Brain Atlas-based Lesion Spatial Distribution and Modeling of Wallerian Degeneration In Multiple Sclerosis

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Introduction: Wallerian degeneration (WD) of axons proximal to inflammatory lesions in multiple sclerosis (MS) has been proposed as one contributor to quantitative MRI abnormalities detected in normal-appearing grey matter (NAGM) and white matter (NAWM). The literature on the role of lesions and their impact on qMRI metrics of normal brain tissue is contradictory [4-7]. The availability of a detailed tabulation of the spatial distribution of lesions in a standardized human brain atlas of deep subcortical, corticospinal GM matter and fiber tracts will help model the effect of lesions on regional qMRI metrics derived using multi-modal MRI methods [8]. In this work, we describe a computational framework that provides human brain atlas-based regional lesion volume, NAWM and NAGM volumetry and their corresponding microstructural qMRI metrics (e.g. relaxation, anisotropy, axial, radial and mean diffusivities). We applied our methods to provide lesion distribution maps of a cohort of relapsing remitting (RR) MS patients relative to anatomical labels of deep GM nuclei, cortical GM matter parcellation and white matter tracts [9] provided by the international consortium for brain mapping (ICBM) [10, 11] and FreeSurfer [12]. We demonstrate the importance of lesion volume distribution and proximity to explain disability in MS.

Methods: Subjects: We included 87 RRMS patients (77% females; age = 42.6±9.9 years), disease duration (DD) = 11.0±2.8 years, extended disability status score (EDSS) = 1.7±1.6 (range=0-6.5) and total lesion load or burden of disease (BOD) = 12.3±11.7 mL (see Figure 1 below). Conventional MRI Acquisition: MRI studies were performed on a 3T Philips Intera scanner with a dual quasar gradient system and an eight-channel SENSE-compatible head coil. The MRI protocol included a T1-weighted 3D-SPGR with isotropic voxel size = 0.9375 mm3 for tissue volumetry, dual fast spin-echo (FSE; TE/TE/TR = 110/90/6800), fluid-attenuate inversion recovery (FLAIR; TE/TR/TE = 8/2500/80) for lesion segmentation [8]. Processing: All MRI data sets were masked to remove non-brain tissues and the intracranial volume (ICV) was computed. MS lesions were segmented using the DSE and FLAIR data as described elsewhere [8]. Tissue volumes were obtained by the application of T2-weighted and T1-weighted atlas-based methods on the lesion demodulated T2-weighted atlas [9,10] and FreeSurfer on the T1-weighted volume [12]. Lesion spatial distribution or probability map was computed using SPM as described elsewhere [3,6,11,13,14]. All volumes (dual-echo, derived lesion masks and qMRI microstructural atlases) were registered with T1-weighted data where regions are labeled using standardized ICBM [10] and FreeSurfer atlases [12]. The FreeSurfer brain volumes demodulated by the lesion masks were used to obtain the regional qMRI average values for all atlas labels. Atlas-based Anatomical Labels: The brain atlas covered the frontal, temporal, parietal, occipital, cingulate and insular cortices and corresponding white matter analogues. The deep GM tissue included the putamen, globus pallidus, hippocampus, amygdala and accumbens. The corpus callosum (CC) subdivisions, insular white matter were also included. Further, we have used the DTI-81 white matter tractography atlas [9,10] in standard space to compute the frequency that lesions intercepted an anatomical label assigned to a host of commissural (e.g. CC), association (e.g. uncinate, inferior and superior longitudinal fasciculus), projection (e.g. corona radiata, corticospinal tract) and limbic pathways (e.g. cingulum, fornix) as described in Wakana et al. [9]. Validation of Volumetry and Lesion Maps: Our automated lesion distribution results were validated using a trained physician who tabulated lesion frequency on all patients. The volumetry results on MS patients were compared with those obtained on healthy controls. Statistical Analysis: Correlations between age, EDSS, DD and regional metrics were computed using the Pearson correlation or Spearman coefficients.

Results: Figure 1 shows the scatter and linear correlations between EDSS, DD, BOD and age on our RRMS cohort. As expected, EDSS increased with BOD and DD [15]. Representative lesion maps on our RRMS cohort using the ICBM, DTI-81 and FreeSurfer atlases are shown in Figure 2 and Figure 3 where lesions are assigned a hot-red color. The volume of frequency in brain atlas labels (e.g. nuclei, tracts, cortex, sub-lobar) were extensively tabulated (only a summary is provided here). Note that lesions in cortical GM are less frequent than subcortical GM regions. Lesions in WM are more frequent than those in GM (e.g. insular GM ~ 35%; insular WM 50%). Lesions in the hippocampus are more frequent (~65%) than in the amygdala (20%). Lesions in the caudate (100%) are more frequent than those in the putamen (10%), and lesions in the thalamus GM are least frequent in our cohort (~15%). As depicted in Figure 3, lesions in the parietal and occipital lobes WM are dominantly intercepting the corona radiata and optic radiations. As one important representative of the quantitative results, Figure 4 shows a scatter plot of the regional lesion volume in the corona radiata and its significant correlation with (A) EDSS and (B) DD (compare Figure 4 & Figure 1 using the entire brain BOD).

Discussion: To our knowledge, this is the first report on RRMS brain spatial distribution of lesions using the ICBM and FreeSurfer gray and white matter atlases that included fiber pathways. Our results on the topology (Figure 2, 3), subcortical and lobar distribution of lesions in gray and white matter are consistent with a postmortem histopathology report by Brownwell B and Hughes in 1962 [16]. The significant correlation between regional lesion volume of the corona radiata with EDSS and DD show the importance of regional lesion mapping as applied to brain function at the system-level and warrant the examination of serial data and different MS phenotypes.