Thalamo-Cortical Abnormalities Correlate with Thalamic Atrophy in CIS Patients at Presentation

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INTRODUCTION: Clinically isolated syndromes (CIS) are isolated events typically involving lapses in sensory function and are the earliest signs of the possible onset of Multiple Sclerosis (MS). There are many studies showing gray matter thalamic atrophy in Multiple Sclerosis patients, and one study has shown that the whole brain atrophy can be detected within a year in CIS patients. While whole brain atrophy cannot be determined in CIS patients at presentation, a previous study has shown the presence of thalamic atrophy using voxel-based morphometry [1]. In addition to atrophy present in CIS patients at presentation, white matter abnormalities have also been detected with quantitative MRI techniques, but the relationship of these abnormalities to atrophy is currently unknown. We have investigated this relationship using diffusion tensor MRI (DTI) fiber tractography to delineate the white matter pathways connected to the thalamus. Localized concentration and volume of gray matter can be compared in a voxel-wise manner between groups of subjects using voxel-based morphometry (VBM). Statistical parametric mapping (SPM) enables the comparison of this data between groups as well as the correlation with metrics associated with each subject, such as age, total intracranial volume, and average EV1 values.

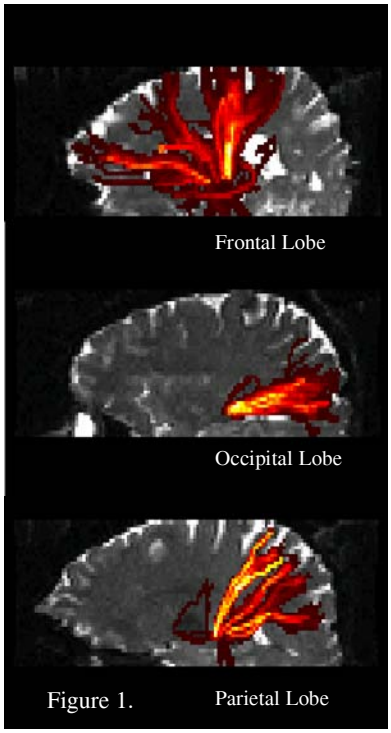

Figure 1.

METHODS: T1-weighted SPGR volumes, 1 x 1 x 1.5 mm resolution, and DTI (b=1000 s/mm2. 1.7x1.7x2.1 mm resolution, 9 averages) were acquired on a 1.5 T GE scanner on 52 subjects ages 21-52, 33 of them CIS patients (scanned within 4 months of clinical symptoms) and 19 control subjects. 3-dimensional ROIs were drawn around the thalamus of each of the control subjects on the T2-weighted b0 diffusion images and around the frontal, occipital, parietal, and temporal lobes on a 152-subject average MNI template, and were verified by an experienced neurologist. The lobar ROIs were registered from MNI-space to the T1-weighted volume in the patient's space using a 12-parameter affine transform and then to each patient's DTI data using a 12-parameter affine followed by a 168-parameter nonlinear transform. Fiber tracking was performed using whole-brain seeding and FACT algorithm with anisotropy threshold of 100 and angle threshold of 70. The tracks were targeted to the thalamus and subsequently to each of the lobes of the brain, as shown in Figure 1. The resulting tracks were transformed back from DTI-space using a 12-parameter affine followed by a 168-parameter nonlinear transform to the patient's T1 space, and then back to MNI-space using a 12-parameter affine transform. These tracks targeted to each lobe were separately binarized and averaged together to form a probabilistic template of white matter regions. Using the same registration procedure as was used to transform the lobar ROIs to patient DTI-space, the probabilistic templates were registered to each of the control and patient's DTI space. The average diffusion major (EV1) and minor (EVT = (EV2 + EV3)/2) eigenvalues, fractional anisotropy (FA), and mean diffusivity (Dav) in the tracks was calculated for each lobe in each side of the brain. A t-test was performed on the averages to determine a significant change between populations. Using the methods outlined in a previous study [1] a local template was created using the subjects included in this study, as well as segmented gray matter, white matter, and CSF, and modulated gray matter images. The procedure was optimized and included the masking of lesions during normalization to prevent large distortions due to the cost function. A correlation analysis was conducted using each patient's average FA values with age and total intracranial volume and covariates to determine atrophy in which gray matter structures correlated with decreasing FA.

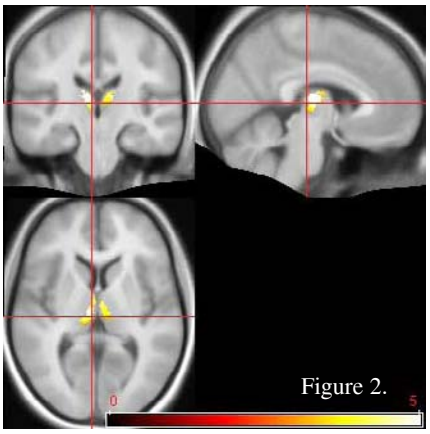

Figure 2.

RESULTS:

	Frontal Left	Frontal Right	Occipital Left	Occipital Right	Parietal Left	Parietal Right	Temporal Left	Temporal Right
Control subjects	248.5	254.4	257.5	254.3	270.7	275.0	249.6	249.1
CIS Patients	240.4	246.0	246.5	242.8	264.2	275.1	238.2	236.4
t-test	0.043	0.042	0.044	0.063	0.139	0.494	0.017	0.006

Table 1. Fractional Anisotropy averages for tracks through each lobe.

The thalamo-cortical frontal and temporal white matter FA values were significantly decreased in the CIS compared to the controls (Table 1). The FA values in all thalamo-cortical white matter regions were significantly correlated ($p < 0.05$ FWE corrected) with the thalamic atrophy from the VBM correlation analysis as shown in Figure 2. Furthermore, 70% of the lesions were determined to occur within the thalamo-cortical white matter, and the lesion volume within the thalamo-cortical white matter was also correlated with the thalamic atrophy ($p < 0.001$ uncorrected).

DISCUSSION: In CIS patients at presentation we have determined that in addition to thalamic atrophy, the white matter connected to the thalami are also abnormal and the thalamo-cortical abnormality is highly correlated with the thalamic atrophy. Furthermore, most of the lesions in the group are within the white connecting the thalamus. These results suggests that even in the earliest stages of MS, the atrophy and white matter abnormalities are strongly related and the possibility remains that visible lesions may play a major part in these pathological effects. Further studies of these data should further elucidate the role of lesions in early thalamic atrophy and normal appearing white matter abnormalities.

REFERENCES:

[1] Shieh et al. ISMRM 2006 #2099