NeuroImage: Clinical 7 (2015) 782–787

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Exposing asymmetric gray matter vulnerability in amyotrophic lateral sclerosis

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ARTICLE INFO

Article history:
Received 23 January 2015
Received in revised form 2 March 2015
Accepted 5 March 2015
Available online 14 March 2015

Keywords:
Motor neuron disease
Amyotrophic lateral sclerosis
Voxel-based morphometry
Asymmetry
Limb dominance

ABSTRACT

Limb weakness in amyotrophic lateral sclerosis (ALS) is typically asymmetric. Previous studies have identified an effect of limb dominance on onset and spread of weakness, however relative atrophy of dominant and non-dominant brain regions has not been investigated. Our objective was to use voxel-based morphometry (VBM) to explore gray matter (GM) asymmetry in ALS, in the context of limb dominance. 30 ALS subjects were matched with 17 healthy controls. All subjects were right-handed. Each underwent a structural MRI sequence, from which GM segmentations were generated. Patterns of GM atrophy were assessed in ALS subjects with first weakness in a right-sided limb ($n = 15$) or left-sided limb ($n = 15$). Within each group, a voxelwise comparison was also performed between native and mirror GM images, to identify regions of hemispheric GM asymmetry. Subjects with ALS showed disproportionate atrophy of the dominant (left) motor cortex hand area, irrespective of the side of first limb weakness ($p < 0.01$). Asymmetric atrophy of the left somatosensory cortex and temporal gyri was only observed in ALS subjects with right-sided onset of limb weakness. Our VBM protocol, contrasting native and mirror images, was able to more sensitively detect asymmetric GM pathology in a small cohort, compared with standard methods. These findings indicate particular vulnerability of dominant upper limb representation in ALS, supporting previous clinical studies, and with implications for cortical organisation and selective vulnerability.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative condition affecting upper (UMN) and lower motor neurons (LMN) (Kiernan et al., 2011; Turner et al., 2013). Understanding the pathophysiology of ALS is challenging, due to significant variability of clinical phenotype, patient characteristics and disease progression (Chiò et al., 2011; Turner et al., 2013).

Despite this variability, common patterns have been observed across a wide range of ALS subjects. A well-studied example is the "split hand" phenomenon, in which there is disproportionate weakness of the thenar/first dorsal interosseous muscle group (Eisen et al., 2014; Eisen and Kuwabara, 2012). Early weakness of ankle dorsiflexors (Eisen et al., 2014) and speech (Devine et al., 2013) has also been observed. These findings have prompted suggestions that functions which humans have evolved more recently, such as the pincer grip and upright stance, are more susceptible to ALS (Eisen et al., 2014; Eisen, 2009).

Onset of weakness in ALS is also typically asymmetric. However, the factors determining the side of onset and direction of spread remain unclear. Since humans have evolved strong population-wide upper limb dominance (Fitch and Braccini, 2013), it is important to explore this as another potential source of vulnerability in ALS. It has been shown that the dominant upper limb, but not lower limb, is more susceptible to onset of weakness (Turner et al., 2011). We have also described that spread of weakness and UMN signs are affected by dominance, suggesting importance of central factors (Devine et al., 2014).

The aim of this study was to investigate gray matter (GM) asymmetry in ALS, and thus identify regions asymmetrically affected by the disease. Applying voxel-based morphometry (VBM) analysis of structural MRI, we performed direct comparisons between ALS subjects and controls, as well as using a novel asymmetry protocol to assess interhemispheric differences (Rose et al., 2012). Our hypothesis was that this asymmetry protocol would detect patterns of disproportionate atrophy

Abbreviations: ALS, amyotrophic lateral sclerosis; VBM, voxel-based morphometry; GM, gray matter; UMN, upper motor neuron; LMN, lower motor neuron.

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http://dx.doi.org/10.1016/j.nicl.2015.03.006

in ALS, which would be affected by whether weakness first occurred in a dominant or non-dominant limb.

2. Materials and methods

2.1. Subjects and recruitment

Ethical approval was obtained from the Royal Brisbane and Women's Hospital (RBWH) Human Research Ethics Committee. All subjects provided written informed consent, and all research was conducted in accordance with the Declaration of Helsinki.

Thirty right-handed subjects were recruited from ALS outpatient clinics at the RBWH (2008–2013). All had diagnoses of clinically probable or definite ALS, according to revised El Escorial criteria (Brooks et al., 2000). We chose to study only right-handed subjects due to their predominance in the population (Meguerditchian et al., 2013), as well as greater uniformity of motor and language lateralisation (Adamo and Taufiq, 2011). Handedness was confirmed using the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects were grouped according to the index limb, defined as the first limb affected by weakness (either the limb of onset, or the first limb affected after bulbar onset) (Devine et al., 2014). Fifteen subjects had a right-sided (dominant) index limb and 15 had a left-sided (non-dominant) index limb. Each subject was administered the ALS Functional Rating Scale—Revised (ALSFRS-R) as a measure of disability. To adjust the degree of disability for the disease duration, we calculated "disease progression" as: (48 − ALSFRS-R score) / (disease duration). Seventeen right-handed healthy controls were closely age and sex-matched with each group of 15 ALS subjects. None of the control or ALS subjects had a history of cerebrovascular events, intracranial pathology, or other neurological diseases.

2.2. MRI acquisition

Each subject underwent an MRI scan acquired with a 3 T Siemens TimTrio (Siemens, Erlangen, Germany), using sequences from VB17 Neuro applications and a 12-channel head coil. A high-resolution structural image was acquired for each subject using a 1 mm^3 isotropic 3D T1 MPRAGE (FOV 24 × 25.6 × 17.6 cm, TR/TE/TI 2300/2.26/900 ms, flip angle 9). Slice thickness was 1 mm and image acquisition time was 9:14 min.

2.3. Image processing

Structural images were processed according to the protocol previously reported (Rose et al., 2012). The software package FSL-VBM (Version 4.1), an optimised VBM protocol (Good et al., 2001a) carried out with FSL tools (Smith et al., 2004), was used for all image processing and analysis. The brain was extracted using BET (Smith, 2002). GM segmentation was performed using FAST (Zhang et al., 2001), with the segmentations then aligned to MNI152 standard space using affine registration, FLIRT (Jenkinson and Smith, 2001), followed by non-linear registration using FNIRT (Andersson, 2007). The resulting images were averaged to create a study-specific GM template. Each image was non-linearly re-registered to that template, before being modulated by dividing by the Jacobian determinant of the warp field and smoothed with an isotropic Gaussian kernel (sigma = 4 mm). Mirror images were then generated for each of the smoothed, modulated GM images in standard space, for each of the 47 subjects.

2.4. Statistical analysis

All statistical comparisons were performed using Randomise (Nichols and Holmes, 2002), and adjusted for multiple comparisons using threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009).

2.4.1. ALS and controls

Firstly, a voxelwise unpaired t-test was performed, comparing the GM density of all ALS subjects (n = 30) with all controls (n = 17). ALS subjects were then subdivided into two groups (15 with a right-sided index limb, and 15 with a left-sided index limb), and each group was compared with 15 age and sex-matched controls. Finally, the ALS subjects with a right-sided index limb were compared directly with those having a left-sided index limb. For each test, age and disease progression were introduced as nuisance covariates.

2.4.2. Asymmetry analysis

In order to identify areas of hemispheric asymmetry, a voxelwise paired t-test was performed between the native and mirror images. This was performed separately for each of the three groups of subjects (17 controls, 15 ALS subjects with a right-sided index limb and 15 with a left-sided index limb). The limb subscore (questions 4–9) of the ALSFRS-R was introduced as a covariate. The anatomical location of each cluster of GM asymmetry was determined using the Talairach Daemon. The threshold for statistical significance was set at $p \leq 0.01$ (TFCE-corrected).

3. Results

3.1. ALS and controls

Specific subject characteristics are presented in Table 1. Compared with controls (n = 17), subjects with ALS (n = 30) showed a multifocal cluster of reduced GM density, involving the left precentral gyrus and adjacent regions of the left middle frontal gyrus and bilateral medial frontal gyri (2087 voxels; centre-of-gravity: −22, −11, 52; $p \leq 0.05$). There was a separate cluster of reduced GM density involving bilateral anterior cingulate gyri (425 voxels; centre-of-gravity: 1, 39, 6; $p \leq 0.05$). These patterns of atrophy are illustrated in Fig. 1A.

Across all 47 subjects, there was a negative correlation ($p \leq 0.05$) between age and GM density in widespread regions of the frontal, parietal, temporal and occipital lobes, representative of age-related atrophy. However, there was no confounding effect of age or disease progression on the patterns of atrophy in ALS.

3.2. ALS (according to index limb) and controls

As illustrated in Fig. 1B, ALS subjects with a right (dominant) index limb (n = 15) showed patchy reductions in GM density affecting the left precentral gyrus, at a threshold of $p \leq 0.05$. These changes were not significant at a higher threshold of $p \leq 0.01$. Subjects with a left (non-dominant) index limb (n = 15) did not demonstrate any significant reductions in GM density at either the left or right precentral gyri at a threshold of $p \leq 0.05$ (Fig. 1C).

Direct voxelwise comparison between ALS subjects with either a right or left index limb also did not reveal any significant differences in GM density.

3.3. GM asymmetry in controls

In the 17 right-handed control subjects, multiple statistical clusters of both rightward and leftward asymmetries were identified (Table 2, Fig. 2A). Of particular note was an area of leftward asymmetry ($p \leq 0.01$) encompassing a dorsolateral region of the precentral and postcentral gyri. This area corresponded closely with the centre-of-gravity of the dominant thenar representation area, previously defined using transcranial magnetic stimulation (TMS) (Niskanen et al., 2010). Control subjects also demonstrated significant leftward asymmetry of a region of the superior and transverse temporal gyri, adjacent to the Sylvian fissure. There were no significant asymmetries of lower limb or bulbar representation areas, indicating that these regions were of a similar density in the right and left hemispheres.