

Reductions of Thalamic Volume and Regional Shape Changes in the Vegetative and the Minimally Conscious States

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Abstract

The thalamus is known to play a key role in arousal regulation and support of human consciousness. Neuro-pathological studies have identified thalamic damage as one of the most common abnormalities present in the brains of patients who were in a vegetative state (VS) or a minimally-conscious state (MCS) state at the time of their deaths. Nonetheless, no *in vivo* studies of thalamic abnormalities in these patients have been conducted. Using high-resolution T1-weighted magnetic resonance images and a novel approach to shape analysis, we investigated thalamic global and regional changes in a sample of patients in a VS or an MCS. Group comparisons and correlations with clinical variables were performed for the total thalamic volume and for each surface vertex. Total thalamic volume was significantly lower in patients than in healthy volunteers. Shape analysis revealed significant bilateral regional atrophy in the dorso-medial body in patients compared to controls; this atrophy was more widespread in VS than in MCS patients. Lower thalamic volume was significantly correlated with worse Disability Rating Scale scores. Shape analysis suggested that the dorso-medial nucleus and the internal medullar lamina were the main regions responsible for this correlation. Our findings suggest that MCS and VS patients present different patterns of regional thalamic abnormalities, and that these differences partially explain their clinical profile.

Key words: disorders of consciousness; magnetic resonance imaging; shape analysis; traumatic brain injury; thalamus

Introduction

THE THALAMUS IS KNOWN to play a key role in arousal regulation and support of human consciousness (Schiff, 2008). Direct widespread thalamic injuries can themselves produce a generally transient coma state, but also more persistent disturbances of consciousness in terms of goal-directed behavior and communication skills (Schiff and Plum, 2000).

The thalamus may also be critically involved in non-focal brain injuries such as diffuse axonal injury (DAI). Post-mortem neuropathological studies of traumatic brain injury (TBI) patients who were in a vegetative state (VS) at the time of their deaths demonstrated that the thalamus was se-

verely injured in 80% of the sample, in most cases associated with grades II or III DAI (Adams et al., 1999, 2000).

Patients in a VS show wakefulness without awareness (Jennett and Plum, 1972), while patients in a minimally-conscious state (MCS) demonstrate inconsistent, but reproducible, evidence of awareness of self or environment (Giacino et al., 2002). MCS typically describes a spectrum of severity and is generally associated with a better prognosis (Katz et al., 2009); in exceptional cases late recovery is possible (Lammi et al., 2005; Voss et al., 2006). By comparing histopathological findings in a group of VS patients and a group of severely disabled patients, including some who were considered to fulfill the diagnostic criteria for MCS, Jennett and colleagues

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(2001) demonstrated that half of the MCS patients had no evidence of thalamic injury or grade II or III DAI.

In the present study, we assessed thalamic volumetric atrophy and shape abnormalities in a sample of TBI patients in a VS or an MCS in comparison with healthy volunteers. Our main aim was to determine whether not only global, but also regional atrophy, could be detected *in vivo* in these patients, using a novel approach that allows automatic segmentation of the subcortical structures, and an analysis of the shape on a per-vertex basis (Patenaude, 2007). Similar analyses have been performed in the thalami of patients with Parkinson's disease (McKeown et al., 2008), schizophrenia (Coscia et al., 2009; Harms et al., 2007; Kang et al., 2008; Qiu et al., 2009a), and Alzheimer's disease (Qiu et al., 2009b; Zarei et al., 2010).

We hypothesized that regional differences would be more prominent in VS patients than in MCS patients, and would partially explain their respective clinical profiles.

Methods

Subjects

Twelve severe TBI patients (11 male, 2 female; age range 18–48 years) and 20 healthy volunteers (8 male, 12 female; age range 19–49 years) with no history of psychiatric or neurological disorders were recruited. Four patients met the diagnostic criteria for VS (Royal College of Physicians, 1996, 2003), and eight met the diagnostic criteria defining MCS (Giacino et al., 2002). All patients were scanned within the first year after injury (mean 148 days). To characterize their clinical profiles we recorded the scores on the Disability Rating Scale (DRS; Rappaport et al., 1982), and the Rancho Los Amigos Level of Cognitive Functioning Scale (LCFS; Hagen et al., 1979). As three MCS patients were subsequently excluded because of motion artifacts in the MR images (see below), the final patient group comprised 9 patients. Clinical and demographical data of the 9 patients included in the analysis are summarized in Table 1. There were no statistically significant differences in age between patients and healthy subjects ($U = 82$; $p = 0.706$). The study was approved by the Ethics Committee of the Hospital Clinic, Barcelona. Informed written assent was obtained from the patient's legal representative. All healthy subjects gave informed written consent.

MRI acquisition

High-resolution ($1 \times 1 \times 1$ mm) T1-weighted MR rapid gradient-echo images were acquired on a 3T scanner (Magnetom Trio Tim; Siemens, Berlin, Germany) at the Center for Image Diagnosis of the Hospital Clinic, Barcelona (TR = 2300 msec, TE = 2.98 msec, TI = 900; matrix size = 256×256 ; flip angle = 9°).

Image analysis

Image analysis was carried out using tools from FSL (FMRIB Software Library; <http://www.fmrib.ox.ac.uk/fsl>). The images were visually inspected prior to analysis. We excluded three MCS patients because of motion-related artifacts.

We applied SIENAX for an estimation of brain parenchymal volume, normalized for head size as described elsewhere (Smith et al., 2002). Brain and skull images were extracted. Then brain images were registered to the MNI standard

TABLE 1. CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF THE NINE PATIENTS INCLUDED IN THE ANALYSIS

Patient	Age/gender	Cause of trauma	Lesions on MRI/CT	Time since injury	GCS	Diagnosis	DRS	LCFS	PBV	Left thalamus	Right thalamus
Patient 1	48/M	Fall	Right temporal and parietal cortex	33	5/–	VS	24	2	1397.84	6.83	6.27
Patient 2	18/M	RTA	Right frontal cortex, brainstem atrophy, TAI	95	3/3	VS	24	2	1494.15	6.63	6.45
Patient 3	48/M	RTA	Left temporo-parieto-occipital junction, TAI, basal ganglia	85	5/–	VS	26	2	1493.03	5.92	5.86
Patient 4	44/F	Fall	Left occipital cortex, bilateral prefrontal and parietal cortex, TAI	129	4/3	VS	25	2	1345.95	5.49	5.47
Patient 5	34/M	Hit	Diffuse cortical atrophy, right temporal cortex, bilateral orbital and prefrontal cortex, TAI	354	3/3	MCS	18	5	1293.56	7.08	6.59
Patient 6	18/F	RTA	Bilateral frontal	235	3/3	MCS	21	3	1374.13	6.13	5.45
Patient 7	18/M	RTA	Right temporal cortex and thalamus, bilateral frontal, TAI	82	5/3	MCS	20	5	1349.95	6.69	6.39
Patient 8	36/M	RTA	Right temporal and frontal cortex, TAI	198	5/5	MCS	21	5	1348.38	5.76	4.63
Patient 9	21/M	RTA	Right frontal, temporal and parietal cortex, basal ganglia	124	5/5	MCS	21	5	1523.10	8.08	8.07

Time since injury is in days. Volumes are in cm^3 .

MCS, minimally conscious state; VS, vegetative state; RTA, road traffic accident; GCS, Glasgow Coma Scale (on admission/minimum); DRS, Disability Rating Scale; LCFS, Rancho Los Amigos Level of Cognitive Functioning Scale; TAI, traumatic axonal injury; PBV, parenchymal brain volume.

template using the skull image as a scaling constraint to normalize for head size. Finally segmentation was performed in order to obtain normalized brain parenchymal volume (BPV). This value allows a better estimation of the relative brain atrophy by removing the effects of head size variation. The results of each step were carefully examined by a neuroscientist (D.F.E.) to ensure their accuracy.

Thalamus segmentation

Automated segmentation of the thalamus was performed using FIRST from FSL, which uses a Bayesian probabilistic approach based on multivariate Gaussian assumptions. The shape and appearance models used were constructed from manually segmented images provided by the Center for Morphometric Analysis, Massachusetts General Hospital, Boston. The manual labels are parameterized as surface meshes and then modeled as a point distribution. Using the models, FIRST searches through linear combinations of shape modes of variation for the most probable shape instance given the observed intensities from the input image. The thalamus segmentation was performed by running a two-stage affine registration to standard space. The first stage is a 12 degrees of freedom (DOF) registration to the non-linear MNI152 template, and the second one is a 12-DOF registration using a subcortical mask, to exclude voxels outside the subcortical regions. After that each thalamus was automatically segmented, producing both mesh and volumetric outputs from this structure in native space.

Statistical analysis

The distribution of the dependent measures (BPV and thalamic volume) was inspected using the Kolmogorov-Smirnov test to ensure that they did not deviate from normality. Group comparison for BPV was examined using the Student *t*-test. Group comparisons for thalamic volumes were examined by repeated-measures analysis of covariance (ANCOVA). Group served as the between-subjects factor, hemisphere served as the repeated-measures factor, and BPV was used as the statistical covariate. Significance was set at $p < 0.05$.

To assess the relationship between thalamic volume and clinical variables we performed partial correlations using the BPV as covariate. Left and right thalamic volumes were combined into a single measure for the correlation analysis. Because we worked with an *a priori* hypothesis, significance was set at a one-tailed $p < 0.05$. Graphs were produced using SigmaPlot 10.

Vertex analysis

Shape differences between groups as well as correlations with clinical DRS and LCFS scores were assessed on a per-vertex basis. FIRST creates a surface mesh for each thalamus composed of a set of triangles, whose apexes are called vertices. Vertex correspondence is crucial for investigating focal shape differences through the examination of group differences in the spatial location of each vertex. FIRST guarantees this correspondence by using deformable models to parameterize the data in terms of meshes. The number of vertices and their labeling is fixed so that corresponding vertices can be compared across individuals and between groups.

Mesh images are saved in native space and aligned to the mean shape from the shape model using a 6-DOF transformation, to remove pose (rotation and translation). Group comparison of vertices and correlations with clinical variables were performed with F-statistics using BPV as a covariate. The statistic was rendered on the shape surface, providing a map of the regions where the structure differed significantly between groups (i.e., significant displacements of the mean vertex location between groups).

Results

Thalamic volumes

Brain parenchymal volume was significantly lower in patients than in healthy volunteers (patient BPV = $1402.33 \pm 81.35 \text{ cm}^3$ and healthy volunteer BPV = $1574.32 \pm 65.63 \text{ cm}^3$; $t = -6.065$; $p < 0.001$). For the thalamic volumes, using BPV as a covariate, the ANCOVA revealed a significant main effect of group, with total thalamic volume being lower in patients than in healthy volunteers (patients = $6.32 \pm 0.86 \text{ cm}^3$; healthy volunteers = $8.53 \pm 0.88 \text{ cm}^3$; $F_{1,26} = 9.888$; $p = 0.004$). Neither the effect of hemisphere nor the group by hemisphere interaction was statistically significant. Additional analyses revealed that the main effect of group was statistically significant when comparing VS patients and controls (VS patients = 6.11 ± 0.52 ; $F_{1,21} = 12.167$; $p = 0.002$), but not when comparing MCS patients and controls (MCS patients = 6.49 ± 1.10 ; $F_{1,22} = 3.577$; $p = 0.072$). Adjusted (for BPV) mean thalamic volumes for the right and left hemispheres are reported in Table 2.

In the patient group, we found a significant negative correlation between total thalamic volume and DRS score ($r = -0.717$; $p = 0.023$). The correlation between thalamic volume and LCFS score failed to reach statistical significance, but it showed a clear trend toward a negative relationship between these two variables ($r = 0.567$; $p = 0.071$; Fig. 1).

TABLE 2. ADJUSTED THALAMIC VOLUMES

	DOC versus CON		VS versus CON		MCS versus CON	
L	6.84 (0.40)	8.47 (0.23)	6.51 (0.57)	8.57 (0.20)	7.30 (0.57)	8.49 (0.22)
R	6.54 (0.42)	8.25 (0.24)	6.26 (0.54)	8.39 (0.20)	6.84 (0.62)	8.28 (0.24)

Values are the predicted marginal means adjusted for brain parenchymal volume effects. There was a main effect of group on thalamic volume for the DOC versus CON ($F_{1,26} = 9.888$; $p = 0.004$) and the VS versus CON ($F_{1,21} = 12.167$; $p = 0.002$) comparisons, but not for the MCS versus CON comparison. Values in parentheses are standard errors.

DOC (disorders of consciousness) is the total number of patients including VS and MCS patients.

CON, control group; VS, vegetative state patient group; MCS, minimally conscious state patient group; L, left; R, right.

Volumes are in cm^3 .

Thalamic shape

Comparison of vertex locations between patients and controls revealed significant regional atrophy (i.e., inward movement of vertices in the patients) bilaterally in the dorsal and dorso-medial regions, which also affected the anterior and posterior regions with a left predominance. Comparing MCS patients with healthy volunteers, regions with pronounced volume reduction were more focused on the dorsal body, and the anterior and posterior regions were relatively spared, except for two patches of shrinkage in the right lateral posterior region. Comparison of VS patients with healthy volunteers revealed a more widespread pattern of atrophy in the VS patients, affecting not only the dorsal and dorso-medial body, but the left anterior body and the medial-posterior body bilaterally as well (Fig. 2).

Correlation analysis revealed a significant correlation between DRS and shrinkage in the dorso-medial and ventro-medial bodies, with a left predominance. This measure also correlated with two small patches of shrinkage in the left

lateral-medial body and the right anterior-medial body. This pattern was similar, although less significant, for the correlation with LCFS, but with a greater involvement of the right dorso-medial body (Fig. 3).

Discussion

In this study, we evaluated thalamic volume and patterns of shape changes and their clinical correlates in patients in a VS or an MCS. To our knowledge this is the first study to report thalamic local shape differences *in vivo* not only in VS and MCS patients, relative to controls but also relative to each other. This is also the first time that a relationship between thalamic local changes and clinical profile has been reported in these patients.

The dorso-medial body was the most affected region in both groups of patients. Its inward deformation can be explained by atrophy in both the dorso-medial nucleus (DMN), and the internal medullar lamina (IML), consistent with previous neuropathological findings (Adams et al., 1999; Maxwell et al., 2004; 2006). The DMN has reciprocal connections with the prefrontal, orbital, and temporal cortices, connections with the amygdala and the limbic system, and connections with other thalamic nuclei and associated areas of the parietal and temporal lobes (Maxwell et al., 2004). Intralaminar thalamic neurons are part of an ascending pathway that originates in the midbrain reticular formation, and has a primary role in maintaining wakefulness (Schiff, 2008).

Several mechanisms, whose evaluation is beyond the scope of the present study, may explain the thalamic atrophy seen in cases of severe TBI. It has been suggested that thalamic atrophy may reflect DAI or ischemia, arising as a result of post-traumatic transneuronal and retrograde degeneration, excitotoxicity, or as a result of neuronal loss due to hypoxic mechanisms (Adams et al., 1999). Considering the relative heterogeneity of the lesions present in our patients, their thalami probably combine both types of damage. In any case, thalamic atrophy could be interpreted as a surrogate marker of more diffuse damage that interrupts thalamo-cortical connectivity.

Interestingly, we also identified differences in the patterns of atrophy of VS and MCS patients. VS patients showed a more widespread pattern of atrophy than controls, producing differences in global thalamic volume. MCS patients did not show volumetric differences compared to controls, and regionally they showed a less pronounced inward collapse in both the dorsal and ventral areas, with the anterior-ventral body significantly spared. Neuropathological studies have demonstrated that thalamic damage is less common in MCS than in VS patients (Jennett et al., 2001). Maxwell and colleagues (2004, 2006) assessed regional differences in TBI outcome groups using the Glasgow Outcome Scale, but did not separate MCS patients within the more general severely disabled category, thus precluding the identification of differences between MCS and VS patients and comparison with our results.

Besides a more complex repertoire of behaviors (Giacino et al., 2002), MCS patients generally demonstrate greater distribution of cerebral network activation in fMRI and PET studies than VS patients (see Monti et al., 2009 for a review). The less severe pattern of thalamic atrophy seen in MCS

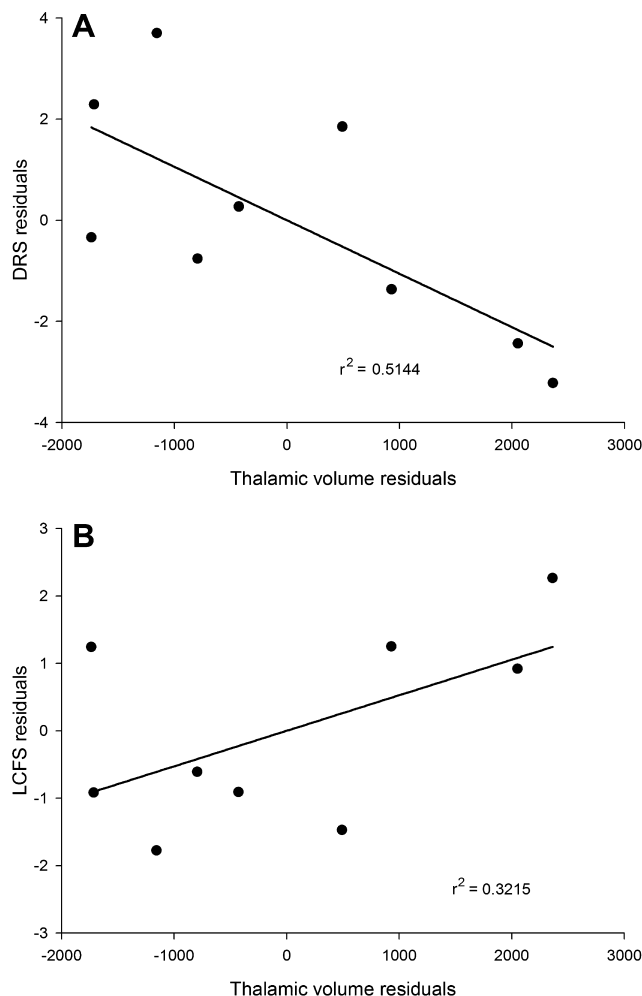


FIG. 1. Partial regression plots showing the relationship between each clinical measure, (A) Disability Rating Scale (DRS) and (B) Level of Cognitive Functioning Scale (LCFS), and thalamic volume, after controlling for brain parenchymal volume effects, in the patient group.

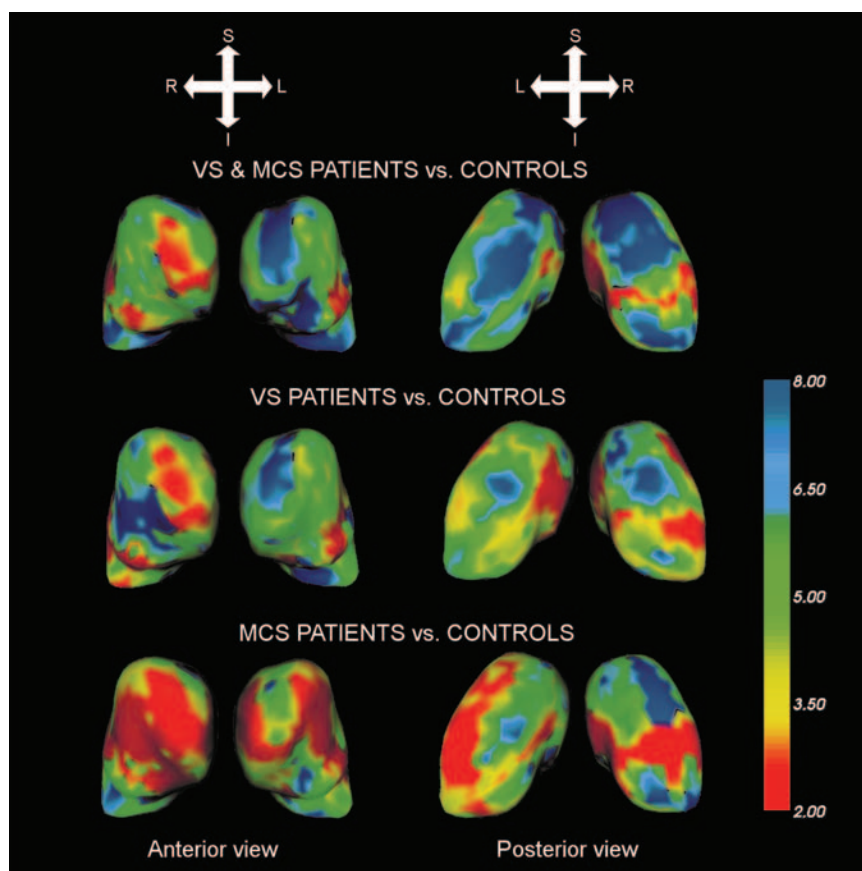


FIG. 2. Thalamic shape abnormalities in the MCS and VS patient group (top), the VS patients only (middle), and the MCS patients only (bottom), compared to controls. The color bar indicates F-statistics. F-statistics have degrees of freedom 3, 24 giving $p = 0.05$ ($F = 3$), $p = 0.008$ ($F = 5$), and $p = 0.0007$ ($F = 8$; L, left; R, right; S, superior; I, inferior; MCS, minimally-conscious state; VS, vegetative state).

patients reported here may reflect the potential availability of cerebral networks in some MCS patients that allows residual cerebral function and improved functional outcomes (Schiff et al., 2007; Voss et al., 2006).

We also found that total thalamic volume was correlated with DRS score. Of note, the regional shape correlations with this measure were specifically located mainly over the IML

and DMN. This result reinforces the notion that these thalamic nuclei are involved in supporting human consciousness and in explaining the outcome after severe TBI. Recently, Schiff and associates (2007) used deep brain electrical stimulation of the central thalamus, defined as the intralaminar and adjacent paralaminar regions of thalamic association nuclei, in a patient who remained in a MCS for 6 years following TBI, and

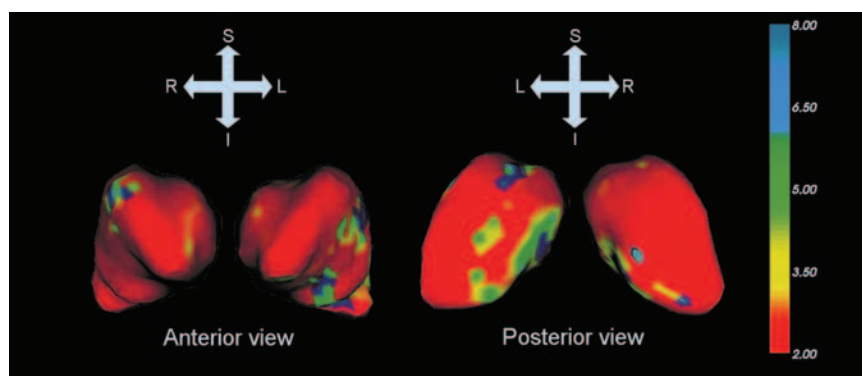


FIG. 3. Correlation maps of Disability Rating Scale score and thalamic shape in the all-patient group. The color bar indicates F-statistics. F-statistics have degrees of freedom 3, 4, giving $p = 0.16$ ($F = 3$), $p = 0.05$ ($F = 7$), and $p = 0.04$ ($F = 8$; L, left; R, right; S, superior; I, inferior).

they showed increased frequency of cognitively-mediated behaviors.

The main limitation of our study is the small sample size, which may preclude the generalization of the results to the general population, and reduces the statistical power and the magnitude of the correlations found; therefore our results must be taken as preliminary. Nevertheless, we believe that their consistency with previous neuropathological findings with larger cohorts partially mitigates this limitation and supports their reliability. Disorders of consciousness are rare, and it is extremely difficult to accumulate large cohorts for inclusion in research studies. This is a common problem in the neuroimaging literature with this population, and most of the studies have been performed with similar or smaller numbers of patients than the present work (Owen and Coleman, 2008; Tshibanda et al., 2010). We believe that multicenter studies that allow recruitment of larger cohorts may allow a more accurate characterization of the specific patterns of local atrophy in VS and MCS patients, which could lead to a better understanding of the structural basis of these clinical conditions.

Several approaches for shape analysis have been proposed in the literature. They employed different methodologies to ensure correspondence between vertices across subjects and guarantee the reliability of the analysis. However, their applications to the study of pathological brain abnormalities are relatively new, and standards have not yet been established. Comparison of their performance in both healthy volunteers and pathological groups would be necessary to assess their sensitivity and reliability, but an in-depth discussion of this topic is beyond the scope of this article. We believe that the accuracy of the segmentation in our sample, and the consistency of our results with previous neuropathological findings, provide enough support for its reliability.

In conclusion, we report *in vivo* evidence of different patterns of regional thalamic shape abnormalities in VS and MCS patients, as well as their clinical correlates. The potential for noninvasively detecting subtle thalamic shape changes in these patients may make the technique described here a powerful tool for identifying patients who might retain enough structural substrate to benefit from rehabilitative and neuromodulatory interventions.

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Author Disclosure Statement

No competing financial interests exist.

References

- Adams, J.H., Graham, D.I., and Jennett, B. (2000). The neuropathology of the vegetative state after an acute brain insult. *Brain* 123, 1327–1338.
- Adams, J.H., Jennett, B., McLellan, D.R., Murray, L.S., and Graham, D.I. (1999). The neuropathology of the vegetative state after head injury. *J. Clin. Pathol.* 52, 804–806.
- Coscia, D.M., Narr, K.L., Robinson, D.G., Hamilton, L.S., Sevy, S., Burdick, K.E., Gunduz-Bruce, H., McCormack, J., Bilder, R.M., and Szeszko, P.R. (2009). Volumetric and shape analysis of the thalamus in first-episode schizophrenia. *Hum. Brain Mapp.* 30, 1236–1245.
- Giacino, J.T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D.I., Kelly, J.P., Rosenberg, J.H., Whyte, J., Zafonte, R.D., and Zasler, N.D. (2002). The minimally conscious state: definition and diagnostic criteria. *Neurology* 58, 349–353.
- Hagen, C., Malkmuss, D., Dirham, P., and Bowman, K. (1979). Levels of cognitive functioning, in: *Rehabilitation of the Head Injured Adult. Comprehensive Physical Management*. Professional Staff Association of Rancho Los Amigos Hospital (eds), Downey, CA.
- Harms, M.P., Wang, L., Mamah, D., Barch, D.M., Thompson, P.A., and Csernansky, J.G. (2007). Thalamic shape abnormalities in individuals with schizophrenia and their nonpsychotic siblings. *J. Neurosci.* 27, 13835–13842.
- Jennett, B., Adams, J.H., Murray, L.S., and Graham, D.I. (2001). Neuropathology in vegetative and severely disabled patients after head injury. *Neurology* 56, 486–490.
- Jennett, B., and Plum, F. (1972). Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet* 7753, 734–737.
- Kang, D.H., Kim, S.H., Kim, C.W., Choi, J.S., Jang, J.H., Jung, M.H., Lee, J.M., Kim, S.I., and Kwon, J.S. (2008). Thalamus surface shape deformity in obsessive-compulsive disorder and schizophrenia. *Neuroreport* 19, 609–613.
- Katz, D.I., Polyak, M., Coughlan, D., Nichols, M., and Roche, A. (2009). Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1–4 year follow-up. *Prog. Brain Res.* 177, 73–88.
- Lammi, M.H., Smith, V.H., Tate, R.L., and Taylor, C.M. (2005). The minimally conscious state and recovery potential: A follow-up study 2 to 5 years after traumatic brain injury. *Arch. Phys. Med. Rehabil.* 86, 746–754.
- Maxwell, W.L., MacKinnon, M.A., Smith, D.H., McIntosh, T.K., and Graham, D.I. (2006). Thalamic nuclei after human blunt head injury. *J. Neuropathol. Exp. Neurol.* 65, 478–488.
- Maxwell, W.L., Pennington, K., MacKinnon, M.A., Smith, D.H., McIntosh, T.K., Wilson, J.T.L., and Graham, D.I. (2004). Differential responses in three thalamic nuclei in moderately disabled, severely disabled and vegetative patients after blunt head injury. *Brain* 127, 2470–2478.
- McKeown, M.J., Uthama, A., Abugharbieh, R., Palmer, S., Lewis, M., and Huang, X. (2008). Shape (but not volume) changes in the thalamus in Parkinson disease. *BMC Neurol.* 8, 8.
- Monti, M.M., Coleman, M.R., and Owen, A.M. (2009). Neuroimaging and the vegetative state: resolving the behavioral assessment dilemma? *Ann. N.Y. Acad. Sci.* 1157, 81–89.
- Owen, A.M., and Coleman, M.R. (2008). Functional neuroimaging of the vegetative state. *Nat. Rev. Neurosci.* 9, 235–243.
- Patenaude, B. (2007). Bayesian Statistical Models of Shape and Appearance for Subcortical Brain Segmentation. D.Phil. Thesis, University of Oxford.
- Qiu, A., Fennema-Notestine, C., Dale, A.M., Miller, M.I., and Alzheimer's Disease Neuroimaging Initiative. (2009b). Regional shape abnormalities in mild cognitive impairment and Alzheimer's disease. *Neuroimage* 45, 656–661.
- Qiu, A., Zhong, J., Graham, S., Chia, M.Y., and Sim, K. (2009a). Combined analyses of thalamic volume, shape and white matter integrity in first-episode schizophrenia. *Neuroimage* 47, 1163–1171.

- Rappaport, M., Hall, K.M., Hopkins, K., Belleza, T., and Cope, D.N. (1982). Disability rating scale for severe head trauma: coma to community. *Arch. Phys. Med. Rehabil.* 63, 118–123.
- Royal College of Physicians of London. (1996). The permanent vegetative state [Report of a working party]. *J. R. Coll. Physicians Lond.* 30, 119–121.
- Royal College of Physicians of London. (2003). The vegetative state: Guidance on diagnosis and management [Report of a working party]. *Clin. Med.* 3, 249–254.
- Schiff, N.D. (2008). Central thalamic contributions to arousal regulation and neurological disorders of consciousness. *Ann. N.Y. Acad. Sci.* 1129, 105–118.
- Schiff, N.D., Giacino, J.T., Kalmar, K., Victor, J.D., Baker, K., Gerber, M., Fritz, B., Eisenberg, B., Biondi, T., O'Connor, J., Kobylarz, E.J., Farris, S., Machado, A., McCagg, C., Plum, F., Fins, J.J., and Rezai, A.R. (2007). Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature* 448, 600–603.
- Schiff, N.D., and Plum, F. (2000). The role of arousal and “gating” systems in the neurology of impaired consciousness. *J. Clin. Neurophysiol.* 17, 438–452.
- Smith, S.M., Zhang, Y., Jenkinson, M., Chen, J., Matthews, P.M., Federico, A., and De Stefano, N. (2002). Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage* 17, 479–489.
- Tshibanda, L., Vanhaudenhuyse, A., Boly, M., Soddu, A., Bruno, M.A., Moonen, G., Laureys, S., and Noirhomme, Q. (2010). Neuroimaging after coma. *Neuroradiology* 52, 15–24.
- Voss, H.U., Uluc, A.M., Dyke, J.P., Watts, R., Kobylarz, E.J., McCandliss, B.D., Heier, L.A., Beattie, B.J., Hamacher, K.A., Vallabhajosula, S., Goldsmith, S.J., Ballon, D., Giacino, J.T., and Schiff, N.D. (2006). Possible axonal regrowth in late recovery from the minimally conscious state. *J. Clin. Invest.* 116, 2005–2011.
- Zarei, M., Patenaude, B., Damoiseaux, J., Morgese, C., Smith, S., Matthews, P.M., Barkhof, F., Rombouts, S., Sanz-Arigita, E., and Jenkinson, M. (2010). Combining shape and connectivity analysis: an MRI study of thalamic degeneration in Alzheimer's disease. *Neuroimage* 49, 1–8.

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