Cognitive Impairment and Magnetic Resonance Changes in Multiple Sclerosis

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Background

- MS inflammatory lesions interrupt white matter tracts, resulting in impaired cognition
- Studies have identified associations between cognitive performance, cortical lesions and regional gray matter atrophy
- Longitudinal studies comparing MRI abnormalities and cognitive decline have relied upon brain MRIs acquired every 6-12 months

Hypotheses

Cognition will be more impaired in the presence of acute contrast-enhancing lesions compared to no active lesions

Cortical atrophy over 2 years will be associated with impaired cognition.

Materials & Methods

- 75 subjects with RRMS
- MRIs were performed monthly for at least the first year of this 2-year study
- Comprehensive neurocognitive battery was administered at 0, 6, 12, and 24 months

Cognitive Sets and Represented Domains

Set	Domain	Subtest
(A) Information Processing/Memory	Visual Learning	Ruff Figural Fluency Test error ratio
	Auditory Processing	PASAT
	Verbal Learning	California Verbal Learning Test trials 1-5 total
	Processing Speed	WAIS-III Digit Symbol
(**B**) Visual-Spatial/ Executive Function	Visual-spatial	WMS-III Spatial Span
	Problem Solving	Wisconsin Card Sorting Perservative Responses
	Visual Scanning	WAIS-III Symbol Search
	Planning/Sequencing	Tower of London % Planning Time (Problem solving time)
	Visual Interference	Stroop Color-Word Test
(**C**) Verbal Memory/ Attention	Verbal Abilities	WAIS-III Information Scale
	Attention Span	WAIS-III Digit Span

Criteria for Cognitive Impairment

None
- Impairment on 0-1 Individual Tests

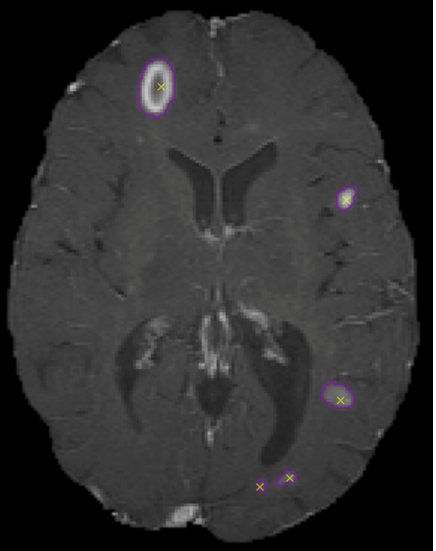
Mild
- Impairment on 2-3 Individual Tests
  Significant Impairment 1/3 Sets

Moderate
- Impairment on 4-5 Individual Tests
  Significant Impairment 2/3 Sets

Severe
- Impairment on ≥6 Individual Tests
  Significant impairment 3/3 Sets

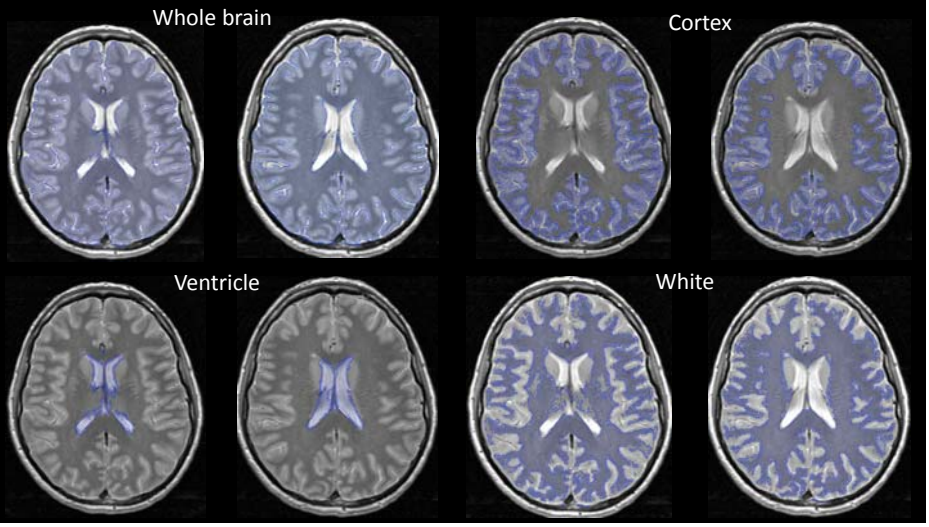
- Impaired = 1 SD
- Significant Impairment = 2 SD

- T1- weighted fat-saturated sequences acquired with Gadolinium were reviewed using Amira ® imaging software.
- Maximal lesion volume (mm^3) of the CEL was measured using volume rendering, indicated by the purple circle



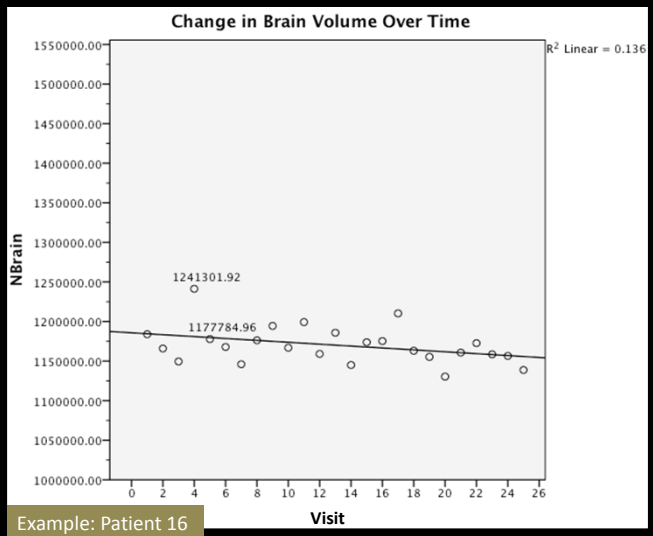
SIENAX

- FSL program that segments various brain regions
- All brain volumes were normalized to the skull



Normalized Brain Volume Variability Over 2 years

- % change in volume over 2 years was determined
- Categories included:
  - Whole brain
  - White matter
  - Peripheral Grey (Cortex)
  - Ventricle



Example: Patient 16

Active Gadolinium-enhancing Lesion vs. Cognitive Impairment

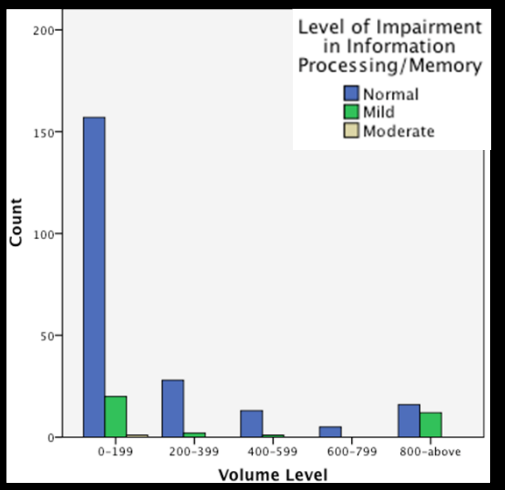
- MRI scans at the time of cognitive testing were evaluated by volume of Gadolinium enhancement
- Cognitive tests were performed at 0, 6, 12, and 24 months
- MRI Gadolinium enhancement was categorized by total volume (mm^3):

  (1) 1.0 to 199 (**2**) 200 to 399 **(3)** 400 to 599

  (**4)** 600 to 799 **(5**) 800 and above

Cognitive Performance vs. Gd Volume

- Patients with Gd enhancement at the time of cognitive testing were more likely to be impaired on information processing/memory ($p<0.01$)
  - Seen with Gd >800 mm^3
  - Effect was mild impairment
  - Driven by PASAT
- No drop in performance based upon total Gd lesion volume was observed for:
  - Visual-spatial/executive
  - Verbal memory/attention



Cognitive Sets and Represented Domains[3]

Set	Domain	Subtest
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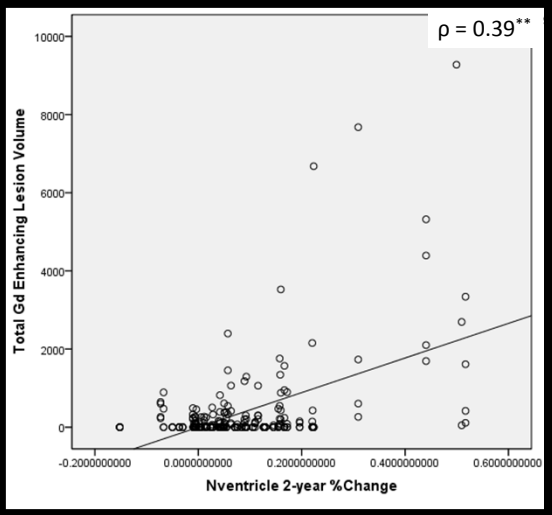
Ventricular Enlargement and White Matter Loss vs. Gadolinium-enhancing lesion volume

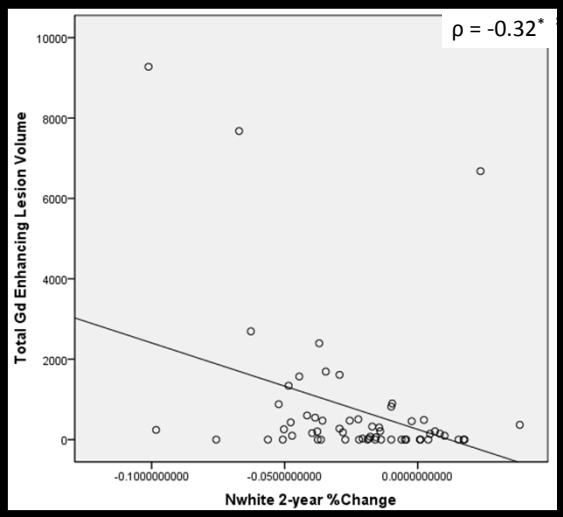
Gadolinium Enhancing Lesion Volume vs. Normalized Ventricle Volume

- Gd lesion volume at baseline was predictive of 2-year % increase in ventricular volume ($p < 0.01$)



Gadolinium Enhancing Lesion Volume vs. Normalized White Matter

- Gd lesion volume at baseline was predictive of 2-year % change in white matter volume ($p < 0.05$)



Gd volume at baseline vs. 2-year% change in whole brain and peripheral grey (cortex)

- No significant relationship was found between Gd volume at baseline vs. 2-year % change whole brain
- No significant relationship was found between Gd volume at baseline vs. 2-year % change peripheral grey (cortex)

Ventricular and White Matter Volume % Change vs. Cognitive Impairment

- Increases in ventricular volume over 2 years was correlated with deficits in:
  (1) Information processing and memory at 24 months**
  (2) Overall cognitive impairment at 24 months*
- Decreases in white matter volume over 2 years was correlated with deficits in:
  (1) Overall cognitive impairment at 24 months*

*$p < 0.05$, **$p < 0.01$

Conclusions

- Processing speed may be mildly impacted when active lesion volume is high in this early MS cohort
- Gd lesion volume at baseline predicted ventricular and white matter atrophy over 2 years
- Two year cognitive impairment was related to ventricular and white matter atrophy over 2 years
- Of the cognitive sets, information processing speed seemed most associated with some MRI changes
- In this dataset, cortical volumes did not appear to be predictive of cognition over 2 years

Future Directions

- The majority of this early MS cohort showed mild to no impairment during cognitive testing over 2 years
- Thus, a 10-year follow-up assessment could demonstrate additional correlations between volume change and cognitive performance as a result of disease progression

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Table 1 Baseline characteristics of the 75 patients randomized in the BECOME study

	IFNβ 1b (n = 36)	GA (n = 39)	p Value
Age, y, mean (range)	36 (18-49)	36 (22-55)	0.96*
Women, n (%)	27 (75)	25 (64)	0.33†
Ethnicity, n (%)			
White	15 (42)	24 (62)	0.12†
Black	10 (28)	11 (28)	
Hispanic	10 (28)	4 (10)	
Indian–Asian	1 (3)	0	
Subtype of MS, n (%)			
Relapsing-remitting	31 (86)	30 (77)	
Clinically isolated syndrome	5 (14)	9 (23)	0.38†
Time since onset of MS			
Median years (range)	0.9 (0.1-24)	1.2 (0.2-34)	0.35‡
Annualized relapse rate, median (range)	1.8 (0-7.5)	1.9 (0.13-7.0)	0.53‡
EDSS, median (range)	2.0 (0-5)	2.0 (0-5.5)	0.98‡
Enhancement on MRIs predrug, n (%)	26 (72)	27 (69)	0.81†
CAL at entry, mean (median)	4.7 (1.75)	3.1 (1)	0.31‡
MSFC, median (range)	0.13 (−1.5 to 1.0)	0.13 (−2.7 to 1.16)	0.82