Evaluation of Associations between Cognitive Function, White Matter Hyperintensity Volumes, and Mean Diffusivity

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Introduction: White matter hyperintensities (WMH) on fluid attenuated inversion recovery (FLAIR) images are a common finding in older people and are associated with cognitive and motor deficits [1-4]. Age-related WMH reflect various underlying tissue pathologies, including ischemic demyelination, microinfarction and axonal loss, and thus may identify tissue abnormalities of varying severity. Diffusion tensor imaging (DTI) parameters such as fractional anisotropy (FA) and mean diffusivity (MD) are proposed to be more sensitive to the underlying white matter structural integrity [2-5] and more closely associated with cognitive function. Using histogram analysis of FA and MD of WMH in subjects with cerebral amyloid angiopathy (CAA) with high WMH burden and healthy age-matched subjects, we have shown that the WMH MD peak was more closely associated with clinically relevant, cognitive impairment than the WMH volume [6]. Although the correlations between MD peak and cognitive functions were significant, more subtle diffusion changes distributed throughout the brain could also contribute to poorer cognitive function. To test this hypothesis, we tested associations between cognitive function and the MD peak from: a) whole brain, b) normal appearing brain parenchyma, and c) WMH histograms from 31 subjects (19 healthy controls and 12 CAA).

Methods: Subjects were recruited from the community and from the Stroke Prevention Program at our institution in accordance with the local ethics review board procedures. CAA subjects were diagnosed according to the validated Boston criteria. Cognitive assessment of subjects included executive function (Trails B minus Trails A), verbal memory (California Verbal Language Test), and visual memory (Rey-Osterrieth Complex figure), and visual perception and processing speed (Digit Symbol Substitution). FLAIR (TE/TR/TI=140 ms/9000 ms/2250 ms, FOV=24 cm, 256 × 256 matrix, slice thickness=3.5 mm) and DTI (TE/TR=75 ms/11000 ms, NEX=2, FOV=22 cm, 128 × 128 matrix, slice thickness=3.5 mm, with diffusion gradients applied in 11 non-collinear directions and b=850 s/mm^2) imaging were performed on a 3.0T scanner (Signa VH/*I*; GE Healthcare, Waukesha, WI). WMH volumes and masks were generated using Quantomo (Cybertrial Medical Software Inc, Calgary, Canada), a semi-automated seed-growing software [7]. FA and MD maps calculated using FSL [8], were co-registered with the FLAIR images using FSL FLIRT and multiplied by WMH masks (Figure 1). Histogram analysis of MD and FA of whole brain excluding cerebral spinal fluid, normal appearing brain parenchyma (NABP), and WMH was performed. WMH volume was logarithmically transformed to a normal distribution. Relationships between MD histogram parameters and normalized cognitive test scores were evaluated by Pearson correlation coefficient.

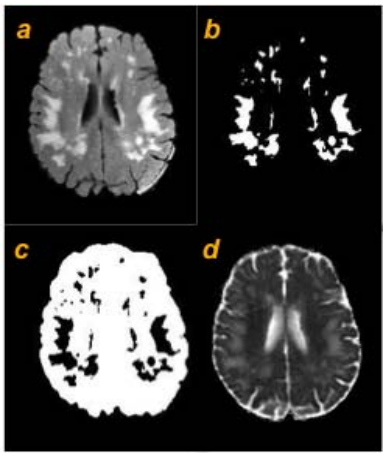

Fig 1. FLAIR image (a) used to identify white matter hyperintensities and create masks of WMH (b) and normal appearing brain parenchyma (c). These masks were applied to the mean diffusivity maps (d) and histograms with 90 bins between 0.2 – 2.0 × 10^{-3} mm^2/s were generated using ImageJ.

Results: Subject demographics are shown in Table 1. Significantly larger WMH volumes (median [interquartile range]) were observed in CAA (39.5 [13.3 – 49.6] mm^3) versus HC (4.8 [2.7 – 6.8] mm^3) p<0.001. MD peak and MD peak height from WB, NABT, and WMH histograms were significantly correlated with all cognitive tests as well as the WMH volume (Table 2). FA peak from WMH was significantly correlated to executive function (r=0.374; p=0.038). FA peak height from WMH was significantly correlated with visual memory (r=-0.374, p=0.038), and visual perception and processing speed (r=-0.357; p=0.049). FA peak height from NABT was also significantly correlated to visual perception and processing speed (r=-0.495, p<0.005).

Table 2. Summary of Pearson correlation coefficients and associated p-values in brackets. WMH volume was not significantly correlated with executive function and visual memory.

		Verbal Memory	Executive Function	Visual Memory	Visual Percept & Processing Speed
WMH	MD peak	-0.587 (0.0005)	-0.401 (0.0255)	-0.556 (0.0012)	-0.695 (<0.0001)
	MD peak height	0.398 (0.0266)	0.536 (0.0019)	0.467 (0.0081)	0.596 (0.0004)
NABT	MD peak	-0.483 (0.0059)	-0.535 (0.0019)	-0.583 (0.0006)	-0.779 (<0.0001)
	MD peak height	0.605 (0.0001)	0.466 (0.0082)	0.750 (<0.0001)	0.750 (<0.0001)
WB	MD peak	-0.532 (0.0021)	-0.407 (0.0229)	-0.502 (0.0040)	-0.712 (<0.0001)
	MD peak height	0.610 (0.0003)	0.457 (0.0098)	0.698 (<0.0001)	0.767 (<0.0001)
	Log (WMH volume)	-0.359 (0.047)	*-0.304 (0.097)*	*-0.251 (0.174)*	-0.550 (0.0013)

	CAA (n = 12)	HC (n = 19)
Age (y)	71.3 ± 8.0	68.5 ± 7.4
Males / Females	9 / 3	10 / 9
Current Smoker	1	1
Past Smoker	9	8
Hypertensive	10	3
Diabetic	2	0
Coronary disease	0	1
Dementia	2	0

Table 1. Summary of participant demographics and medical characteristics.

Discussion: Mean diffusion changes, represented by MD peak and MD peak height, were moderately or strongly correlated with cognitive performance in verbal memory, executive function, visual memory and visual perception and processing speed. By contrast, WMH volume was less strongly correlated with cognitive function and was not significantly associated with executive function or verbal memory in this sample. These data suggest that WMH volume, the most frequently analyzed metric of white matter disease in the literature, fails to account for much of the clinically relevant brain pathology. Diffusion changes in the rest of the brain are also strongly correlated with cognitive performance in all domains, despite the absence of visible lesions on T2-weighted imaging. These data were drawn from an ongoing longitudinal study; future work will seek to determine if MD peak predicts cognitive decline and WMH progression.

References:

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