Relating Thalamic Atrophy and White Matter Lesions at the earliest stages of Multiple Sclerosis

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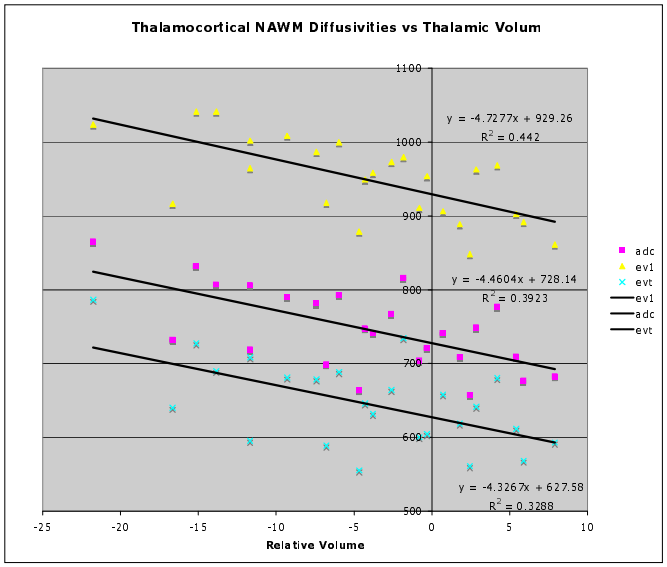
INTRODUCTION: Clinically isolated syndromes (CIS) are isolated events typically involving lapses in sensory function and are the earliest signs of the possible onset of Multiple Sclerosis (MS). While grey matter atrophy cannot be determined in CIS patients at presentation, a previous study has shown the presence of thalamic atrophy and a significant correlation of white matter lesion volume with thalamic volume using voxel-based morphometry. 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. One possibility is that both WM lesions and thalamic atrophy are both due to a common disease mechanism and are therefore do not have a causative relation on each other. Alternatively, the white matter lesions may cause the thalamic atrophy and/or thalamic degeneration may be in part responsible for pathology arising in connected axonal bundles. In order to shed further light on these possibilities, we have investigated this relationship using diffusion tensor MRI (DTI) fiber tractography to delineate the white matter pathways connected to the thalamus. To do this we have used DTI fiber tracking to create a probabilistic thalamocortical white matter template in MNI space and used this template to determine the white matter lesion distribution relative to the thalamocortical white matter, and the differences between CIS and control DTI parameters in normal appearing thalamocortical white matter (TC-NAWM). Secondly, using DTI fiber tracking in the CIS patients, we investigated the relationships between thalamic volumes, lesion volumes, and DTI parameters in lesion-thalamocortical NAWM (L-TC-NAWM), and thalamocortical white matter lesions (TC-lesions).



METHODS: Forty-two subjects (ages 21-52) were scanned with T1-weighted SPGR volumes (1x1x1.5mm resolution), and DTI (b=1000 s/mm2. 1.7x1.7x2.1 mm resolution, 9 averages) were acquired on a 1.5 T GE scanner, 24 of them CIS patients (scanned within 4 months of clinical symptoms) and 18 control subjects. Three-dimensional ROIs were drawn around the thalamus of each of the subjects. Regions of left and right cortical lobes (frontal, occipital, parietal, temporal) were defined on an MNI template by an experienced neurologist. The lobar ROIs were registered from MNI-space to the control subjects' space using nonlinear transforms. Fiber tracking was performed using whole-brain seeding and FACT algorithm. The tracks were targeted to the thalamus and subsequently to each of the cortical lobes of the brain. The resulting tracks were transformed back to MNI-space, binarized, and averaged together to form a probabilistic template of thalamocortical white matter regions. Using non-linear transforms the probabilistic templates were registered to each of the control and patient's DTI space. DTI metrics in TC-NAWM regions were compared between CIS and controls with covariance for age, sex, and total intracranial volumes. The fraction of a region occupied by lesions was defined for the TC and non-TC regions. DTI metrics in NAWM connecting thalami and lesions were also delineated (Lesion-TC-NAWM), TC-NAWM, and in TC lesions, along with TC T1LV were step-wise regressed with thalamic volumes.

RESULTS:

	FRONTAL	OCCIPITAL	PARIETAL	TEMPORAL	ALL
FA CIS	313	288	272	299	270
FA CTL	310	309	317	303	286
p-value	ns	ns	$p < 0.008$	ns	ns
MD CIS	715	753	763	734	747
MD CTL	705	719	708	738	723
p-value	ns	ns	$p < 0.02$	ns	ns
ev1 CIS	945	971	970	956	950
l1 CTL	929	945	939	964	932
p-value	ns	ns	ns	ns	ns
evT CIS	600	644	660	623	646
lT CTL	593	606	593	626	618
p-value	ns	ns	$p < 0.007$	ns	ns

Average of DTI metrics in normal-appearing thalamocortical white matter for CIS and control (CTL) subjects. Region (ALL) is the entire thalamocortical ROI; ev1: axial diffusion; evT: average of minor diffusivities; ns: not significant corresponding to $p > 0.05$.

Furthermore, 70% of the lesions were determined to occur within the thalamo-cortical NAWM, while the TC-NAWM only consisted of 30 % of the total white matter; this constitutes a 10 to 1 bias of lesions in TC NAWM. The lesion volume within the thalamo-cortical white matter and axial diffusivity were correlated with the thalamic atrophy ($p < 0.001$).

DISCUSSION: The bias of lesions occurring in thalamocortical white matter in CIS patients suggests more than a coincidental correlation with thalamic atrophy. Furthermore, corresponding changes were observed in the NAWM connecting lesions to thalami. These results suggests the direct influence on white matter lesions on thalamic atrophy in the earliest stages of multiple sclerosis, or the preferential occurrence of lesions in thalamocortical white matter arising from primary pathology in the thalamus.