Longitudinal analysis of white matter hyperintensity thresholds on cognition

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BACKGROUND

- White matter hyperintensities (WMH) refer to hyperintense patches on PD/T2-weighted MRI scans.
- They are strongly associated with increasing age and thus their cognitive impact must be elucidated. [2]
- WMHs are thought to be of vascular nature, and are a feature of small vessel disease. They are associated with neurological and cognitive symptoms. [5]
- A 10cc threshold has been established by some for cognitive changes to be observed, while others suggest a threshold of 0.5% TIC (approximately 6.1cc in this sample). These have been tested cross-sectionally, but never longitudinally. [3,4]

PURPOSE & HYPOTHESIS

Purpose: To longitudinally evaluate the established thresholds for cognitive decline. Study will elaborate on hypotheses that volumetric WMH changes in the brain must cross the 10cc or 0.5% threshold in order to manifest cognitive symptoms, rather than similar volumetric changes above or below these thresholds.

Hypothesis: Individuals who cross over the threshold will see a significantly greater cognitive decline than those who experience a similar net increase in hyperintensity volume, but remain below or above the respective thresholds.

METHODS

Lesion Explorer (LE) was applied to coregistered T1, PD and T2 images. Quantification of WMH volume was accomplished using T1/T2/PD segmentation.

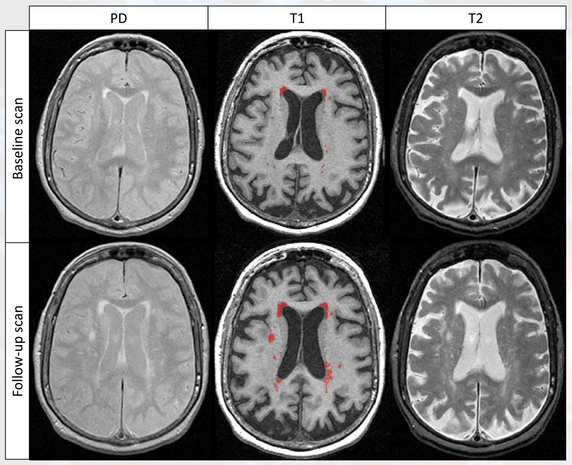

Figure 1. MRI scans showing longitudinal white matter progression. All images are from a single subject. LE WMH segmentation is shown in red on the T1-weighted images.

SUBJECTS

A total of 50 AD±SVD and NC subjects who showed a WMH increase greater than 2cc between scans were sampled from the Sunnybrook Dementia Study, excluding 101 subjects who did not show a large enough increase. There was no significant difference between AD and NC patients for all demographic and volumetric variables, except NCs were significantly more educated ($p<0.05$), and had a lower BPF ($p<0.05$).

ANALYSIS

- Statistical analysis was performed using the 'R' software package, version 3.2.0, including the packages 'gvlma' (version 1.0.02), 'car' (version 2.0-25), and 'visreg' (version 2.2-0).
- Multiple linear regression models and pearson correlation tests were used to evaluate baseline trends in the dataset.
- ANCOVAs and Kruskal-Wallis tests were performed to analyze the threshold effect.

RESULTS

Tests of previously established WMH trends:

1. Baseline WMH vs WMH/yr [1]: correlation of 0.66 ($p=1.90e-7$) and regression yielding BaselineWMH as the only significant predictor ($p=4.33e-6$)
2. Age vs WMH [2]: correlation of 0.44 ($p=0.0012$) and regression yielding Age as the only significant predictor ($p=0.0029$)
3. WMH volume and TIC% vs MMSE [2]: correlations of -0.34 ($p=0.021$) and -0.37 ($p=0.013$), respectively.

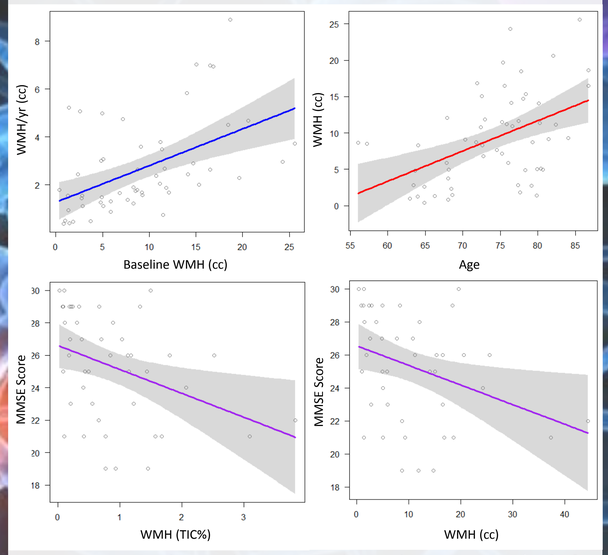

Figure 2. Scatterplots with regression lines showing WMH/yr [cc] by WMH [cc] (top left), WMH [cc] by Age (top right), and MMSE score by WMH [TIC%] (bottom left) and WMH [cc] (bottom right)

Table 1. Demographic, volumetric and neuropsychiatric data for 10cc WMH threshold groups

	under	thresh	over	p-value
Demographics				
n (NC)	19 (6)	11 (2)	20 (3)	N.S.
Age, y	70.6 (6.6)	73.0 (7.7)	77.4 (5.4)	**
Sex, n (%) male	7 (37)	6 (55)	12 (60)	N.S.
Education, y	14.8 (3.1)	12.3 (3.3)	13.2 (3.4)	N.S.
ISI, d	1226 (709)	779 (280)	632 (329)	***
Volumetrics				
BaseWMH	2.79 (1.76)	7.38 (1.68)	18.91 (8.60)	***
FollowWMH	6.29 (2.30)	11.78 (0.66)	25.60 (10.56)	***
BPF	0.76 (0.12)	0.75 (0.09)	0.76 (0.13)	N.S.
Neuropsych				
ΔMMSE	-2.00 (4.35)	-3.64 (5.97)	-1.55 (4.65)	N.S.
ΔDRS				
total	-5.67 (8.22)	5.13 (7.75)	-6.11 (9.61)	N.S.
attention	-0.50 (1.10)	-1.00 (1.69)	-0.68 (2.93)	N.S.
initiation	-2.33 (3.20)	-1.63 (5.04)	-4.11 (5.26)	N.S.
constructional	-0.33 (0.59)	0.00 (0.76)	-0.26 (1.33)	N.S.
conceptualization	0.11 (2.25)	-1.00 (1.60)	0.05 (2.88)	N.S.
memory	-2.56 (3.15)	-1.50 (3.07)	-0.95 (2.48)	N.S.
ΔSF	-3.12 (3.87)	-1.40 (2.55)	-2.21 (3.19)	N.S.
Δrey	-2.53 (3.76)	-0.69 (3.60)	-1.72 (4.87)	N.S.
Δbenton	-1.47 (2.48)	-0.50 (3.16)	-2.71 (6.75)	N.S.
ΔVR1	-3.38 (3.83)	-2.89 (5.53)	-2.11 (6.81)	N.S.
ΔVR2	-2.93 (6.10)	4.22 (7.24)	-1.17 (7.52)	*

*p<0.05, **p<0.01, ***p<0.001

Table 2. Demographic, volumetric and neuropsychiatric data for 0.5% TIC threshold groups

	low	mid	high	p-value
Demographics				
n (NC)	14 (6)	16 (2)	20 (3)	N.S.
Age, y	69.5 (6.2)	73.2 (7.4)	77.4 (5.4)	**
Sex, n (%) male	6 (43)	7 (44)	12 (60)	N.S.
Education, y	15.2 (3.2)	12.8 (3.2)	13.2 (3.4)	N.S.
ISI, d	1337 (783)	822 (292)	632 (329)	***
Volumetrics				
BaseWMH TIC%	0.15 (0.08)	0.56 (0.14)	1.58 (0.78)	***
FollowWMH TIC%	0.45 (0.17)	0.89 (0.14)	2.14 (0.97)	***
BPF	0.74 (0.12)	0.78 (0.09)	0.76 (0.13)	N.S.
Neuropsych				
ΔMMSE[a]	-1.36 (4.07)	-3.69 (5.53)	-1.55 (4.65)	N.S.
ΔDRS				
total	-6.07 (8.3)	-4.83 (7.85)	-6.11 (9.61)	N.S.
attention	-0.57 (1.22)	-0.75 (1.42)	-0.68 (2.93)	N.S.
initiation	-1.79 (2.36)	-2.50 (5.04)	-4.11 (5.26)	N.S.
constructional	-0.36 (0.63)	-0.08 (0.67)	-0.26 (1.33)	N.S.
conceptualization	-0.07 (2.37)	-0.42 (1.83)	0.05 (2.88)	N.S.
memory	-2.57 (3.59)	-1.83 (2.52)	-0.95 (2.48)	N.S.
ΔSF	-3.08 (4.25)	-1.93 (2.64)	-2.21 (3.19)	N.S.
Δrey	-1.27 (2.22)	-2.67 (4.91)	-1.72 (4.87)	N.S.
Δbenton[a]	-1.31 (2.43)	-1.00 (3.05)	-2.71 (6.75)	**
ΔVR1	-2.58 (3.34)	-3.77 (5.28)	-2.11 (6.81)	N.S.
ΔVR2	-3.83 (6.53)	3.33 (6.40)	-1.17 (7.52)	*

[a] Ancova model did not pass the assumptions of the linear model

*p<0.05, **p<0.01, ***p<0.001

Note: Of the 39 AD patients, DRS was available in 34, SF in 35, rey in 32, benton in 31, VR1 in 32 and VR2 in 31. All NCs had complete neuropsychiatric data. Values reported are mean (SD) unless otherwise specified.

DISCUSSION & CONCLUSION

No significant threshold effect was apparent throughout the analysis

- The 10cc total WMH threshold showed no significant differences between groups for cognitive decline in all tests used, except for the VR2.
- Investigation of the alternative 0.5% TIC threshold showed no significant result as well. There was no significant difference between groups for cognitive decline in all tests used, except for the benton and VR2 tests.
- The tests chosen covered a range of cognitive domains, including general function, language, visuospatial and memory function.

Furthermore, two additional threshold tests were conducted as well. In a similar manner as the previous two analyses, pvWMH and %WMH were investigated. For both, there were no significant differences between groups for cognitive decline.

This is the first study to test these thresholds longitudinally rather than cross-sectionally.

Conclusion: While it has been established cross-sectionally, longitudinally our sample did not show a significant threshold for cognitive decline with respect to WMH volume.

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