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Relationship between brainstem neurodegeneration and clinical impairment in traumatic spinal cord injury

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ABSTRACT

Background: Brainstem networks are pivotal in sensory and motor function and in recovery following experimental spinal cord injury (SCI).
Objective: To quantify neurodegeneration and its relation to clinical impairment in major brainstem pathways and nuclei in traumatic SCI.
Methods: Quantitative MRI data of 30 chronic traumatic SCI patients (15 with tetraplegia and 15 with paraplegia) and 23 controls were acquired. Patients underwent a full neurological examination. We calculated quantitative myelin-sensitive (magnetisation transfer saturation (MT) and longitudinal relaxation rate (R1)) and iron-sensitive (effective transverse relaxation rate (R2*)) maps. We constructed brainstem tissue templates using a multivariate Gaussian mixture model and assessed volume loss, myelin reductions, and iron accumulation across the brainstem pathways (e.g. corticospinal tracts (CSTs) and medial lemniscus), and nuclei (e.g. red nucleus and periaqueductal grey (PAG)). The relationship between structural changes and clinical impairment were assessed using regression analysis.
Results: Volume loss was detected in the CSTs and in the medial lemniscus. Myelin-sensitive MT and R1 were reduced in the PAG, the CSTs, the dorsal medulla and pons. No iron-sensitive changes in R2* were detected. Lower pinprick score related to more myelin reductions in the PAG, whereas lower functional independence was related to more myelin reductions in the vestibular and pontine nuclei.
Conclusion: Neurodegeneration, indicated by volume loss and myelin reductions, is evident in major brainstem pathways and nuclei following traumatic SCI; the magnitude of these changes relating to clinical impairment. Thus, quantitative MRI protocols offer new targets, which may be used as neuroimaging biomarkers in treatment trials.

1. Introduction

Traumatic spinal cord injury (SCI) is a devastating condition and causes permanent sensorimotor loss and autonomic dysfunction in most patients, with no cure currently available (Dietz and Fouad, 2014). Usually patients show some degree of recovery which levels off within two years after injury. Using computational neuroimaging approaches, rapid and dynamic trajectories of neurodegenerative processes have been identified above the level of injury that accompanied the recovery. Crucially, the magnitude of neurodegeneration was associated with clinical impairment (Freund et al., 2013; Grabher et al., 2015).

Besides neurodegeneration at the spinal and cortical level (Beaud et al., 2008; Jirjis et al., 2015), retrograde and transneuronal degeneration has been shown in experimental SCI in brainstem pathways (Jirjis et al., 2015; Jones and Pons, 1998) and nuclei (Jones and Pons, 1998; Kwon et al., 2002; Wannier-Morino et al., 2008). The brainstem is phylogenetically highly conserved in mammals and plays a key role in motor (Lemon, 2008) and sensory function (Benarroch, 2012; Liao et al., 2015). Important substructures of the motor system entail the rubrospinal system (i.e. execution of precise limb movements), the vestibulospinal system (i.e. balance and posture), the reticular formation (i.e. initiates and coordinates limb movements and postural support), and the corticospinal system (i.e. skilled motor function) (Lemon, 2008), while the dorsal column nuclei and medial lemniscus (Liao et al., 2015) and the periaqueductal grey (PAG) (Benarroch, 2012) are involved in sensory processing and pain

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modulation. Crucially, structural reorganization of brainstem pathways and nuclei has been associated with functional recovery following experimental SCI (Zaaimi et al., 2012; Zörner et al., 2014). Thus, understanding trauma-induced pathophysiological processes affecting the brainstem pathways and nuclei might offer crucial insights into neurodegeneration and plasticity.

However, the brainstem is still understudied in human SCI as accurate and sensitive neuroimaging tools targeting the brainstem have only recently become available (Lambert et al., 2013b). First attempts using neuroimaging approaches provided evidence of brainstem atrophy (i.e. volume loss) (Freund et al., 2013, 2012; Grabher et al., 2015; Wrigley et al., 2009) and plasticity (i.e. volume increases) during intensive training (Villiger et al., 2015) in human SCI. Recent improvements in quantitative MRI (qMRI) techniques now allow quantification of the underlying microstructural changes (Weiskopf et al., 2015) and segmentation of individual brainstem pathways and nuclei (Lambert et al., 2013b). This is possible because different MR contrasts can be used to calculate quantitative maps (magnetisation transfer saturation (MT), longitudinal relaxation rate (R1), effective transverse relaxation rate (R2*)), which are sensitive to myelin (Schmierer et al., 2004; Turati et al., 2015) and iron (Stüber et al., 2014). Such maps can be used for multiparametric brainstem tissue segmentation (Lambert et al., 2013b). Myelin reductions have been shown to accompany atrophic changes in the cord and cortex, thus offering complementary insights into the sequela of SCI (Freund et al., 2013; Grabher et al., 2015). Furthermore, iron accumulation due to myelin breakdown has been reported in SCI (Kroner et al., 2014; Sauerbeck et al., 2013).

Here, we combined voxel-based quantification and multiparametric tissue segmentation to address our hypotheses that after traumatic chronic SCI, (1) atrophy and myelin reduction are evident in major brainstem pathways and nuclei and, (2) that the extent of atrophy, myelin reduction and iron accumulation relates to clinical impairment, lesion level and severity.

2. Methods

2.1. Participants and study design

We recruited 30 individuals with a chronic traumatic SCI (3 female) and 23 healthy participants (10 female) at the University Hospital Balgrist between August 2011 and May 2015. Fifteen patients were tetraplegic and fifteen paraplegic. All patients were treated surgically for decompression. No participant reported a history of medical, neurological, or psychiatric disorders and all were eligible for MRI examinations.

Patients underwent a comprehensive clinical protocol including (1) the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (Kirshblum et al., 2011) to assess upper and lower extremity motor score (UEMS and LEMS), light touch (LT), pinprick (PP), lesion level, and severity (i.e. ASIA impairment scale (AIS)), and (2) the Spinal Cord Independence Measure (SCIM) (Catz et al., 2007).

To define the level of sensory and motor impairment, the most caudally intact dermatome for light touch and pinprick sensation (2/2 points) and motor function were considered, respectively (according to the ISNCSCI protocol). Lesion-level (neurological level of injury) was defined as the most caudal segment of the cord with intact sensation and motor function against gravity (min. 3/5 points), provided that motor and sensory function above this segment were normal. Lesion completeness was defined as having no motor and sensory function preserved in the sacral levels S4/5 (AIS A).

All participants gave informed written consent prior to study enrolment. The study protocol was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Canton Zurich (reference number: EK-2010-0271).

2.2. Image acquisition

All participants' structural whole-brain data, including the cervical cord up to vertebra C5, were acquired on a 3T Magnetom MRI scanner (Siemens Healthcare, Erlangen, Germany). The system was equipped with a 16-channel radiofrequency (RF) receive head and neck coil and RF body transmit coil. A multiecho 3D FLASH (fast low-angle shot) sequence, with the following parameters, was used within a whole-brain multiparameter mapping (MPM) qMRI protocol (Draganski et al., 2011; Weiskopf et al., 2011): field of view (FoV) of 240 × 256 mm^2, matrix size 240 × 256, isotropic resolution of 1 mm, GRAPPA parallel imaging in phase-encoding direction (anterior-posterior) with speed-up factor of 2, partial Fourier acquisition with 6/8 sampling factor in partition direction (left-right), and a readout bandwith of 480 Hz per pixel. Different weightings were predominantly achieved by choosing repetition time (TR) and flip angle (α): (1) T1-weighted (T1w): 25 ms/23°, (2) proton density-weighted (PDw): 25 ms/4°, and (3) MT-weighted (MTw): 37 ms/9° with off-resonance RF pulse prior to excitation. Echoes were acquired at seven equidistant echo times (TE) from 2.46 ms to 17.22 ms for all volumes, with an additional echo at 19.68 ms for PDw and T1w.

2.3. Image pre-processing

The acquired T1w, PDw, and MTw echoes were first averaged to increase the signal to noise ratio (SNR) and then used to calculate quantitative maps of MT and R1 (Draganski et al., 2011; Weiskopf et al., 2011) in MATLAB (MathWorks, Natick, MA). R2* was calculated from the log signal of the PDw echoes. UNICORT (Weiskopf et al., 2011) was used to correct RF transmit field inhomogeneity.

2.4. Brainstem template generation

We first generated brainstem tissue probability maps (TPMs) for the spatial alignment of brainstem sub-structures in our study cohort and to increase sensitivity for pathophysiological processes. Before generating the TPMs, we extracted the brainstem from quantitative maps from a longitudinal qMRI dataset of 29 subjects over four time points (Freund et al., 2013; Grabher et al., 2015) by label propagation using a set of brain labels (Neuromorphometrics Inc., Somerville, USA). Subsequently, whole-brain deformation fields were derived by segmenting the MT maps (Ashburner and Friston, 2005) and then applying a diffeomorphic image registration algorithm (Ashburner, 2007). The derived deformation fields enabled the extracted qMRI brainstem data to be transformed to the MNI space.

We then used a multivariate Gaussian mixture model to generate brainstem TPMs (Hasselblad, 1966). Such a model assumes that the observed image intensities are drawn from a set of multivariate Gaussian probability density functions, where each Gaussian captures the intensity distribution of one single tissue type. Additionally, we introduced locally-varying, unknown tissue priors, which are learned directly from the observed data, thus providing a set of population-specific, average-shaped TPMs (Blaiotta et al., 2016; Lambert et al., 2013b). The statistical Gaussian mixture model was fit to the spatially normalized qMRI brainstem data, using the Expectation-Maximization algorithm (Moon, 1996), which is a general and well-established technique to obtain *maximum likelihood* or *maximum a posteriori* estimates of the model parameters, for probabilistic latent variable models. Within the neuroimaging community, such a method has been extensively validated for the classification of neural tissue types from MR data (Ashburner and Friston, 2005; Blaiotta et al., 2016; Lambert et al., 2013b). The resulting seven brainstem TPMs (classes 1–7) are shown in Fig. 1 and contained, amongst others, the red nucleus (RN) (class 6), cerebral crus including the corticospinal tracts (CSTs) (class 6), and PAG (class 3). Anatomical locations were validated using a high-field MRI brainstem atlas (Naidich et al., 2009). The tissue probability maps