was observed for two of the three studied geometric relationships in the three evaluated methods. Overall, DOC patients were characterized by an increase of inter-

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thalami distances compared to controls, so this may be related to the structural deterioration observed in DOC postmortem studies. Interestingly, automatic methods resulted in higher discriminative power than manual approach. This behaviour may be explained by the higher variability of manual segmentation compared to the automatic alternatives, and the control of automatic processes, based on its prior knowledge of brain anatomy synthesize in atlases and exploited from their based segmentation methods.

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