Regional Volumes in Brain Stem and Cerebellum Are Associated With Postural Impairments in Young Brain-Injured Patients

David Drijckoningen,^{1†} Inge Leunissen,^{1†} Karen Caeyenberghs,²
Wouter Hoogkamer,¹ Stefan Sunaert,³ Jacques Duysens,¹ and
Stephan P Swinnen^{1,4*}

¹KU Leuven, Movement Control and Neuroplasticity Research Group, Group Biomedical Sciences, Leuven, Belgium

²School of Psychology, Faculty of Health Sciences, Australian Catholic University, Melbourne, Victoria, Australia

³KU Leuven, Department of Radiology, University Hospital, Leuven, Belgium

⁴KU Leuven, Leuven Research Institute for Neuroscience & Disease (LIND), Belgium

Abstract: Many patients with traumatic brain injury (TBI) suffer from postural control impairments that can profoundly affect daily life. The cerebellum and brain stem are crucial for the neural control of posture and have been shown to be vulnerable to primary and secondary structural consequences of TBI. The aim of this study was to investigate whether morphometric differences in the brain stem and cerebellum can account for impairments in static and dynamic postural control in TBI. TBI patients ($n = 18$) and healthy controls ($n = 30$) completed three challenging postural control tasks on the EquiTest® system (Neurocom). Infratentorial grey matter (GM) and white matter (WM) volumes were analyzed with cerebellum-optimized voxel-based morphometry using the spatially unbiased infratentorial toolbox. Volume loss in TBI patients was revealed in global cerebellar GM, global infratentorial WM, middle cerebellar peduncles, pons and midbrain. In the TBI group and across both groups, lower postural control performance was associated with reduced GM volume in the vermal/paravermal regions of lobules I–IV, V and VI. Moreover, across all participants, worse postural control performance was associated with lower WM volume in the pons, medulla, midbrain, superior and middle cerebellar peduncles and cerebellum. This is the first study in TBI patients to demonstrate an association between postural impairments and reduced volume in specific infratentorial brain areas. Volumetric measures of the brain stem and cerebellum may be valuable prognostic markers of the chronic neural pathology, which complicates rehabilitation of postural control in TBI. *Hum Brain Mapp* 36:4897–4909, 2015. © 2015 Wiley Periodicals, Inc.

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*Correspondence to: Stephan Swinnen, Movement Control and Neuroplasticity Research Group, Tervuursevest 101, 3001 Leuven, Belgium. E-mail: stephan.swinnen@faber.kuleuven.be

[†]Both authors contributed equally to the work.

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INTRODUCTION

Traumatic brain injury (TBI) is a major cause of disability in children and young adults and often leads to deterioration of motor function. A common motor impairment after TBI is postural instability, which severely affects performance of daily life activities and increases the risk of falls [Gagnon et al., 2004; Katz-Leurer et al., 2008; McCulloch et al., 2010; Wade et al., 1997].

Injury and degeneration of infratentorial brain structures (i.e., brain stem and cerebellum) can be of major importance in the underlying neuropathology of postural impairments in TBI patients. The cerebellum, in particular, has been shown to play a key role in the neural control of posture [Ilg and Timmann, 2013; Jahn et al., 2004; Konczak et al., 2005; Morton and Bastian, 2004; Schoch et al., 2010; Taube et al., 2015] and is found to be vulnerable to axonal injury as well as secondary degeneration (i.e., Wallerian degeneration) following head trauma [Bendlin et al., 2008; Parizel et al., 1998; Park et al., 2007; Potts et al., 2009; Roberts et al., 2014; Soto-Ares et al., 2001; Spanos et al., 2007]. Other infratentorial structures that are critical for the control of posture are located in the brain stem. Vestibular nuclei and pontine nuclei receive sensorimotor information and project onto the cerebellum through the cerebellar peduncles [Habas and Cabanis, 2007; Salmi et al., 2010]. Moreover, the brain stem contains tracts that carry somatosensory information (i.e., medial lemniscus) and motor commands (i.e., corticospinal tract) between the cerebral cortex and spinal cord. In general, injuries to the brain stem are among the most common structural sequelae of severe head injury [Hilario et al., 2012] and have a strong negative impact on functional recovery and independence after TBI [Blackman et al., 2003; Choi et al., 2008; Firsching et al., 2002; Hilario et al., 2012].

There is some evidence from research in TBI patients that the postural control deficits in TBI relate to damage of the infratentorial structures. For example, our previous diffusion magnetic resonance imaging (MRI) work in young TBI patients has demonstrated that lower anisotropy and/or a higher mean diffusivity of the cerebellar white matter (WM), its peduncles and the medial lemniscus were significantly correlated with worse performance on a postural control task [Caeyenberghs et al., 2010; Drijkoningen et al., 2015a]. Moreover, graph theoretical analysis has shown that these postural impairments are also associated with a decreased structural connectivity of the cerebellum [Caeyenberghs et al., 2012]. The demonstrated alterations in WM microstructure and reduced connectivity could possibly lead to secondary degeneration and volume loss in infratentorial

structures. Yet, the association between infratentorial volume and postural impairments has not directly been evaluated.

Some studies in TBI patients have demonstrated reduced regional volumes in the cerebellum and brain stem as part of whole brain voxel-based analyses [Bendlin et al., 2008; Gale et al., 2005; Kim et al., 2008; Salmond et al., 2005; Sidaros et al., 2009]. However, standard whole-brain normalization procedures generally lead to relatively poor alignments in infratentorial structures [Diedrichsen, 2006] and, thus, do not allow for a precise localization of the volumetric differences. In this study, we made use of a spatially unbiased infratentorial (SUIT) template [Diedrichsen, 2006; Diedrichsen et al., 2009], which preserves more anatomic detail. The use of this template greatly improves the normalization of the isolated cerebellum and brain stem and quantification of regional volume loss in subsequent voxel-based morphometry (VBM) analyses. This approach could provide valuable new information on regional infratentorial volume loss in TBI patients and its relationship with balance impairments.

In this study, we hypothesized that young TBI patients would show regional grey matter (GM) and WM volume loss in the brain stem and cerebellum compared with healthy controls. Moreover, we expected that infratentorial volume loss would be associated with impairments in postural control, particularly in structures that are part of important sensorimotor pathways, such as the cerebellar anterior lobe, (para)vermis and peduncles; ventral mid-brain and dorsal medulla.

METHODS

Subjects

A group of 18 TBI patients ($M_{\text{age}} = 14$ years 2 months, $SD = 2$ years 11 months, nine males and 9 females) and a group of 30 typically developing subjects (TD, $M_{\text{age}} = 14$ years 10 months, $SD = 2$ years 2 months, 13 males and 17 females) were recruited. There was no significant group difference in age ($t(46) = 0.86$, $P = 0.39$) or gender composition ($\chi^2(1, n = 51) = 0.20$, $P = 0.65$). All TBI subjects were recruited from rehabilitation centers in Belgium. They were tested on average 3 years and 10 months (SD 3 years 3 months) postinjury when they did no longer participate in acute inpatient rehabilitation, and neurological recovery was stabilized, corresponding to the chronic stage of injury. See Table I for more information on demographic characteristics. All TBI patients were classified as “moderate-to-severe” using the Mayo classification system [Malec et al., 2007], based on the presence of one or more of the following criteria: loss of consciousness of 30 min or

TABLE I. Demographic and injury characteristics for the TBI group

TBI patient #, age (yrs)/gender/ cause of injury/age at injury (yrs)/time since injury (yrs)	GCS/Coma duration	Lesion location/pathology based on MRI scan
TBI 01; 8.6/M/traffic accident/7.9/0.7	Coma = 5 days	Hemosiderin deposits: R semiovale centre and CC
TBI 02; 18.1/F/traffic accident/15.6/2.5	Coma = 5 days	Small injuries surrounding drain trajectory in RH (superior frontal gyrus, head of caudate nucleus, crus anterior of internal capsule, thalamus and pons)
TBI 03; 9.3/F/traffic accident/7.9/1.4	Coma = 2 weeks	Contusion: R anterior temporal pole and R orbitofrontal cortex; injuries and atrophy in CC (body and splenium); atrophy of R pons; hemosiderin deposits in L cerebellar hemisphere, R nucleus lentiformis, L/R FL, L/R PL and R PL
TBI 04; 16.5/F/traffic accident/7.2/9.3	NA	Injuries in R medial frontal gyrus
TBI 05; 14.2/F/traffic accident/7.7/6.5	NA	Atrophy of the cerebellum; injuries at the level of L FL, premotor cortex, L/R medial frontal gyrus, cingulum, orbitofrontal cortex (L > R); contusion anterior temporal pole (R > L); hemosiderin deposits in CC, L thalamus, striatum (R > L)
TBI 06; 13.4/M/traffic accident/12.5/0.8	LOC (unknown duration)	Hemosiderin deposits: several spread out over L/R PL, R cerebellum, L superior frontal gyrus; hemociderosis as a remnant of subdural hemorrhage
TBI 07; 17.1/F/traffic accident/12.7/4.4	GCS = 3, coma = 6 weeks	Contusion/atrophy: R superior frontal gyrus, R temporal gyrus; injuries at the level of the R supramarginal gyrus, R angular gyrus, R precentral gyrus (M1), central sulcus, R postcentral gyrus, R medial frontal gyrus, R insula, R head and body of caudate nucleus, R globus pallidus, R putamen, anterior part of R thalamus; hemosiderin deposits in LH (superior/inferior frontal gyrus, paraventricular WM) and several in RH
TBI 08; 19.0/F/fall/12.5/6.5	LOS (unknown duration)	Hemosiderin deposits R cerebellar vermis
TBI 09; 15.6/M/traffic accident/12.5/3.2	Coma = 10 days	Atrophy cerebellum; contusion R FL WM
TBI 10; 13.9/M/traffic accident/13.5/0.3	GCS = 3	Hemosiderin deposits: L FL, periventricular WM, body and genu CC, L thalamus, R external capsule, anterior TL (L > R), L/R cerebellum; limited atrophy cerebellum
TBI 11; 10.9/M/sports injury (equestrian)/7.9/3.1	GCS = 4, LOC (unknown duration)	Injuries in RH: orbitofrontal cortex, inferior frontal gyrus and anterior part of medial/superior frontal gyrus; hemosiderin deposits in L superior frontal gyrus and L cerebellar hemisphere
TBI 12; 11.4/M/sports injury (equestrian)/9.8/1.5	Coma (unknown duration)	Hemosiderin deposit: splenium CC
TBI 13; 13.3/M/traffic accident/12.1/1.2	LOC = 15 min	Hemosiderin deposits L FL, genu CC
TBI 14; 13.3/M/traffic accident/12.8/0.5	LOC = 20 min	Shearing injuries in body and genu cc; mild WM loss (enlarged ventricles); hemosiderin deposits L/R paramedian FL, R thalamus, several in L temporal pole, L cerebellum, L OL
TBI 15; 14.1/F/sports injury (ski)/6.0/8.0	LOC (unknown duration)	No or small tissue damage
TBI 16; 16.0/F/NA/NA/NA	NA	Mild atrophy in cerebellum and cerebrum, more pronounced atrophy in frontal cortices, enlarged ventricles; contusion L/R anterior temporal pole and L/R orbitofrontal cortex; hemosiderin deposits in cerebellum, R FL
TBI 17; 17.8/M/NA/12.2/5.7	NA	Hemosiderin deposits: thalamus, L TL, L/R parietal
TBI 18; 13.8/F/object against head/3.0/10.8	NA	Contusion: L anterior middle frontal gyrus and L anterior superior frontal gyrus

Anatomy codes: WM = white matter; RH = right hemisphere; LH = left hemisphere; FL = frontal lobe; TL = temporal lobe; PL = parietal lobe; OL = occipital lobe; CC = corpus callosum; R = right; L = left. Other codes: yrs = years; GCS = Glasgow Coma Scale score; M = male; F = female; NA = information not available.

more; worst Glasgow Coma Scale score in the first 24 h lower than 13; or evidence of contusions, microbleedings or hematoma on computed tomography or MRI images, identified immediately after the injury. TBI patients with focal lesions (i.e., lesion volume $>0.5 \text{ cm}^3$) in the brain stem or cerebellum, as determined by an expert neuroradiologist (see MRI Data Acquisition section), were excluded to avoid distortion during normalization ($n = 2$). All subjects were able to stand independently without aid. The Bilateral Coordination and Balance subtests of the Bruininks-Oseretsky Test of Motor Proficiency [2nd ed.; Bruininks and Bruininks, 2005] were used to identify patients with gross motor impairments. Four TBI patients (Patients #5, #7, #8 and #16 in Table I) were identified scoring below or equal to the fifth percentile (corrected for age). Exclusion criteria for both groups were pre-existing developmental disorders, central neurological disorders, intellectual disabilities and musculoskeletal disease. The study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the local ethics committee for biomedical research. Written consent was obtained from all subjects and their parents.

Posturography

Postural control was tested using the EquiTest System (NeuroCom International, Clackamas, OR) which contains a visual surround and a force plate that measures the vertical forces under the subject's feet. Balance control was tested using three test protocols of the Equitest (same protocols as in our previous work [Drijkoningen et al., 2015a]), including the Sensory Organization Test (SOT), Rhythmic Weight Shift test (RWS) and the Limits of Stability test (LOS). All tests were performed bare-foot and with a safety harness. The total administration time of the three tests was approximately 20 min.

The SOT is a measure of static postural control in which the subject is instructed to stand on the platform (forceplate) as still as possible while sensory resources (i.e., somatosensory inputs, visual inputs or both) are systemically disrupted. The four sensory conditions included: (1) eyes open and fixed platform; (2) eyes closed and fixed platform; (3) eyes open and platform tilting in response to body sway to reduce movement in the ankle joint (altered somatosensory feedback) and (4) eyes closed and tilting platform. To familiarize the subject with the test and to avoid any initial surprise effect of the sensory manipulations, we included one practice trial for each condition before the onset of the actual measurement. After that, each condition was repeated three times in a randomized order. Each trial lasted 20 s. Trials in which a fall occurred were excluded. An established protocol was used to calculate the centre of pressure trajectory from the forceplate recordings (100 Hz) [Van Impe et al., 2012]. An inverse score was calculated from the centre of pressure trajectory to acquire a SOT balance score in which higher scores reflect better balance con-

trol (and less body sway). Finally, a composite score was calculated as the average across all conditions, to obtain a general measure of balance control on the SOT test.

The LOS test is a more dynamic test of balance control requiring goal-directed postural adjustments. The subjects intentionally displaced their center of gravity (COG) in different directions without stepping, falling or lifting the heel or toes. At the beginning of each trial, the COG (as provided by the force plate of the Equitest) was positioned in the center as indicated by a representation on a screen in front of the subject. On presentation of a visual cue, the subject had to move the COG towards one of the targets presented on the screen as quickly and accurately as possible by leaning over in the right direction. The following eight target directions were administered: front, right front, right, right back, back, left back, left and left front. After two practice trials, each direction was performed once, in a randomized order. The trial was interrupted and repeated in case the subject fell or stepped. The trial with the fall or step was not analyzed. The outcome measure (directional control) was computed as the difference between on-target (in target direction) and off-target movement (extraneous movement) divided by the amount of on-target movement, expressed as a percentage, as shown by the following formula: $(\text{amount of on-target movement} - \text{amount of off-target movement}) / (\text{amount of on-target movement}) \times 100\%$. Higher scores reflect better directional control. Only a straight line towards the target would result in a 100% score meaning no off-target movements. Directional control scores were averaged across the eight target directions for further analysis.

Similar to the LOS, the RWS is a dynamic test of balance control. It measures the ability to rhythmically move the COG from right to left or forward to backwards between two target positions. Each direction (backward-forward and left-right) was performed at three different speeds: slow (3 s pacing between each target), medium (2 s pacing) and fast (1 s pacing). Each combination of speed and direction (total of six combinations) was performed in a separate trial of six movement repetitions, which were preceded by four practice repetitions. The trial was interrupted and repeated in case the subject fell or stepped. Again, directional control was calculated in the same way as for the LOS task. Directional control scores were averaged across directions and velocities for further analysis.

MRI Data Acquisition

MR examination was performed on a Siemens 3T Magnetom Trio MRI scanner (Siemens, Erlangen, Germany) with a 12-channel matrix head coil. A high-resolution T1-weighted image was acquired using a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE; repetition time = 2,300 ms, echo time = 2.98 ms, voxel size = $1 \times 1 \times 1.1 \text{ mm}^3$, slice thickness = 1.1 mm, field of view = $256 \times 240 \text{ mm}^2$, 160 contiguous sagittal slices).

All T1-weighted images were inspected visually in Mricron [www.mricron.com; Rorden et al., 2007] for motion-related artefacts such as blurring, ghosting and striping, as well as general criteria that can affect image quality, e.g., head coverage, ringing artefacts or signal inhomogeneity [Reuter et al., 2015]. Moreover, prior to image processing, the images were inspected by an expert neuroradiologist who classified both infra- and supratentorial injuries in the TBI group (Table I). The following infratentorial injuries were observed in the group of included patients: atrophy of the brain stem (pons or midbrain) in one patient, atrophy of the cerebellum in one patient, signs of diffuse axonal injury (small hemosiderin deposits) in the cerebellum in seven patients and signs of diffuse axonal injury in the brain stem (in the cerebral peduncle) in one patient.

Image Preprocessing

As a first preprocessing step, the anatomical MRI scan of each participant was segmented into GM, WM, cerebrospinal fluid, skull, skin and out-of-brain using SPM8. To optimize further spatial normalization of the infratentorial structures, we made use of the SUIT toolbox v2.7 [http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm; Diedrichsen, 2006; Diedrichsen et al., 2009]. First, the cerebellum and brain stem were isolated from the anatomical images. These isolated maps were manually corrected in MRIcron (http://www.cabiatl.com/mricro/mricron/index.html) to remove parts of the transverse sinus, cerebellar tentorium or bone marrow, when erroneously identified as cerebellar GM. The cropped images were subsequently normalized to the SUIT template using the DARTEL engine [Ashburner, 2007], while correcting for volume changes induced by normalization (i.e., affine modulation). The resulting normalization parameters were used to reslice the GM and WM segments of each participant into SUIT atlas space.

Global Pattern of Volumetric Changes

Global infratentorial GM and WM volume were quantified by integrating the tissue probabilities over all voxels in the native segmented images. To avoid possible edge effects around the border between GM and WM, we used an absolute GM and WM threshold of $P < 0.2$. Global differences in volume between groups were assessed using a univariate linear regression analysis that considered total intracranial volume (TIV) as a covariate.

Voxel-Based Morphometry: Localized Pattern of Volumetric Changes

To preserve precision in the definition of cerebellar structures, a 4-mm default full width at half maximum Gaussian kernel was used for smoothing. Regional differences in volume between groups were assessed with two-

sample *t*-tests using the general linear model, while controlling for TIV.

The association between infratentorial GM and WM volume on one hand and postural control on the other hand was assessed within the two groups and across all participants with univariate linear regression models that included the balance scores of the LOS, RWS or SOT and TIV as covariate of no interest. We made use of an explicit brain mask including all voxels with a 0.2 probability for that tissue class in 80% of all healthy control subjects. We opted this approach, as opposed to the standard absolute threshold masking to reduce the risk of false-negative findings due to exclusion of voxels in the mask that are particularly sensitive to atrophy [Ridgway et al., 2009]. Statistical inference was performed at the cluster level (cluster defining height threshold $P < 0.001$), correcting for multiple comparisons over the search volume using family-wise error correction at $P < 0.05$.

Anatomical localization of the cerebellar lobules was determined using the probabilistic MRI atlas of the human cerebellum [Diedrichsen et al., 2009]. For localization within the infratentorial WM, we made use of the Talairach atlas [Lancaster et al., 2007; Talairach and Tournoux, 1988] and the ICBM-DTI-81 WM labels atlas [Mori et al., 2005].

RESULTS

Group Differences in Postural Control

Figure 1 displays the means and standard errors of the TBI and TD groups on each of the three postural controls tests (SOT, RWS and LOS). Lower scores indicate poorer balance (i.e., larger anterior/posterior body sway in the SOT and less directional control over the centre of gravity in the LOS and RWS). Poorer performance was observed in the TBI group on the SOT ($t(45) = 3.17$, $P < 0.01$) and the RWS ($t(45) = 2.50$, $P < 0.05$) tasks as compared with TD subjects. Performance on the LOS task was not significantly different between the groups ($t(44) = 1.59$, $P = 0.25$).

Group Differences in Global Volume of the Cerebellum and Brain Stem

TIV did not differ between groups (TD: $1,462.0 \pm 155.8$; TBI: $1,417.3 \pm 115.9$; $t(46) = 1.054$, $P = 0.297$). Compared with the TD group, TBI patients had a reduced volume in global infratentorial GM (TD: 107.9 ± 9.3 ; TBI: 100.6 ± 7.6 ; $F(1,45) = 9.27$, $P = 0.004$) and global infratentorial WM (TD: 67.1 ± 8.4 ; TBI: 61.6 ± 6.0 ; $F(1,45) = 7.87$, $P = 0.007$). The mean total cerebellar volume as a percentage of TIV was $12.2\% \pm 0.8\%$ in the TD group and $11.7\% \pm 0.6\%$ for the TBI group. This was a significant difference ($t(46) = 2.542$, $P = 0.014$).

Figure 1.

Performance on the three postural control tasks. Higher scores reflect better directional control over the centre of gravity (RWS and LOS tests) or lower body sway (SOT test). Error bars indicate SEM. *Indicates significant difference between TBI and TD subjects.

Group Differences in Regional Volume of the Cerebellum and Brain Stem

The VBM analyses revealed local volume differences in infratentorial WM. TBI patients had significantly lower WM volume in a cluster consisting of the middle cerebellar peduncle (left and right), pons and midbrain (tegmentum and inferior tectum; Table II and Fig. 2). The analysis of regional volume differences in GM between groups did not show any significant differences.

Associations Between Postural Control and Volume of the Cerebellum and Brain Stem

To establish the relationship between infratentorial volume and postural control performance, correlations were computed between infratentorial GM and WM volume and performance on the balance tests. Within the TBI group, and across the whole group, worse performance on the RWS test was associated with lower GM volume in the vermal and paravermal regions of lobules I–IV, V and VI (Table III and Fig. 3A).

Moreover, worse performance on the RWS test across all subjects was associated with a lower volume in a WM cluster that included the entire pons, dorsal medulla, midbrain (tegmentum), the convergence of the superior cerebellar peduncles with the brain stem and a major part of the middle cerebellar peduncles extending into the cerebellar WM (Table III and Fig. 3B). Similarly, lower WM volume of the pons and a part of the left middle cerebellar peduncle was associated with a worse performance (lower score; higher amount of body sway) on the SOT, across all participants (Table III and Fig. 3C). In the TD group, no significant correlations were observed between postural performance and WM or GM volume.

DISCUSSION

This study explored infratentorial volume loss in young patients with TBI, and addressed the associations between infratentorial volume and balance performance on three challenging postural control tasks. In the TBI group and across both groups, statistically significant correlations were observed indicating that reduced volume in specific areas of the brain stem and cerebellum are associated with

TABLE II. Group difference: stereotactic coordinates of the local maxima

Contrast	Cluster size	P-value	Anatomical label	x	y	z	t-value
Group difference in WM volume: TD > TBI	13,482	<0.001	MCP	17	-31	-40	4.21
				-15	-35	-42	3.96
				21	-35	-36	3.86
			MCP/pons	7	-21	-40	3.76
				-11	-36	-26	3.74
			Midbrain	7	-37	-15	4.21
				4	-16	-14	4.07
			Midbrain/cerebellar WM	5	-39	-10	3.71

Infratentorial VBM analysis with cluster defining height threshold $P < 0.001$, corrected for multiple comparisons using cluster-level family-wise inference at $P < 0.05$. Stereotactic coordinates are reported in Montreal Neurological Institute (MNI) space. Anatomy codes: WM = white matter, MCP = middle cerebellar peduncle. Other codes: TD = typically developing, TBI = traumatic brain injury patients.

Figure 2.

Cluster with significantly lower white matter volume in the TBI group compared with the TD group. Infratentorial VBM analysis with cluster defining height threshold $P < 0.001$, corrected for multiple comparisons over the search volume using family-wise error correction (FWE) at $P < 0.05$.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

poorer performance on both static and dynamic postural control tasks. To the best of our knowledge, this is the first time that associations between GM volume and measures of postural performance have been established in TBI patients. Our findings highlight the importance of infratentorial structures in the neural control of posture and suggest that atrophy in these structures can be an important marker of the neural pathology that leads to balance impairment after brain injury.

Group Differences in Postural Control

We demonstrated impaired postural control in TBI patients as compared with control subjects on a static test with compromised sensory feedback (SOT), and on a dynamic postural control task involving aimed weight shifts (RWS test). This is consistent with previous studies reporting balance deficits in young and adult mild and more severe TBI patients by means of clinical assessments [Dahl and Emanuelson, 2013; Gagnon et al., 1998, 2004; Katz-Leurer et al., 2008; McCulloch et al., 2010] or instrumented tests [Geurts et al., 1996], such as the SOT [Basford et al., 2003; Caeyenberghs et al., 2010; Drijkoningen et al., 2015a,b; Kaufman et al., 2006; Riemann and Guskiewicz, 2000].

Reduced postural control in TBI patients can have serious consequences for mobility, fall risk and independent functioning in daily life [Basford et al., 2003; Katz-Leurer et al., 2008; McCulloch et al., 2010]. Moreover, this study and previous research show that postural instability is a long-term consequence of TBI that can be observed months or even years after injury [Basford et al., 2003; Caeyenberghs et al., 2010; Geurts et al., 1996; Kaufman et al., 2006; Rossi and Sullivan, 1996].

In contrast to the RWS task, no group difference was observed in the performance on the LOS task. This may be due to differences in skills that are required for each of the

tasks. Both tasks require target-aimed shifting of the centre of gravity. However, in the LOS, the movement velocity is not imposed. In contrast, the RWS may have an additional complexity as it requires the tracking of a visually presented target at a specific speed and rhythm (visuomotor tracking). It may, therefore, be a more sensitive test for dynamic deficits in TBI patients.

Group Differences in Volume of the Brain Stem and Cerebellum

Using global infratentorial analysis, we observed reduced WM volume in TBI patients as compared with TD participants. Moreover, the regional (voxelwise) analysis revealed significantly reduced volume in TBI patients in the middle cerebellar peduncles, pons and midbrain (tectum and inferior tectum). This is the first time that a more precise localization of regional infratentorial atrophy has been performed in TBI patients by using optimized and isolated infratentorial normalization. Yet, the pattern of WM loss corresponds well with other studies reporting reduced volumes in the WM of the cerebellum and/or brain stem in TBI patients, using whole-brain voxel-wise approaches [Bendlin et al., 2008; Kim et al., 2008; Sidaros et al., 2009] or regions-of-interest analyses [Bigler et al., 2010; Fearing et al., 2008; Spanos et al., 2007].

Volume loss in the infratentorial WM may primarily result from secondary degeneration following diffuse axonal injury, which is widely considered as one of the most common types of primary injury in severe TBI patients [Parizel et al., 1998; Sahuquillo et al., 1989; Tong et al., 2003; Wen et al., 2014]. Secondary axonal degeneration in the WM develops progressively after the diffuse injury through chronic WM inflammation, axonal swelling, impaired axoplasmic transport and ultimately disconnection [Povlishock and Katz, 2005]. Long-term longitudinal

TABLE III. Association between postural control and volume: stereotactic coordinates of the local maxima

Contrast	Cluster size	<i>P</i> -value	Anatomical label	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i> -value				
Association between RWS and GM volume in the TBI group	2,782	<0.001	Lobule I-IV	-1	-55	-17	7.19				
				9	-52	-20	4.93				
			Lobule VI	-7	-65	-17	5.55				
				-7	-72	-22	4.23				
			Lobule V	-18	-71	-16	3.54				
				-8	-60	-10	3.96				
				-11	-58	-23	3.92				
				-8	-60	-21	3.63				
			Association between RWS and GM volume across all participants	2,152	0.005	Lobule I-IV	-1	-55	-18	4.20	
							8	-53	-20	3.85	
Lobule V	-8	-66				-17	3.75				
	-6	-52				-22	3.36				
	-7	-57				-17	3.50				
	-11	-59				-13	3.50				
	-12	-58				-22	3.42				
	-17	-69				-16	2.77				
Association between RWS and WM volume across all participants	29,005	<0.001				MCP/cerebellar WM	-28	-49	-33	6.91	
							30	-46	-34	6.05	
			MCP/Pons	-11	-39	-31	5.01				
				2	-19	-37	4.98				
			SCP	6	-37	-24	5.39				
				11	-36	-23	5.36				
			Pons	-2	-23	-34	4.94				
				6	-44	-42	4.85				
				Association between SOT and WM volume across all participants	2,537	0.047	MCP/Pons	2	-19	-38	3.53
								-9	-33	-39	2.95
1	-28	-38	3.12								
-9	-38	-32	2.93								
3	-33	-28	2.92								
5	-37	-25	2.90								
-13	-38	-42	2.76								

Infratentorial VBM analysis with cluster defining height threshold $P < 0.001$, corrected for multiple comparisons using cluster-level family-wise inference at $P < 0.05$. Stereotactic coordinates are reported in Montreal Neurological Institute (MNI) space. Anatomy codes: GM = grey matter, WM = white matter, MCP = middle cerebellar peduncle, SCP = superior cerebellar peduncle.

decrease in cerebellar volume [Bendlin et al., 2008; Roberts et al., 2014], along with changes in diffusion metrics [Bendlin et al., 2008], suggests that the process of cerebellar degeneration can develop for several months after the injury.

The global volumetric analysis also revealed a significant volume loss in cerebellar GM. No significant regional GM differences were observed between TBI and TD participants. This may suggest that global GM loss in TBI is subtle and not strongly concentrated in specific areas.

Several other studies found that reduction in GM volume in TBI patients is widespread across multiple brain regions including the cerebellum, which is consistent with the widespread nature of TBI and diffuse axonal injury [Bendlin et al., 2008; Bigler 2001; Gale et al., 2005; Kim et al., 2008; Salmond et al., 2005]. Spanos et al. (2007) revealed that atrophy of the cerebellum in TBI patients is associated with smaller volumes in known projection areas, including the dorsolateral prefrontal cortex and pons. This suggests that cerebellar volume loss after head trauma is not independent from volumetric changes in the other brain regions.

The exact nature of the underlying mechanisms of GM loss after TBI remains largely unknown. Similar to loss of WM, the loss of GM may be largely attributed to the effects of secondary degeneration. Specifically, the degeneration of WM resulting from the disconnection of axons may ultimately lead to degeneration of cerebellar cortical areas. Animal models of brain injury have revealed a selective pattern of Purkinje cell loss and microglial activation in the cerebellum as a secondary consequence of brain injury, even when the primary injury was located in the cerebral cortex distant from the cerebellum [Ai et al., 2007; Igarashi et al., 2007; Park et al., 2006, 2007; Potts et al., 2009].

Associations Between Cerebellar GM Volume and Postural Control

A significant correlation between RWS task performance (dynamic posture) and GM volume in the vermal/paravermal regions of lobules I–VI was found across all participants

Figure 3.

VBM regression analyses with cluster defining height threshold $P<0.001$, corrected for multiple comparisons over the search volume using family-wise error correction (FWE) at $P<0.05$. **(A)** Significant relationship between GM volume and performance on the RWS test in the TBI group and across all participants. **(B)** Significant relationship between WM volume and

performance on the RWS test across participants. **(C)** WM cluster where a significant association was found between WM volume and performance on the SOT test across participants. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(TBI and TD subjects). The locations of correlating cerebellar regions are in line with previous findings. Evidence from studies using positron emission tomography [Ouchi et al., 1999], lesion mapping [Konczak et al., 2005; Morton and Bastian, 2004] and fMRI on motor imagery of postural tasks [Jahn et al., 2004] confirm that the cerebellar vermis and paravermis play an important role in maintenance of posture. Specifically, the vermis has been suggested to play a primary role in regulating the tone of extensor muscles to sustain upright stance and dynamic balance control [Morton and Bastian, 2004]. Moreover, lobules I–V are part of the anterior lobe, which, together with neighboring lobule VI, is involved in sensorimotor processing [Debaere et al., 2004; Stoodley and Schmahmann, 2010; Stoodley et al., 2012] and show high functional connectivity to the cerebral somatosensory cortex [Buckner et al., 2011]. With regard to postural control, the anterior lobe is implicated in accurately tuning the magnitude of postural responses [Horak and Diener, 1994]. This is in line with findings by Spraker et al. (2012), showing that activations in lobule V and VI are associated with the magnitude of force output during muscle contractions, which further supports the role of this area in the scaling of motor output.

A similar (but higher) correlation was observed within the TBI group. Specifically, lower postural control levels on the RWS task were associated with reduced volume in the vermal/paravermal regions of lobules I–IV, V and VI. The results corroborate with a recent resting-state fMRI study in a subgroup of the same TBI patient sample, which has shown that postural impairments are also related with reduced long-range functional connectivity of the vermis of the anterior cerebellum [Caeyenberghs et al., *in press*]. Future studies using a longitudinal approach may shed light on the time course and causal relationships between GM loss and changes in functional and structural connectivity and how they affect the neural control of posture. One possible explanation is that diffuse axonal injury leads to altered functional connectivity through disconnection of axons while indirectly causing cerebellar volume loss through secondary (Wallerian) degeneration (as discussed in Group Differences in Volume of the Brain Stem and Cerebellum section). In turn, these structural changes may lead to reduced functional connectivity and reduced processing resources in cerebellar areas that are important for postural control. It has been demonstrated that cerebellar activity is particularly strong during dynamic postural conditions, such as gait [Jahn et al., 2004, 2008], posture in unstable situations [Slobounov et al., 2006] or postural perturbations [Taube et al., 2015], which may explain why reduced cerebellar volumes correlate highly with poor performance on the dynamic RWS task.

Degeneration or focal injury in the cerebellum can typically give rise to cerebellar ataxia, which involves instability during gait and posture [Brandauer et al., 2008; Hoogkamer et al., 2015; Ilg et al., 2008; Morton and Bastian, 2004; Timmann et al., 2008]. TBI can also lead to signs

of ataxia [Hong et al., 2009; Vasudevan et al., 2014]. However, in many cases, cerebellar clinical dysfunction is not apparent or difficult to diagnose in TBI [Soto-Ares et al., 2001], which may be due to the widespread/diffuse nature of TBI involving the brain stem, cerebellum and cerebrum. Postural deficits in TBI patients can potentially result from (combinations of) different injury locations. There is strong evidence that deterioration of supratentorial sensorimotor pathways also contributes to postural control deficits in TBI patients [Caeyenberghs et al., 2010]. Moreover, there may also be a direct association between injuries to supratentorial and infratentorial structures. Animal models of brain injury have revealed selective neuronal loss in the cerebellar cortex as a consequence of primary injury that was induced in the cerebral cortex [Ai et al., 2007; Igarashi et al., 2007; Park et al., 2006; Potts et al., 2009; Taylor et al., 2006]. Specifically, WM inflammation and disconnection resulting from diffuse axonal injury can lead to downstream degeneration of WM [Povlishock and Katz, 2005] and may ultimately cause degeneration in the brain stem or cerebellum. The challenge for future research is, therefore, to disentangle how specific postural deficits can be explained from different locations of injury or degeneration. In any case, the current findings advocate a prominent role of the cerebellum in the neuropathological origins of postural dysfunction in TBI patients.

Associations Between Infratentorial WM Volume and Postural Control

Across all subjects, lower volume in the brain stem (pons, dorsal part of the medulla and midbrain), superior and middle cerebellar peduncles and cerebellar WM were associated with a worse performance on the static SOT task and the dynamic RWS task. The involvement of such an extensive part of the infratentorial structure is not surprising considering the fact that it contains different pathways that are crucial in the maintenance of posture. Besides important WM pathways, the brain stem also comprises relevant GM nuclei within the clusters of correlating voxels such as the vestibular nuclei, mesencephalic locomotor region and pontine nuclei. The cluster also encompasses the deep cerebellar nuclei, which are embedded within the cerebellar WM and receive projections from the cerebellar cortex. It is possible that volumetric differences in the nuclei contribute to the findings in the WM segmentation. Therefore, some caution is warranted regarding the anatomic interpretation of these findings.

Our findings are consistent with previous work in other patient groups showing that injury in the cerebellar WM, peduncles, cerebellar nuclei or brain stem results in increased body sway during postural tasks [Brandauer et al., 2008; Konczak et al., 2005; Prosperini et al., 2013; Starr et al., 2003]. Moreover, in TBI patients, it has been demonstrated that balance impairments are associated with microstructural properties in the cerebellar WM,

cerebellar peduncles and medial lemniscus using diffusion MRI [Caeyenberghs et al., 2010; Drijkoningen et al., 2015a]. In this study, one of the areas that correlated with the performance on the RWS task was the dorsal medulla, which contains the cuneate and gracile nuclei that give rise to the medial lemniscus. This finding, therefore, provides credibility to the hypothesis that degeneration of the somatosensory pathways can be an important factor in the deterioration of postural control.

The role of the midbrain in balance control is confirmed by studies using functional MRI and positron emission tomography, which have shown that the execution or motor imagery of postural tasks does not only activate cortical regions in the cerebellum and cerebrum, but also the midbrain [Ferraye et al., 2014; Ouchi et al., 1999]. It has been suggested that the midbrain is part of a network involving the cerebellum, frontal areas and thalamus working interactively to control dynamic balance [Ferraye et al., 2014].

The functional contributions of the cortex and brainstem (including the midbrain) to postural control have been debated for a long time. More recent evidence suggests that fast postural responses are likely initiated in the brainstem. These responses are subsequently modified by cortical circuits during its later phases [for an overview, see Jacobs and Horak, 2007]. This is supported by evidence from studies on the decerebrate cat (without connections to the cortex), which showed that basic postural reactions to perturbations persist [Honeycutt et al., 2009; Honeycutt and Nichols, 2010]. It is still unknown to what extent this translates to human postural control. Yet, it has been observed that basic postural responses in humans are similar to, and may partially rely on, startle reflexes that involve brainstem centers [Campbell et al., 2013; Duysens, 2015; Nijhuis et al., 2010; Nonnekes et al., 2015].

CONCLUSION

This study provides a detailed analysis of volume loss in the brain stem and cerebellum, structures which are often overlooked in the study of the structural consequences of TBI. Moreover, this is the first report demonstrating a relationship between infratentorial volume loss and balance impairments in young TBI patients. Volumetric analysis of the brain stem and cerebellum may lead to valuable prognostic markers of the chronic neural pathology, which complicates rehabilitation of postural control. Additional studies are needed to further investigate the mechanisms of GM and WM atrophy in TBI patients and the extent to which it may contribute as a causal factor to functional disorders such as postural control impairments.

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