Thalamic volume as a biomarker for Disorders Of Consciousness

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ABSTRACT

Disorders of consciousness (DOC) may be characterized by the degree at which consciousness is impaired, and include for example vegetative state (VS) and minimally conscious state (MCS) patients. Using a reliable marker as a measure of the level of consciousness in such patients is of utmost necessity and importance for their appropriate diagnosis and prognosis. Identification of VS and MCS states based on their behaviors sometimes leads to incorrect inferences due to the influence of a range of factors like motor impairment, fluctuating arousal levels and rapidly habituating responses to name a few.[1] The extent of damage in the thalamus, a structure known for its role in arousal regulation, may provide an imaging biomarker to better differentiate between VS and MCS. In this study, we manually segmented the thalamus from T1-weighted brain MRI images in a large cohort of 19 VS and 23 MCS subjects that were examined using the French version of the Coma Recovery Scale Revised (CRS-R).[2] This scale is the most trustworthy behavioural diagnosis tool[3] for patients with DOC available. The aim was to determine whether a relationship between thalamus volume and consciousness level exists.

Results show that total thalamic volume tends to decrease over time after a severe brain injury. Moreover, for subjects in chronic state, the thalamic volume seems to differ with respect to the degree of consciousness that was diagnosed. Finally, for these same chronic patients, the total thalamic volume is varying linearly as a function of the CRS-R score obtained, indicating that thalamic volume may be used as a biomarker to measure the level of consciousness.

Keywords: Thalamus segmentation, Magnetic Resonance Imaging, Vegetative State, Minimally Conscious State, Coma Recovery Scale Revised

1. PURPOSE

Nowadays, there are a lack of reliable markers to precisely assess level of consciousness in patients suffering from DOC. The identification of VS and MCS states is mainly performed using behavioral tests, such as Coma Recovery Scale Revised (CRS-R).[2] This scale is the most trustworthy behavioural diagnosis tool[3] for patients with DOC available, but it is known that the identification of DOC based on behavior sometimes leads to wrong

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conclusions, due to the influence of a range of factors like motor impairment, fluctuating arousal levels and rapidly habituating responses to name a few.[1]

On the other hand, it is well-known that the thalamus is implicated in multiple brain functions, and in particular, plays a major role in regulating arousal, level of awareness, and activity. Patients suffering from DOC such as VS or MCS present impairements in all three attributes. Hence here we study the thalamus of patients suffering from DOC, in order to exhibit some relationships between the degree of thalamic atrophy and the level of consciouness.

In this study, we demonstrate that thalamus volume, measured using MRI images, may provide a biomarker for disorders of consciouness. Previous pilot work[4] on a small cohort (4 VS, 5 MCS) found a volume reduction and shape change of the thalamus in DOC patients compared to controls. In this study, a larger cohort of patients is analyzed, and we directly compared the VS and MCS groups to each other rather than to controls, in order to highlight volume differences between VS and MCS pathologies.

2. MATERIALS AND METHODS

The data acquisition was performed at the University and University Hospital of Liège, Belgium. Written informed consent to participate in the study was obtained from all patients or their legal surrogates.

2.1 Subjects

This study was conducted on 19 VS and 23 MCS patients. All patients were clinically examined using the French version of the Coma Recovery Scale Revised (CRS-R).[2] The CRS-R is a standardized behavioural scale that is currently considered to be the most trustworthy behavioural diagnosis tool[3] for patients with DOC available and is therefore used in most DOC neuroimaging studies as a behavioural diagnosis reference point.

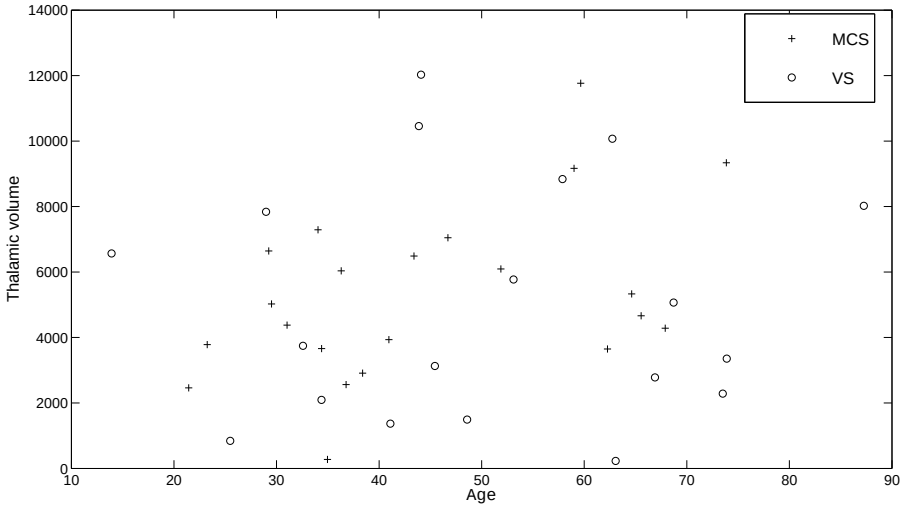

Figure 1. Volume of the thalamus with respect to the age of the patients.

The patients under study present heterogenous profiles. The age, time since injury and the cause of injury vary widely among the cohort.

Regarding age, the VS patients were 49.55 ± 37 years old, the MCS patients were 45 ± 28 years old. This wide disparity in the age of the patients could be an issue, while it has been shown[5] that the volum of brain structures (and in particular thalamus) tends to decrease with age. But in our study this is somewhat balanced by the fact that the ages are heterogenous in each group of patients (VS and MCS). Moreover, in the cohort under study, no clear relationship between age and thalamic volume can be exhibited, as seen in **Figure 1**.

The time since injury varied from 7 to 9900 days. 15 patients had an anoxic brain injury, while 25 patients suffered from traumatical brain injury and a patient suffered from both.

2.2 MR Image acquisition

For our analysis, we used T1 structural magnetic resonance images acquired on a 3T Siemens Magnetom scanner. Scanning parameters were as follows: Siemens AG, Munich, Germany; TR = 2300 ms, TE = 2.47 ms, T1-weighted 3D gradient echo images with 1 x 1 x 1.2 mm voxels in the sagittal plane, flip angle = 9 degrees, matrix size = 256 x 240 x 144 mm, field of view = 256 mm.

2.3 Manual segmentations of the thalamus

Manual segmentations of the thalamus were performed using the ITK-SNAP software,[6] a free open source software dedicated to manual and automatic segmentations. ITK-SNAP allows for simultaneous viewing of MR images in three orthogonal orientations. All resulting segmentations were carefully checked and validated by an expert neuroradiologist.

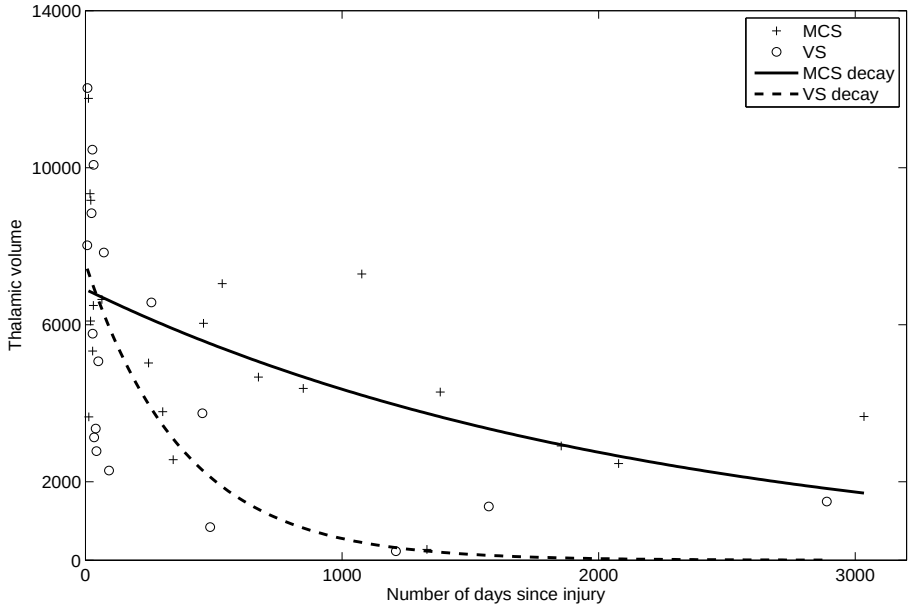

Figure 2. Volume of the thalamus with respect to the number of days since injury. The exponential decay curves show that the thalamic volume for VS patients tends do decrease faster than for MCS ones.

3. RESULTS

The segmentations volumes were calculated for the entire thalamus, as well as for left and right thalami separately. Then, these volumes were put in correspondances with subjects level of consciouness and other subject-dependent characteristics, in order to highlight relationships between thalamic volume and patient state. Promising results were exhibited, as explained in the following.

3.1 Thalamic volume as a diagnostic tool for VS/MCS distinction

The first remarkable result is that the thalamic volume tends to decrease as a function of the number of days since injury, as shown in **Figure 2**. The most important information is that the VS and MCS patients seem to behave differently over the time. After an exploratory study of the segmented data, we found out that the

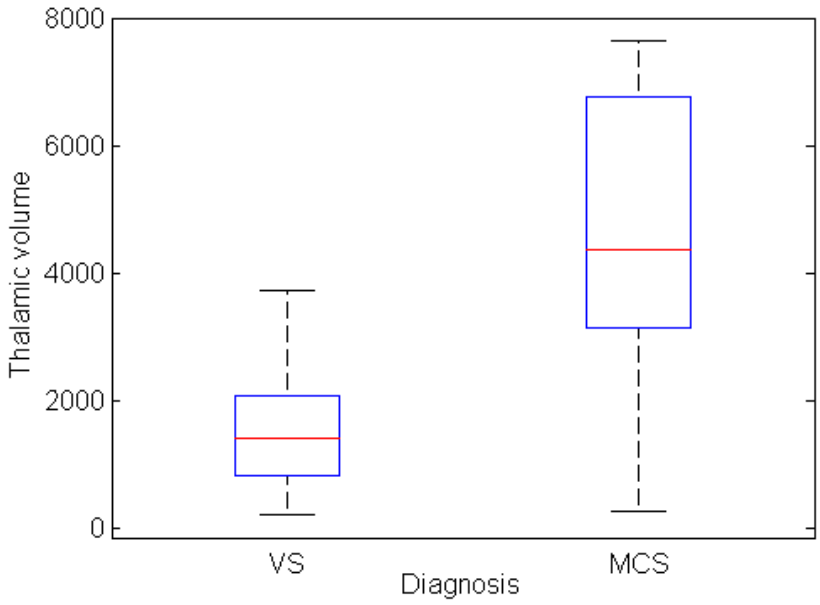

Figure 3. Volume of the thalamus for chronic VS and MCS subjects. An important thalamic volume difference is observed (p-value = 0.0029).

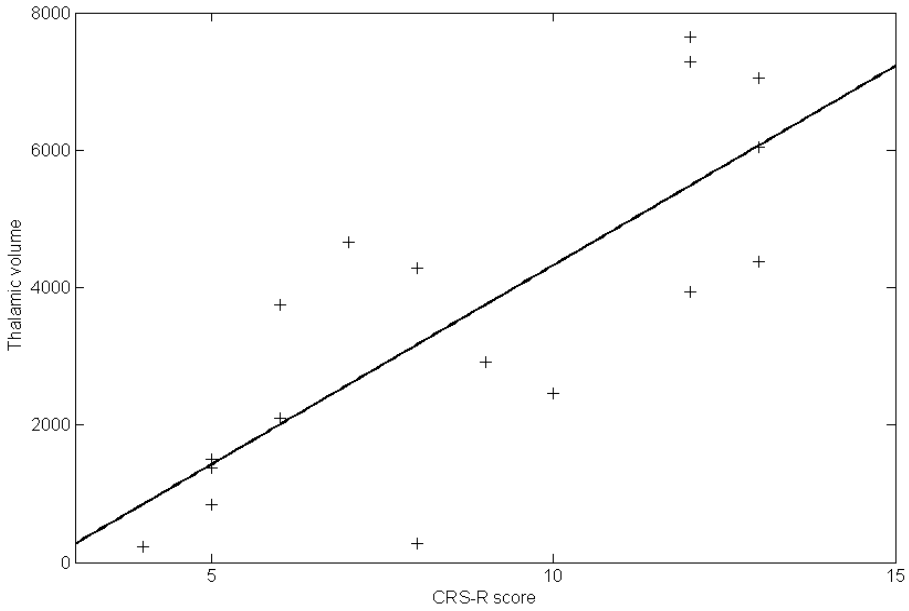

Figure 4. Volume of the thalamus with respect to the CRS-R score. This plot displays clear linear relationship between both.

VS and MCS thalamus volumes tend to follow an exponential regression curve. Equation of the curve for MCS patients (black curve in **Figure 2**) is given by:

$$y(t) = 6900e^{-\frac{t}{2174}} \quad (1)$$

whereas the one for VS patients (dotted curve in **Figure 2**) is given by:

$$y(t) = 7564e^{-\frac{t}{382}} \quad (2)$$

Comparing these equations shows a much bigger decay constant for MCS compared to VS. This would indicates that VS patients thalamus volume decrease faster than MCS patient space ones.

We also focus on the subjects that remain in persistent state. Here, we consider that patients are chronic if their consciousness state did not evolved during at least one year after their injury. This definition of persistency could nevertheless be discussed. For example, in,[7] the author considers that the temporal criterion to decide if the VS state is expected to remain permanent depends on the initial etiology. Considering this subset of patients, we observed that the mean thalamic volume for the VS subjects ($1630mm^3$) is almost three times lower than for MCS patients ($4630mm^3$), as seen in **Figure 3**. The t-test performed on these volumes exhibited a p-value of 0.0029, which means that this volume difference between VS and MCS patients is statistically significant. This is closely related to the first result described above, since chronic VS patients seem to lose thalamus volume faster than MCS ones. But it especially means that thalamic volume may be used as a tool to distinguish between VS and MCS persistent patients.

3.2 Thalamic volume as a complementary to behavioural assessment tools

Secondly, we concentrated on the correlation between the CRS-R behavioral diagnostic tool described above and the thalamic volumes, to see if the thalamic volume could be used to evaluate the level of consciouness. To do so, once again, we selected the persistent state patients, since the non-persistent subjects under study exhibit a wide range of characteristics. The results that are shown in **Figure 4** are again promising. Indeed, the plotted curve of the total thalamic volume with respect to the assigned CRS-R score exhibits an unambiguous linear relationship. This means that for persistent patients, the thalamic volume could be added to the list of already available behavioural diagnostic tools (see Table 1 of[8]) to assess level of consciousness.

4. CONCLUSION AND PERSPECTIVES

In this preliminary study, the feasibility of using thalamic volume as a biomarker for disorders of consciousness has been investigated. Two important results have been demonstrated. First, it has been shown that the thalamic volume tends to decrease over time after a brain injury. This volume variation differs with respect to initial diagnosis, and could be used to distinguish between VS and MCS patients. Then we also demonstrated that the CRS-R scale, which is the most trustworthy available mean to diagnose a patient with DOC at present, exhibits a linear relationship with the thalamic volume. This suggests that thalamus volume could be used as a biomarker to measure level of consciouness.

These preliminary results are really promising, but they have to be received with great care, due to the small number of subjects. For these results to be confirmed, several points need to be addressed.

First, no final conclusions should be drawn before these results would have been confirmed on a larger set of patients. Indeed, such a small cohort of patients necessarily induces bias in the results: parameters like the age or gender of the patients could also play a role in thalamic volume, and hence in the final conclusions. We demonstrate that age did not seem to play such a role here, but it still need to be confirmed.

Secondly, it would be very interesting to include control subjects in this study, as it was done in,[4] in order to compare the results between healthy and impaired patients. This will certainly strengthen the results previously obtained.

Finally, it would also be interesting to perform a follow-up of the patients under study, in order to see if intra-patient behavior corroborates inter-patient studies.

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