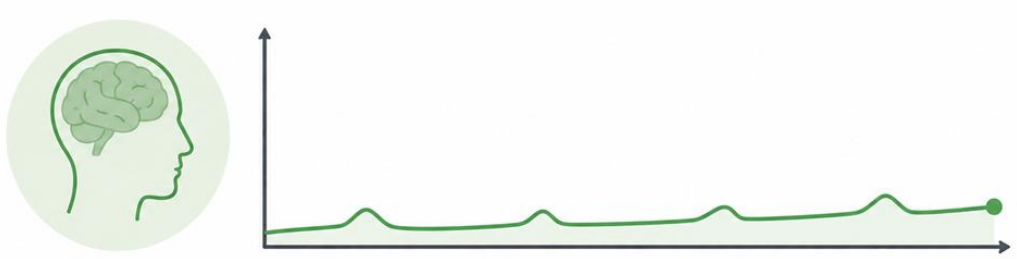
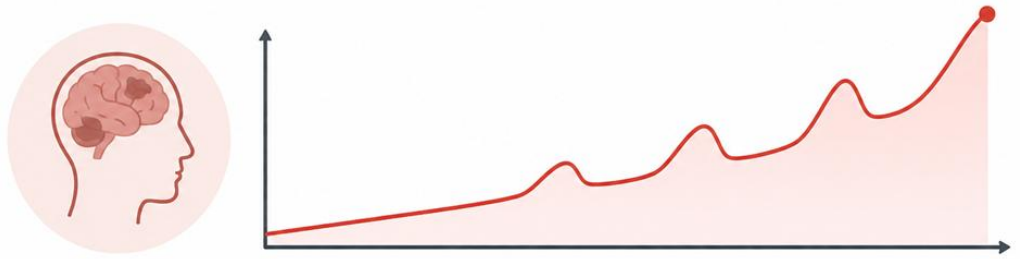
Amsterdam UMC

MS Center Amsterdam

Cognitive decline as a window into progressive disease in multiple sclerosis

Tom A.N. Fuchs, MD PhD

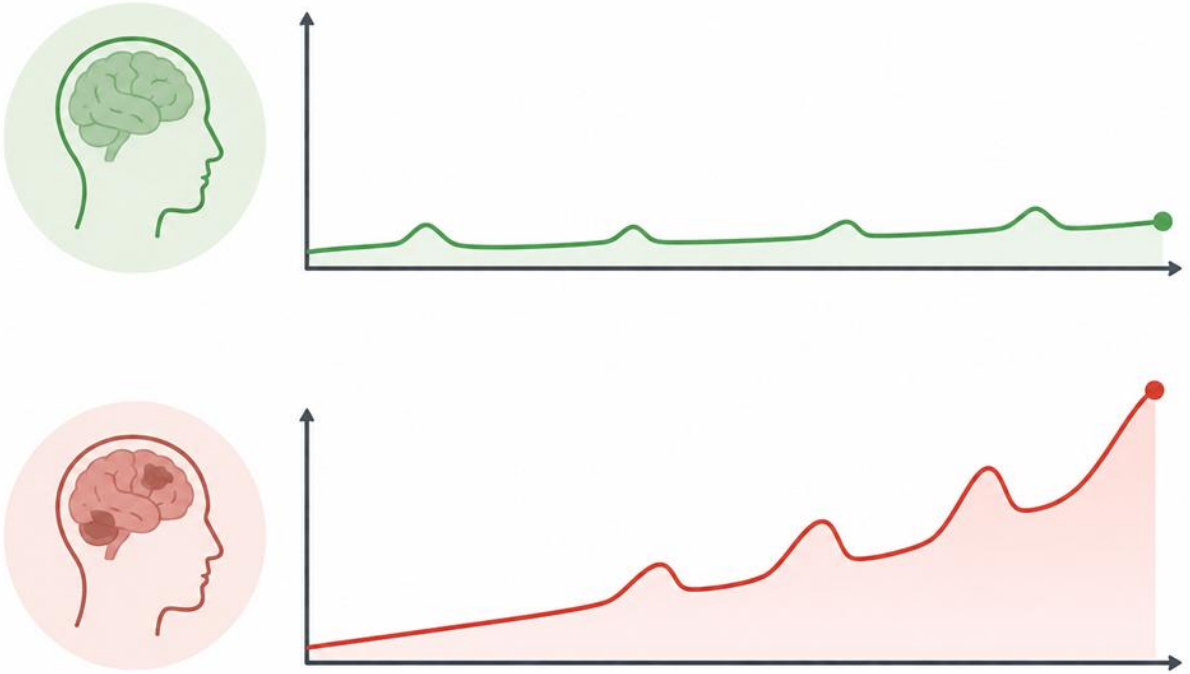




Funding & disclosures

TAN Fuchs received research support from the European Committee for Treatment and Research in Multiple Sclerosis, serves on the editorial board of Frontiers in Neurology, and received consulting fees for Click Therapeutics.

Hypothesis: Cognitive decline is a window into progressive disease



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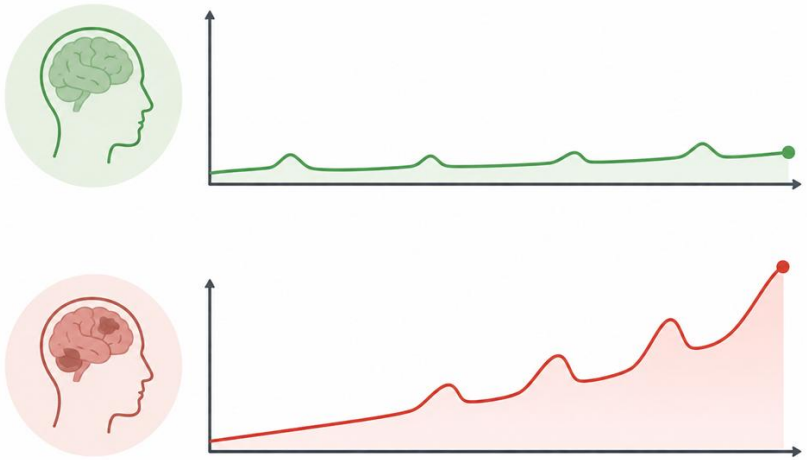

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2. How does cognitive decline occur?
3. What biologically co-occurs with cognitive decline?
4. What happens to people with cognitive decline?

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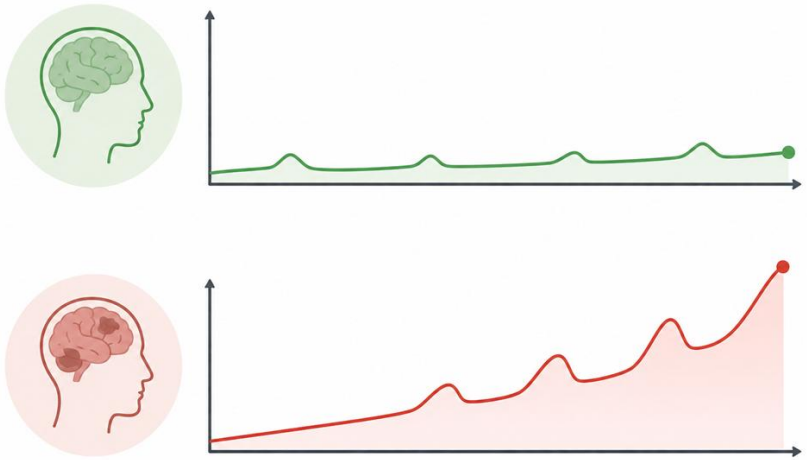

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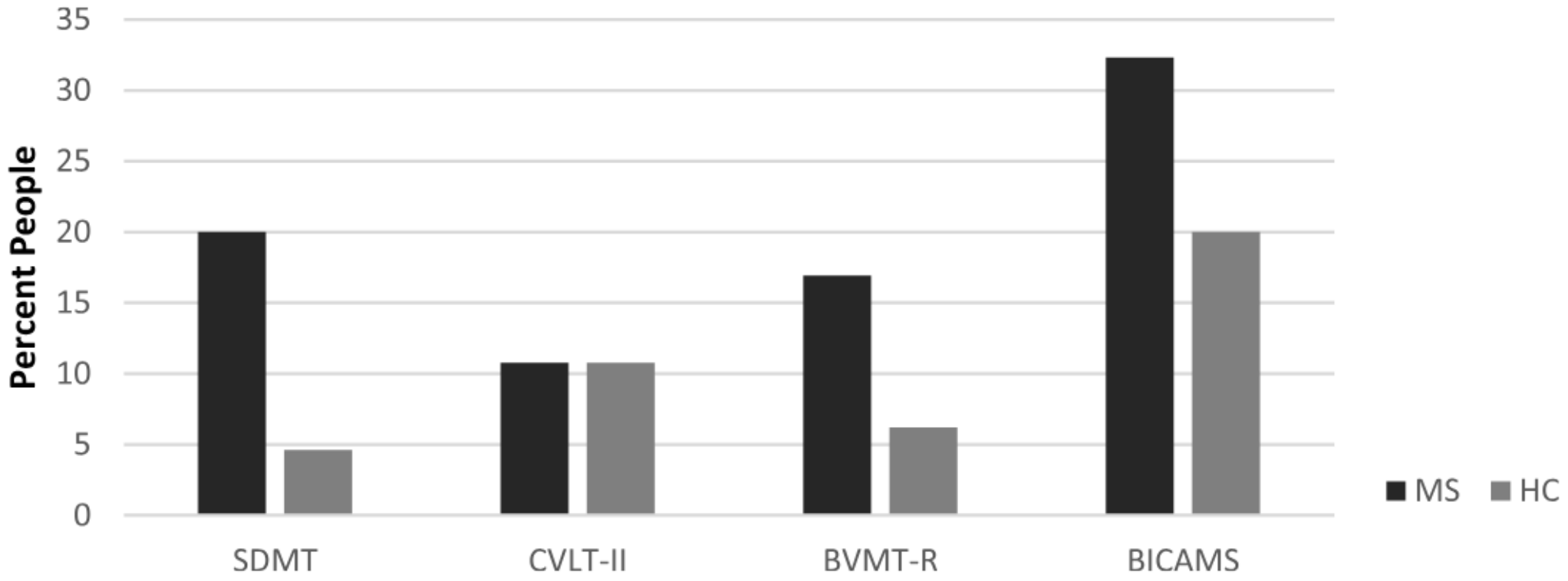

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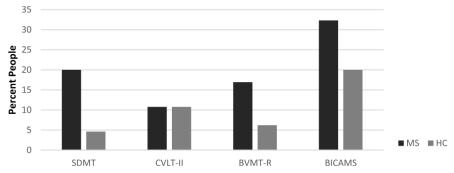

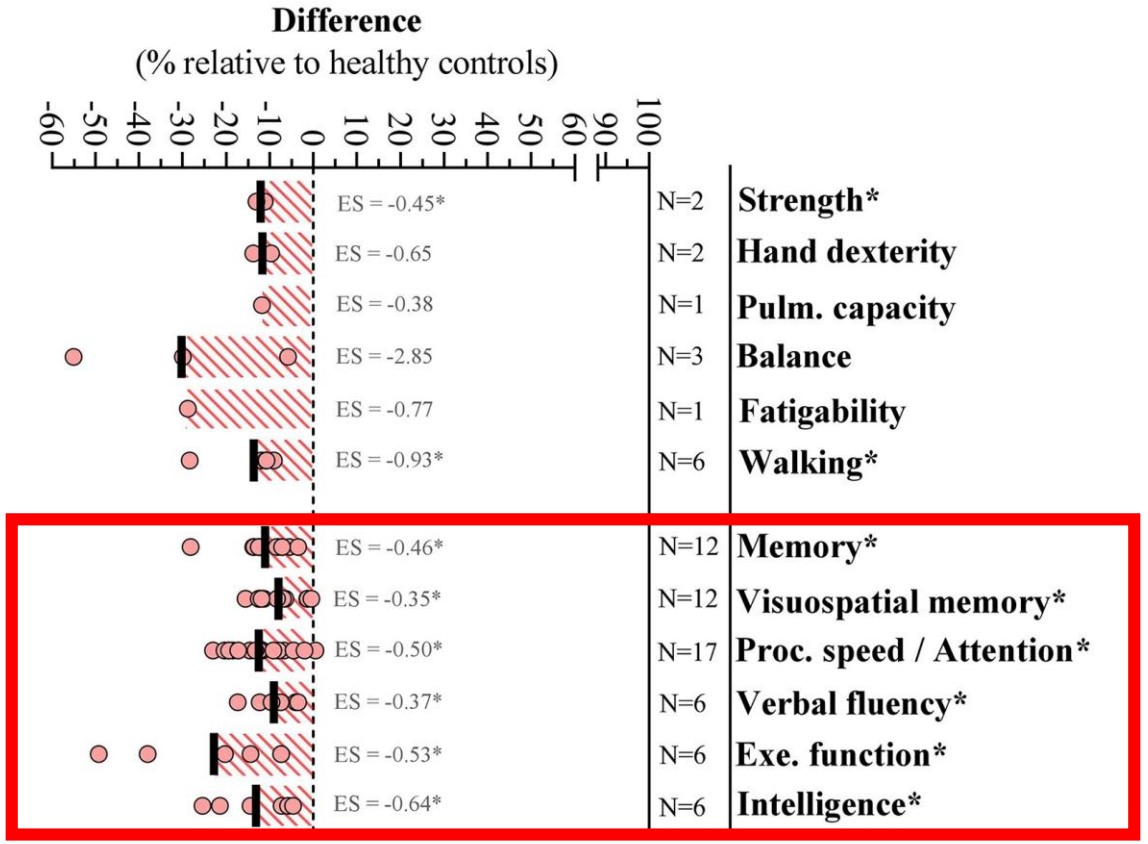

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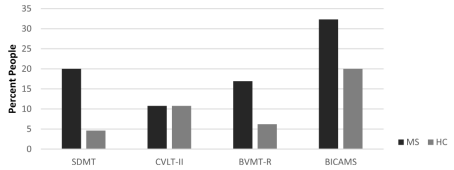

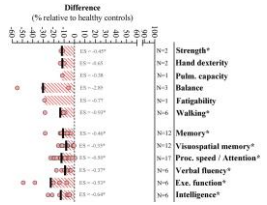

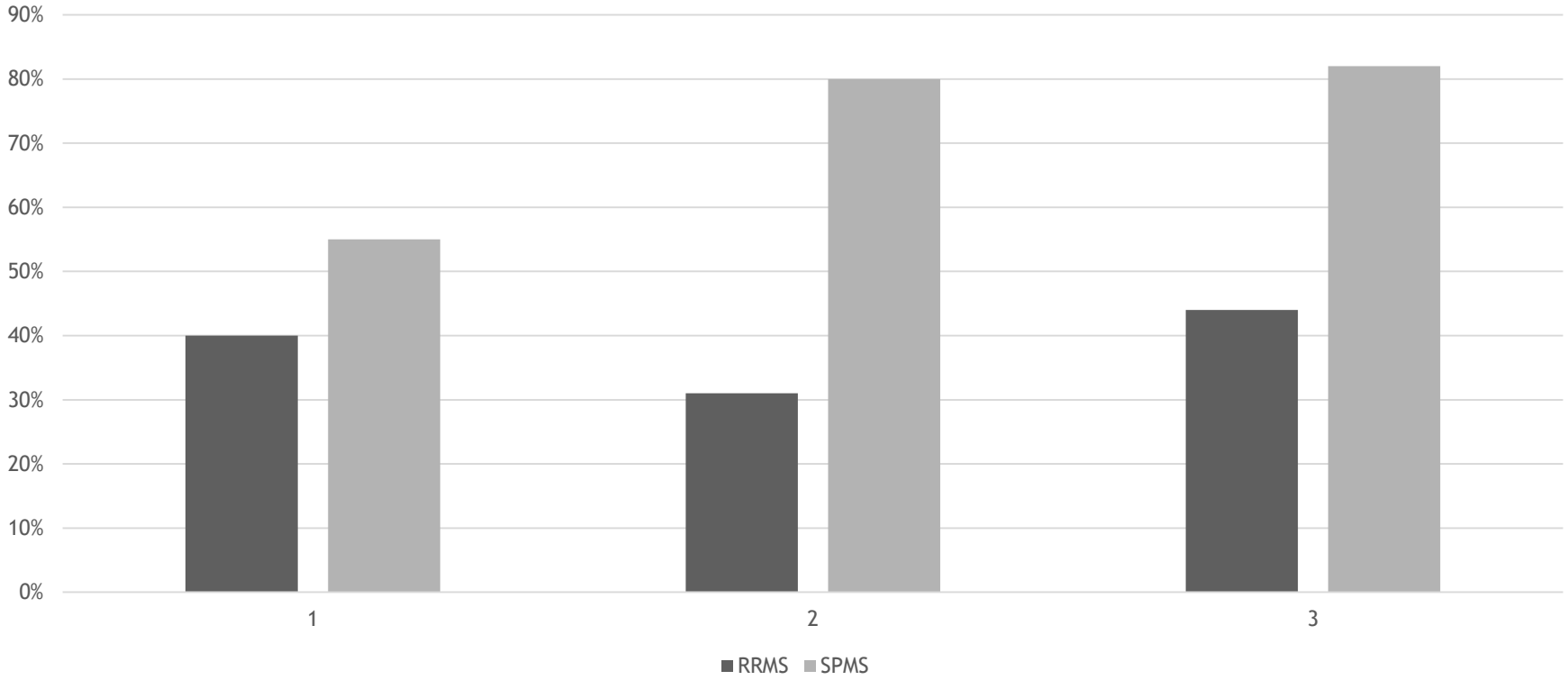

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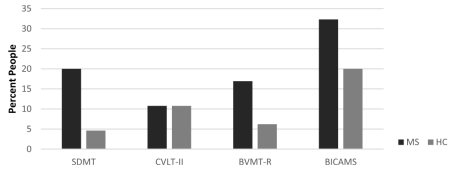
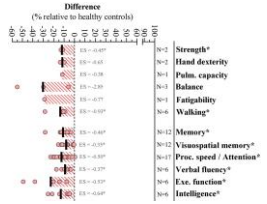
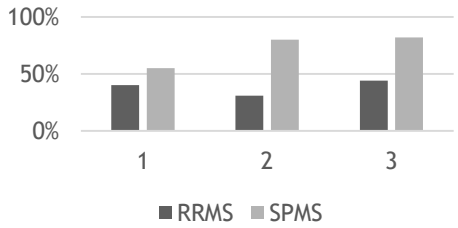
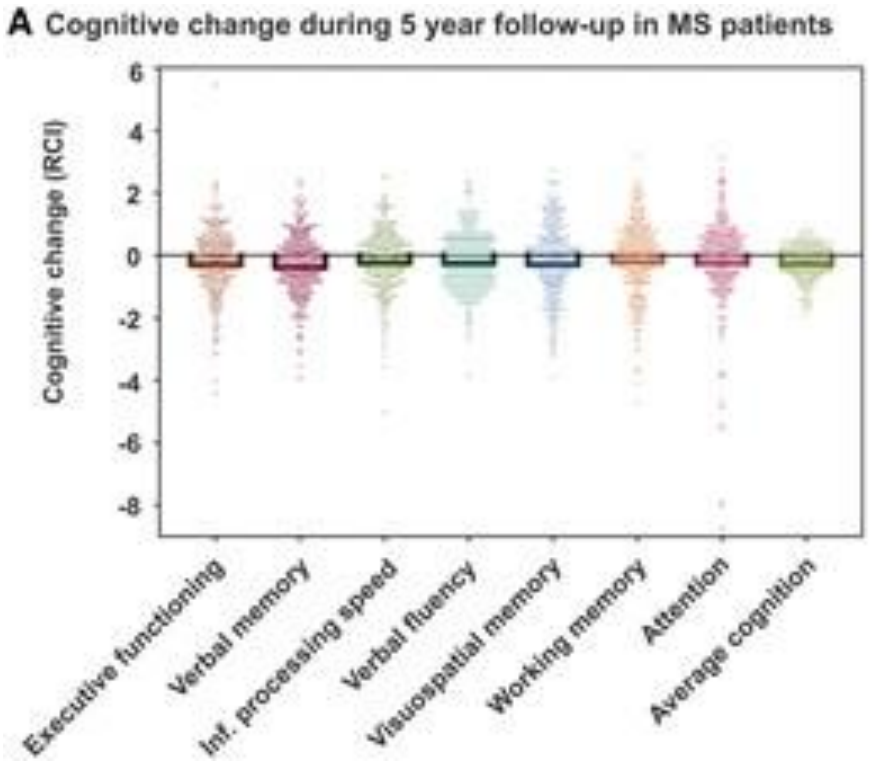
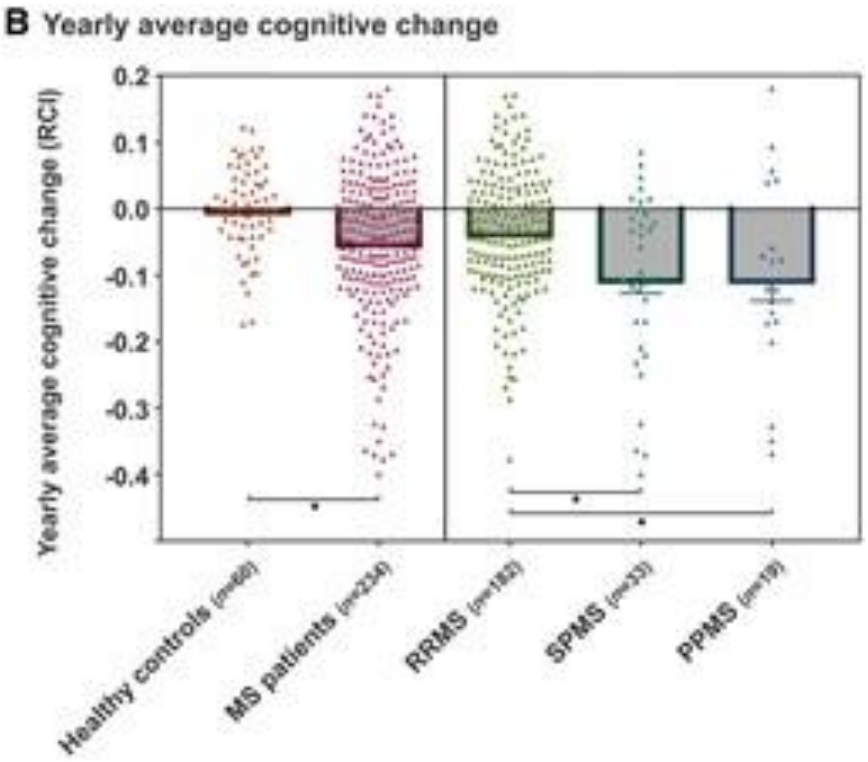


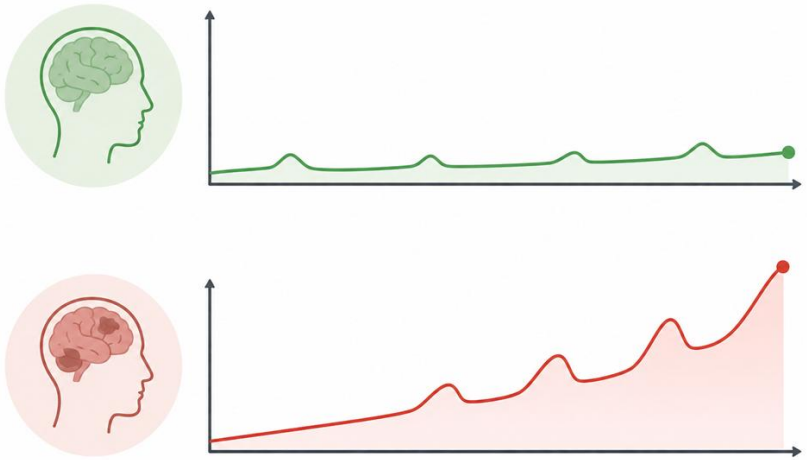








Hypothesis: Cognitive decline is a window into progressive disease



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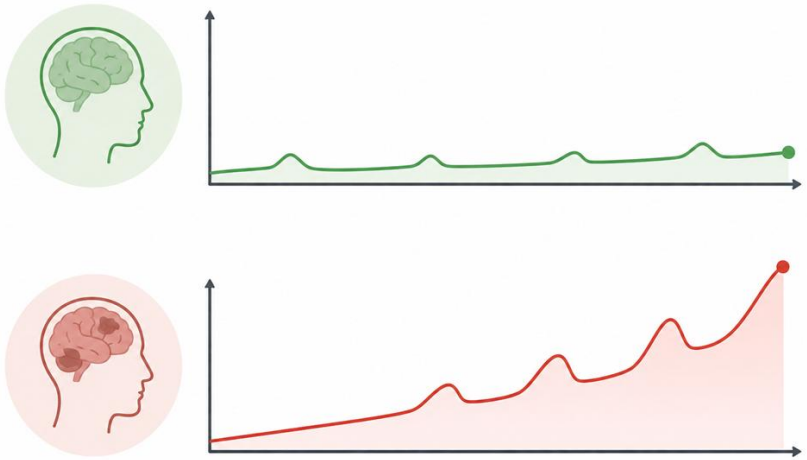

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People with progressive clinical phenotypes and some even at early RRMS stages.

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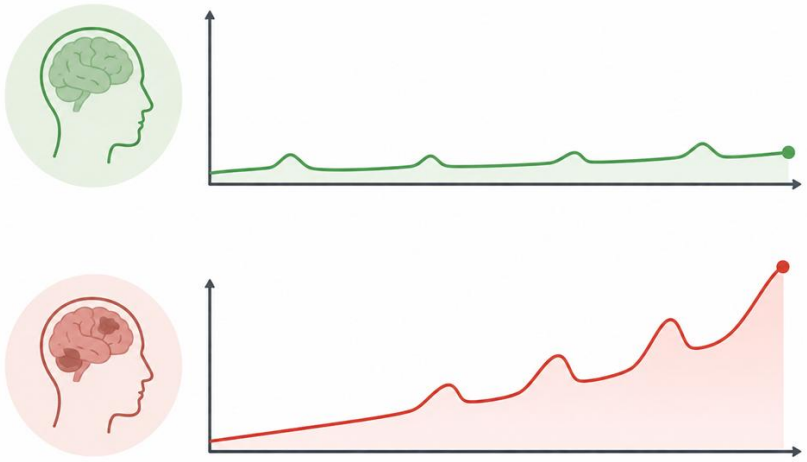

1. Who has cognitive impairment?
2. **How does cognitive decline occur?**
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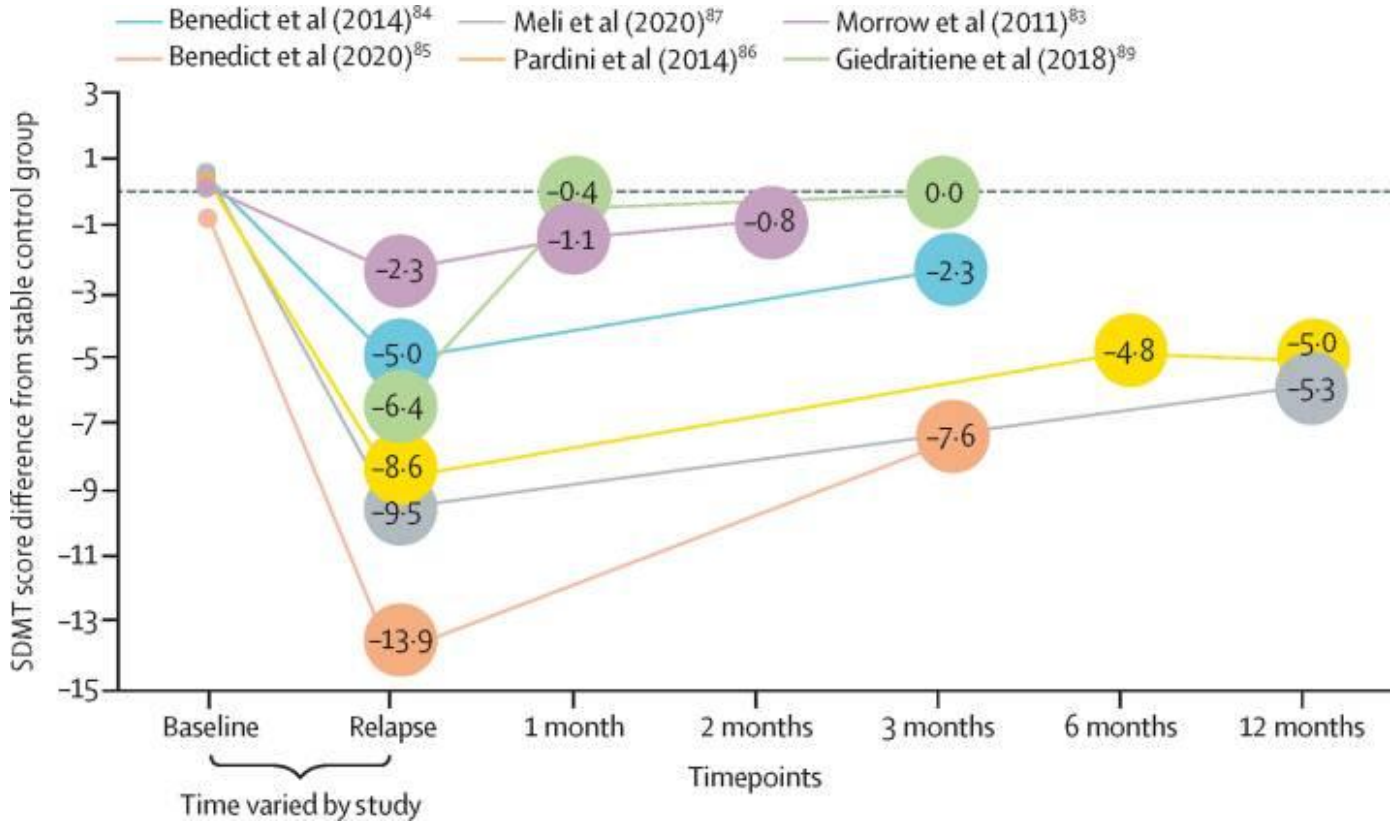
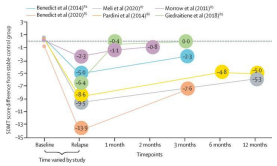
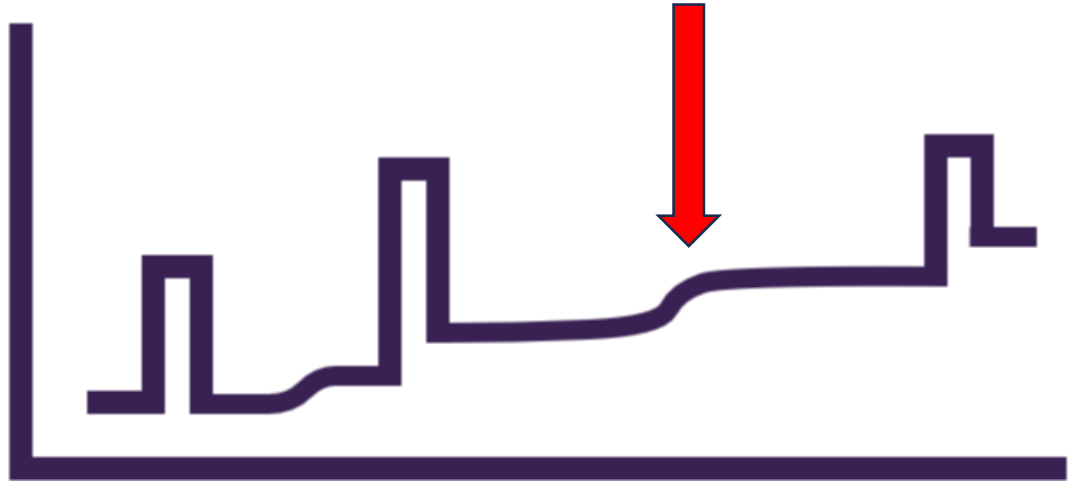
Cognition during relapse



Cognitive PIRA





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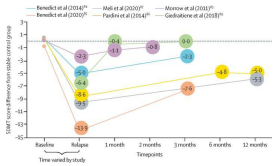
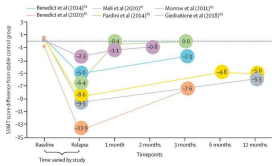
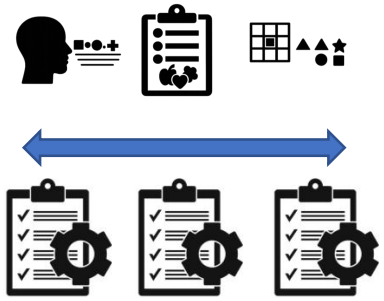


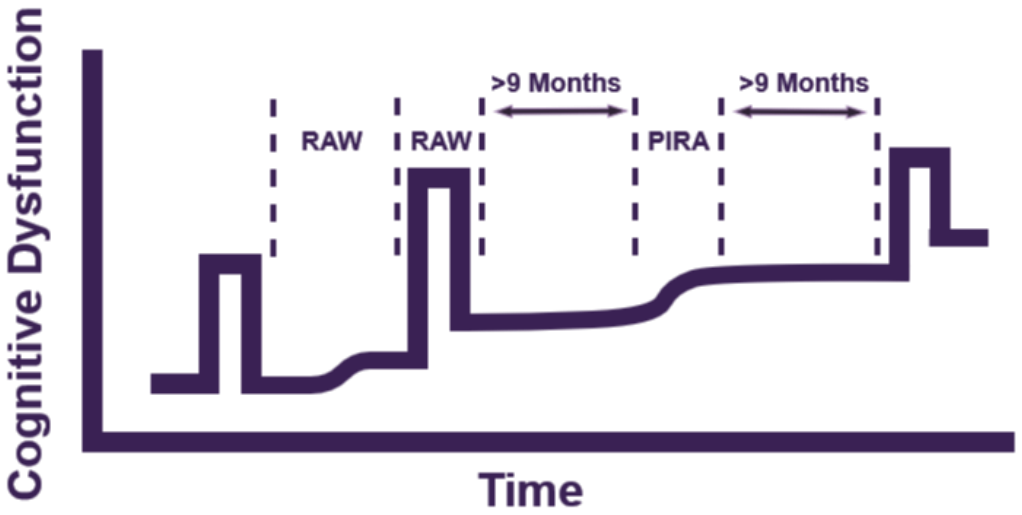
~3 years

Cognitive PIRA





1. $SEM_1 = SD_1\sqrt{1 - r_{1,2}}$
2. $SEM_2 = SD_2\sqrt{1 - r_{1,2}}$
3. $SE_{1,2} = \sqrt{{SEM_1}^2 + {SEM_2}^2}$
4. $RC_{90\%} = 1.64 * SE_{1,2}$



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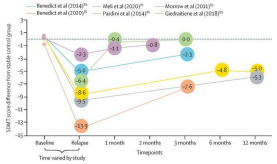

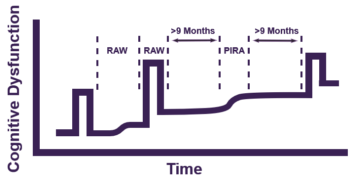

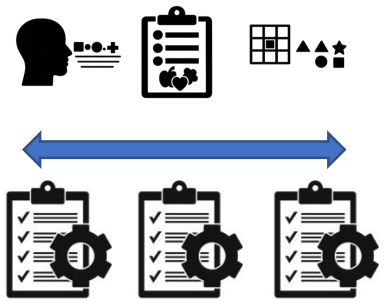

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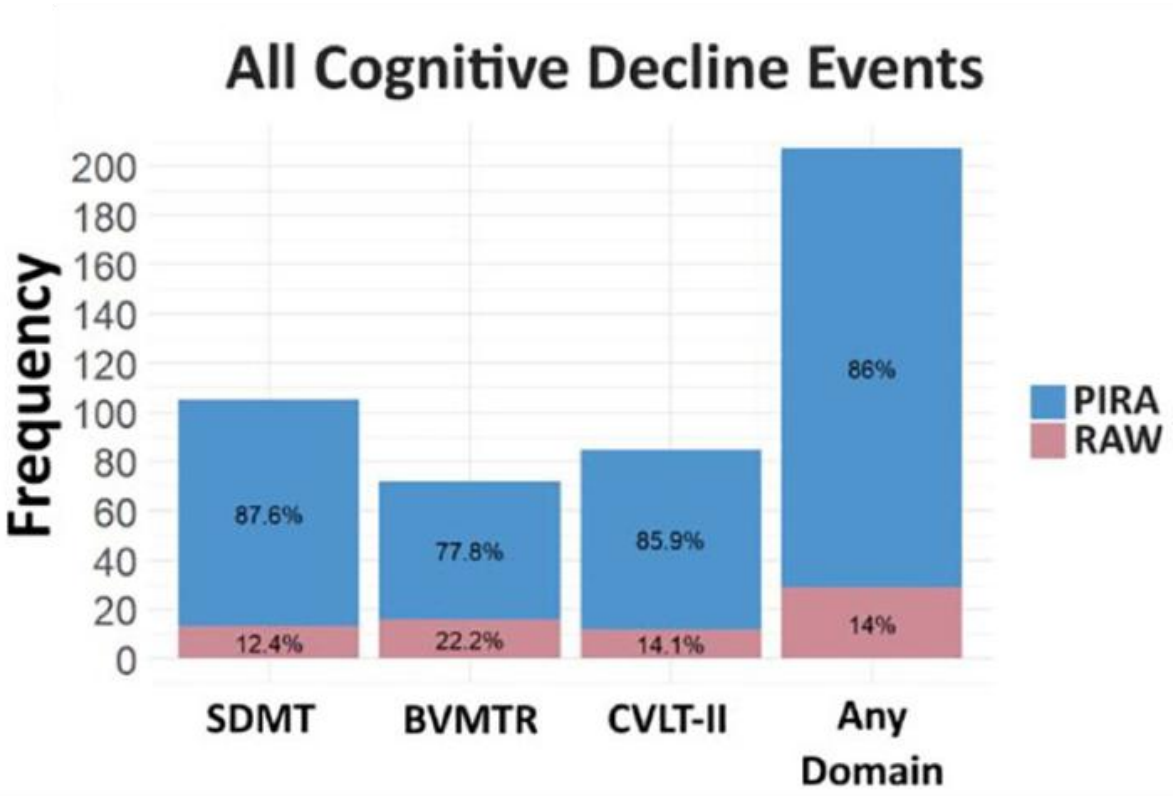

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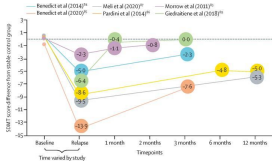

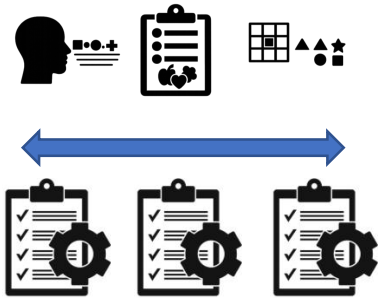

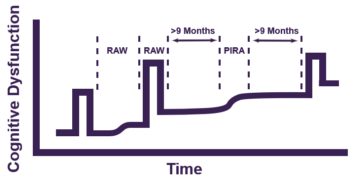

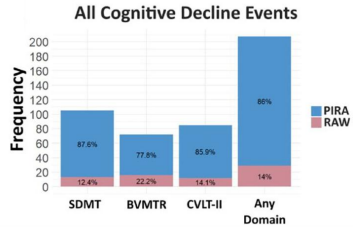

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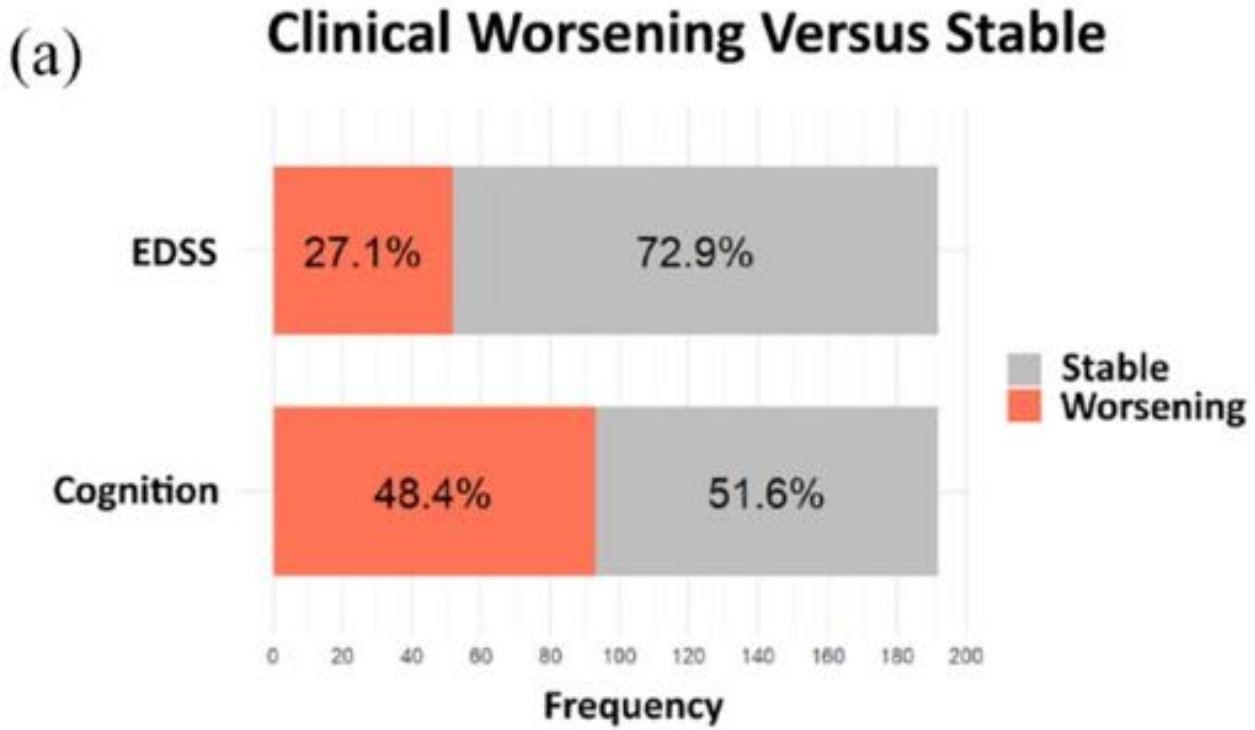

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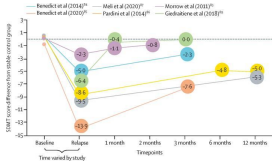

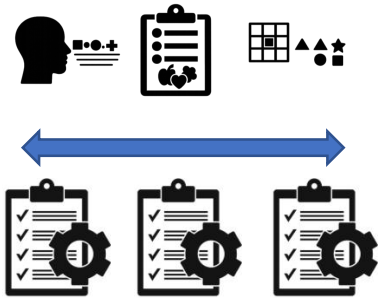

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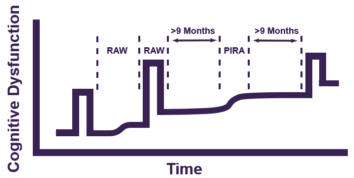
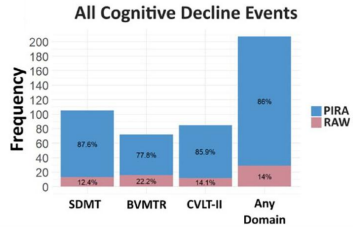
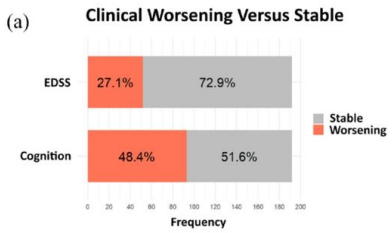
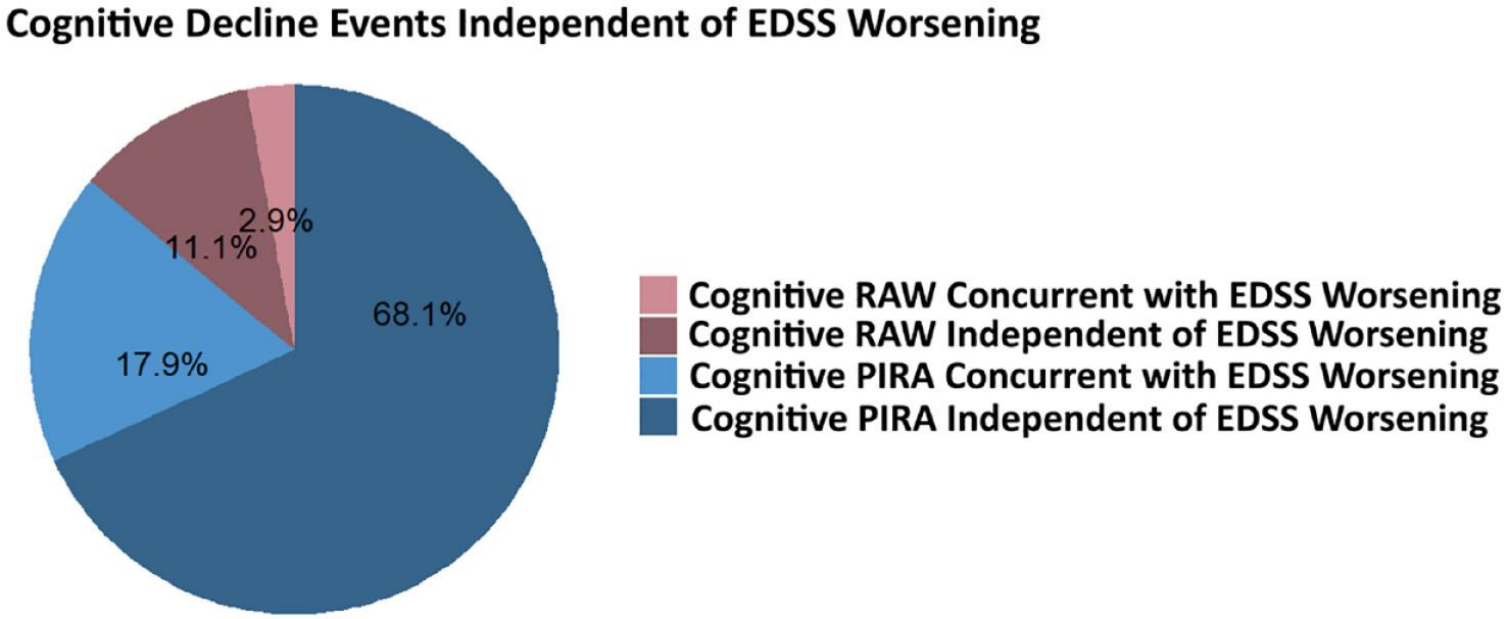
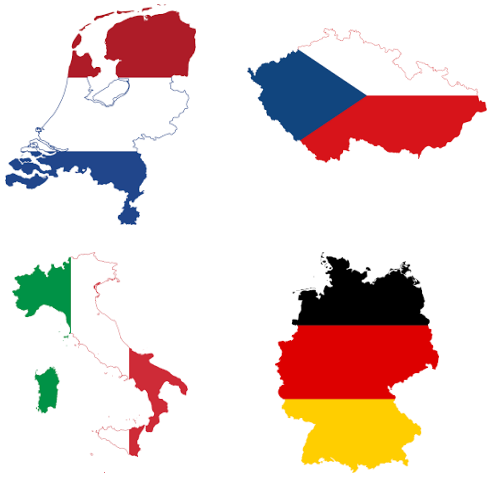


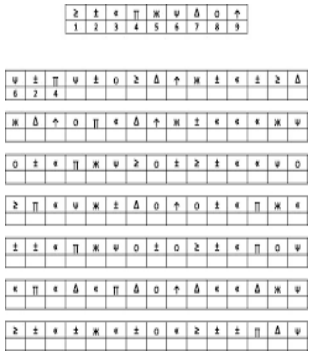






Cognitive PIRA across sites





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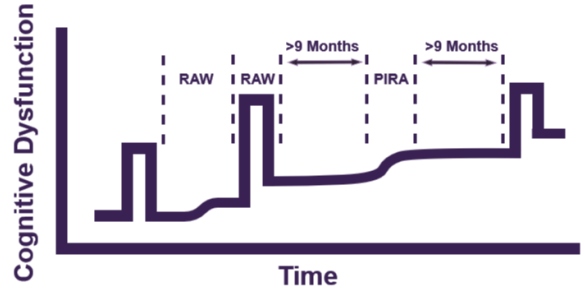

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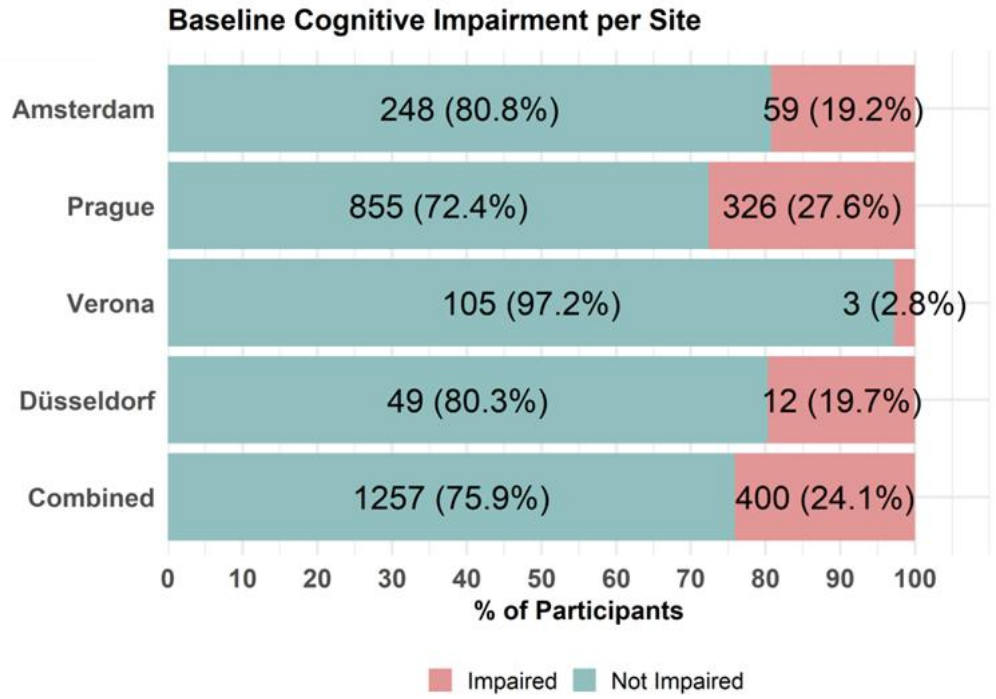

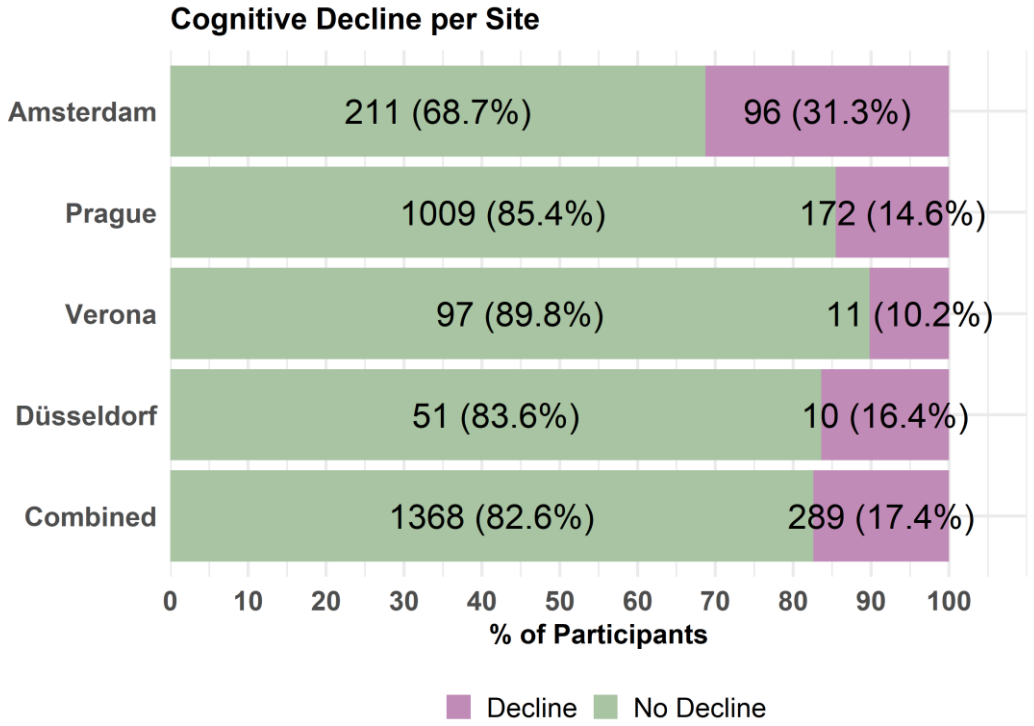

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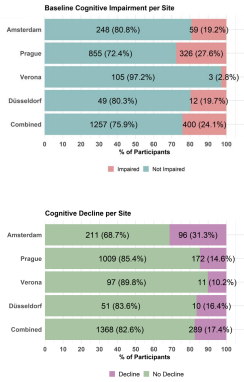

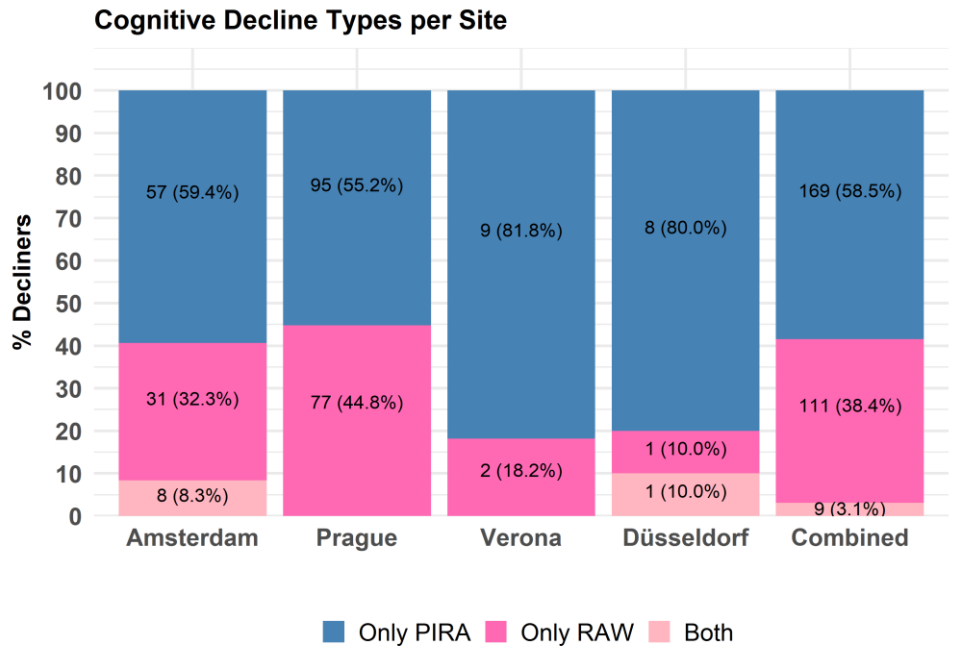

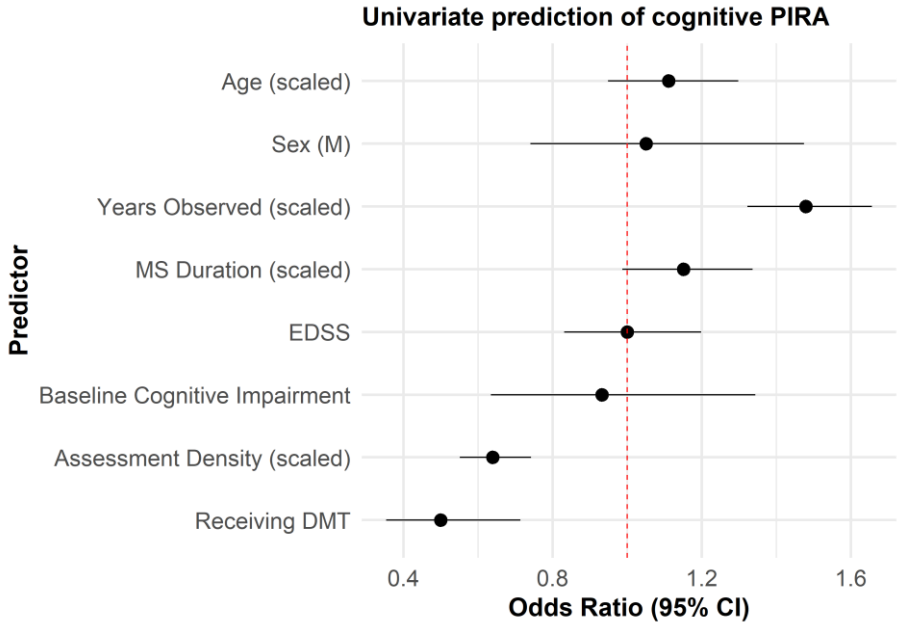

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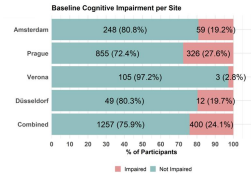
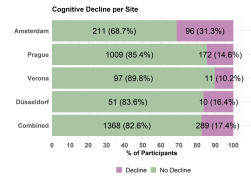
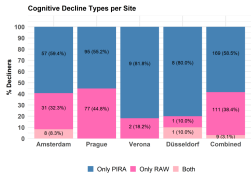
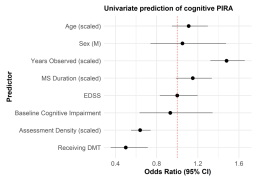
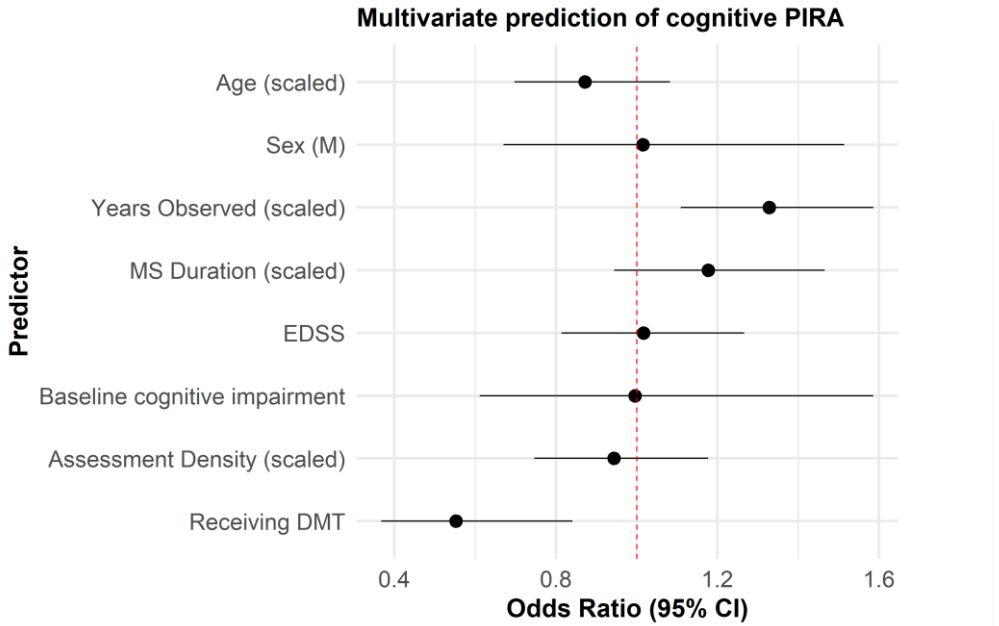
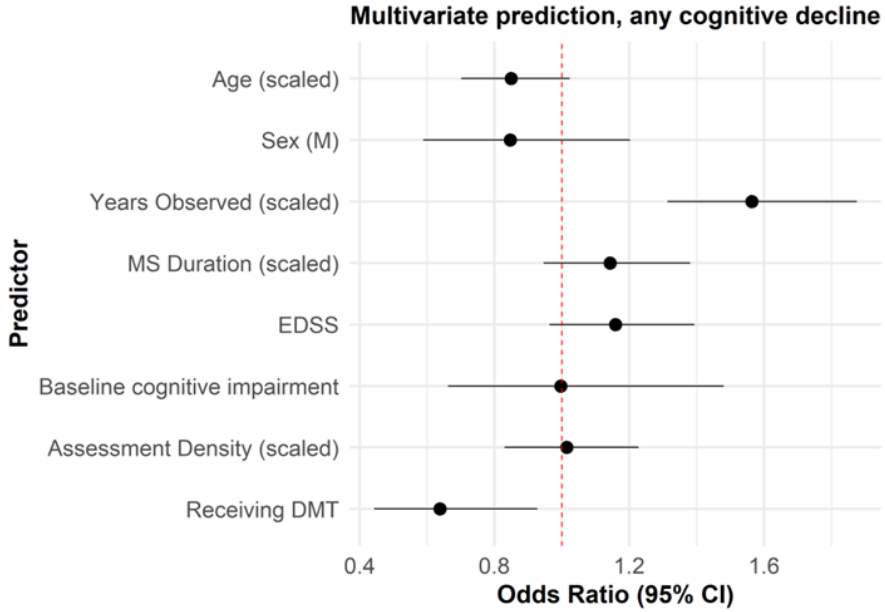




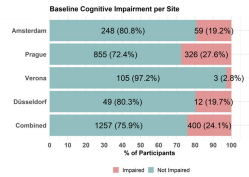


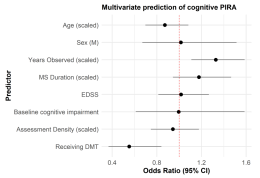


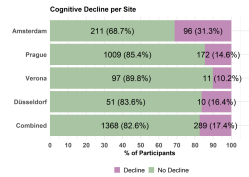


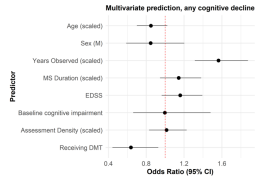


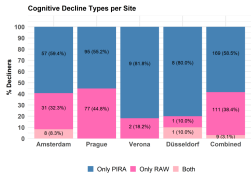
Cognitive PIRA across sites

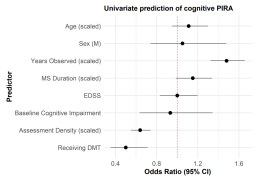


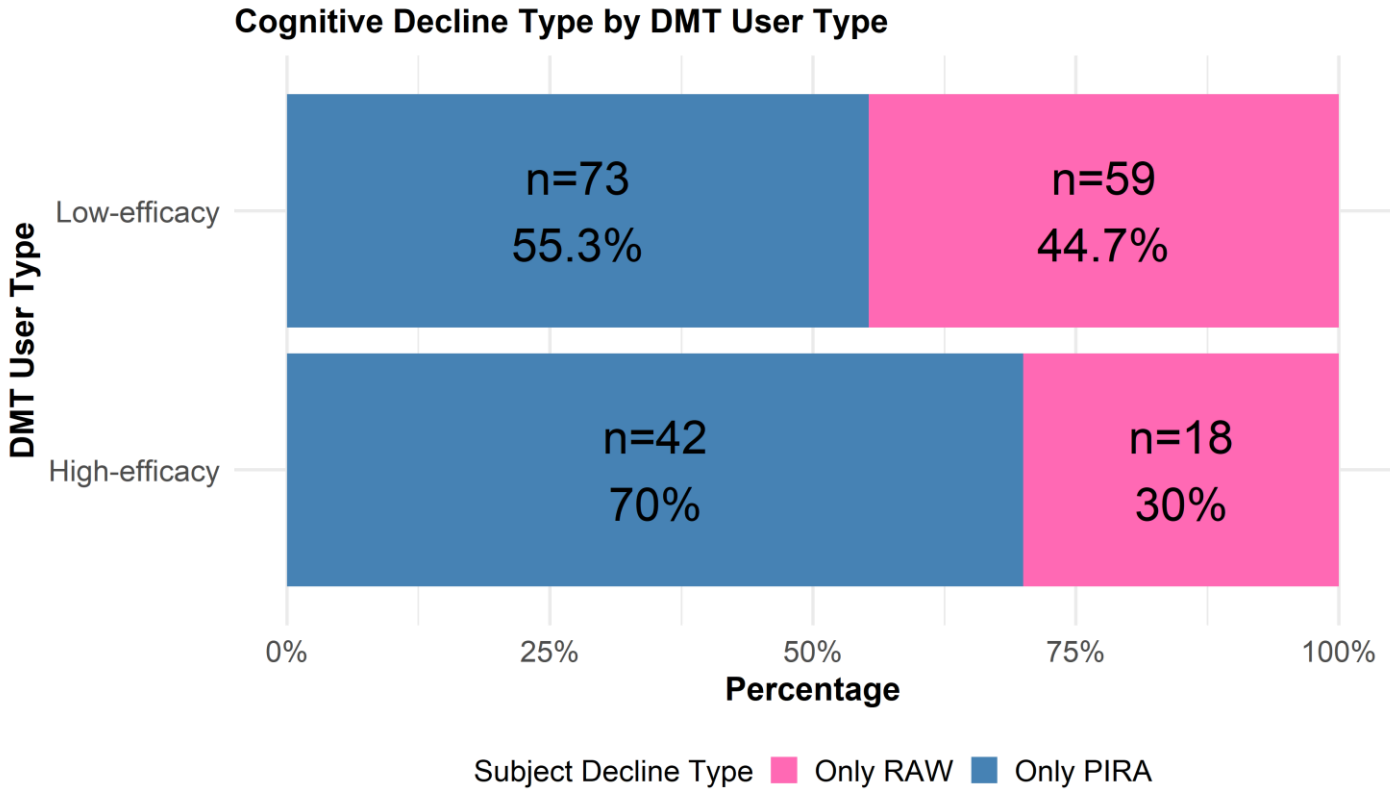




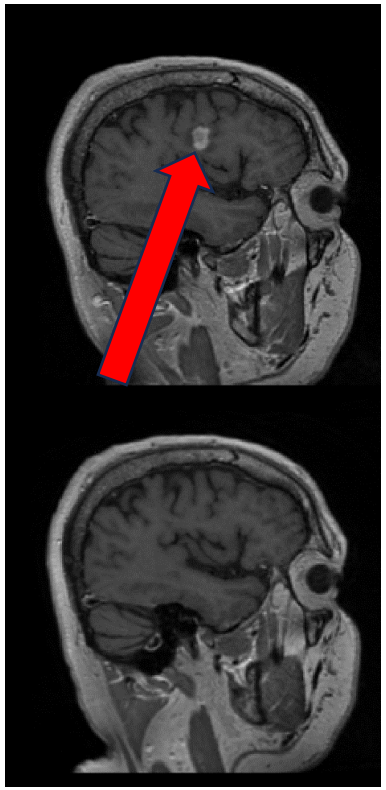


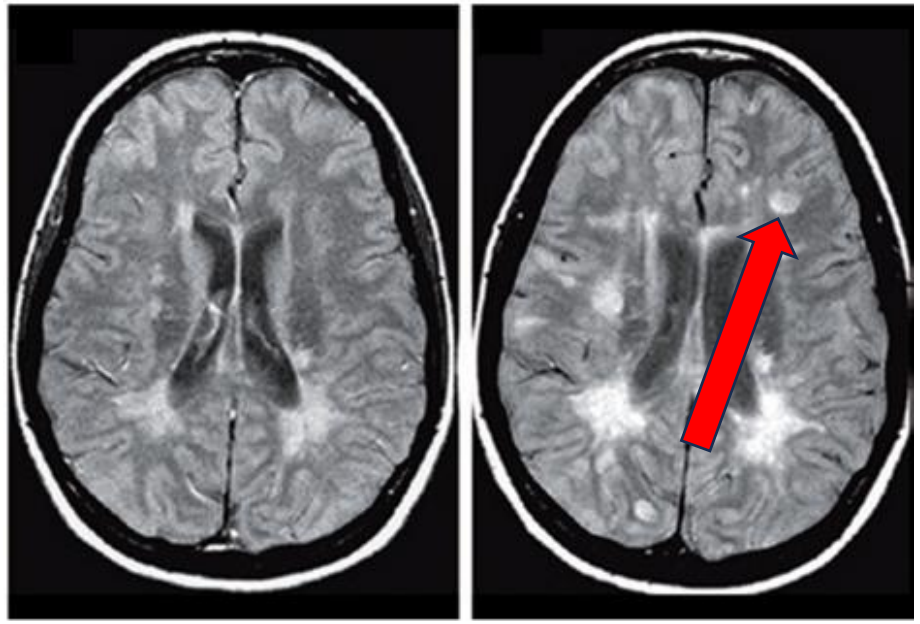


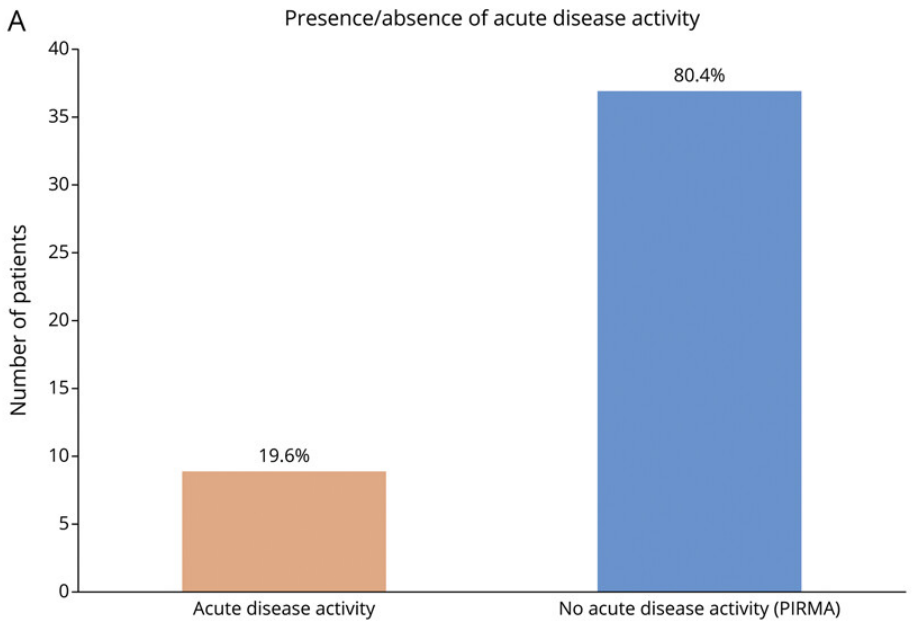




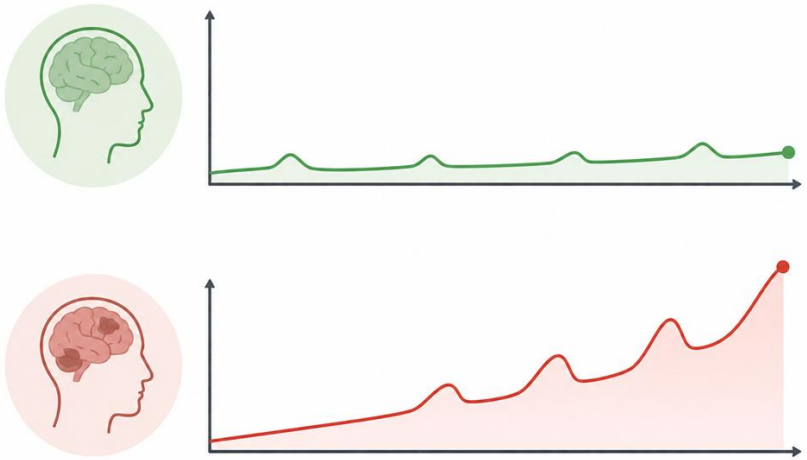
What about acute MRI activity?





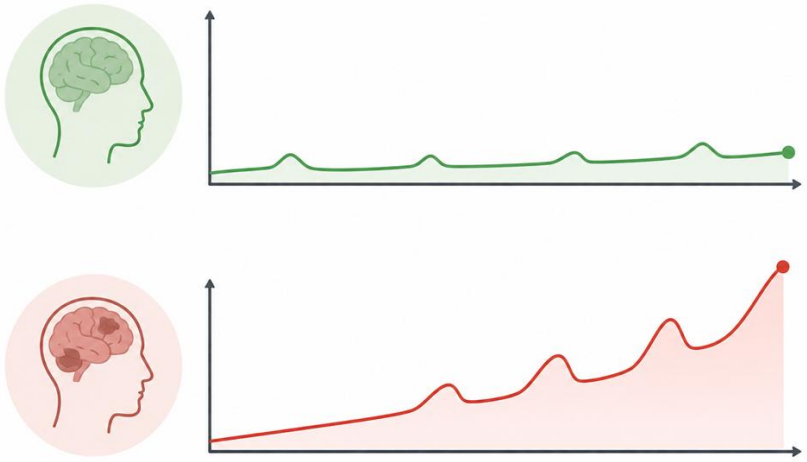


Hypothesis: Cognitive decline is a window into progressive disease



How does cognitive decline occur?

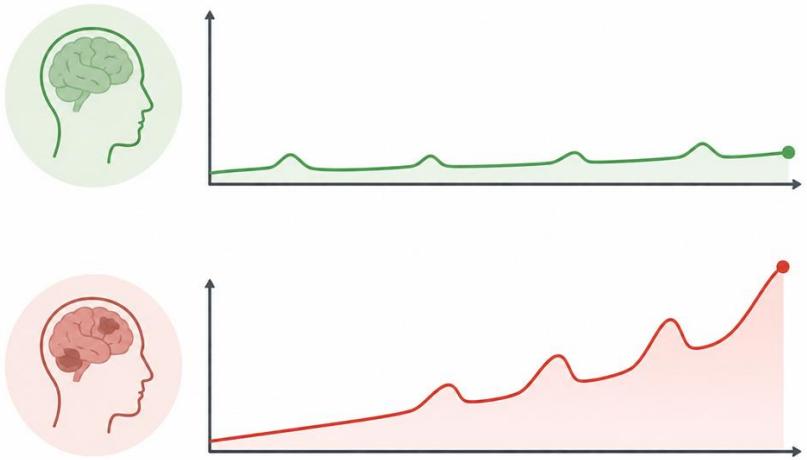
Hypothesis: Cognitive decline is a window into progressive disease



How does cognitive decline occur?

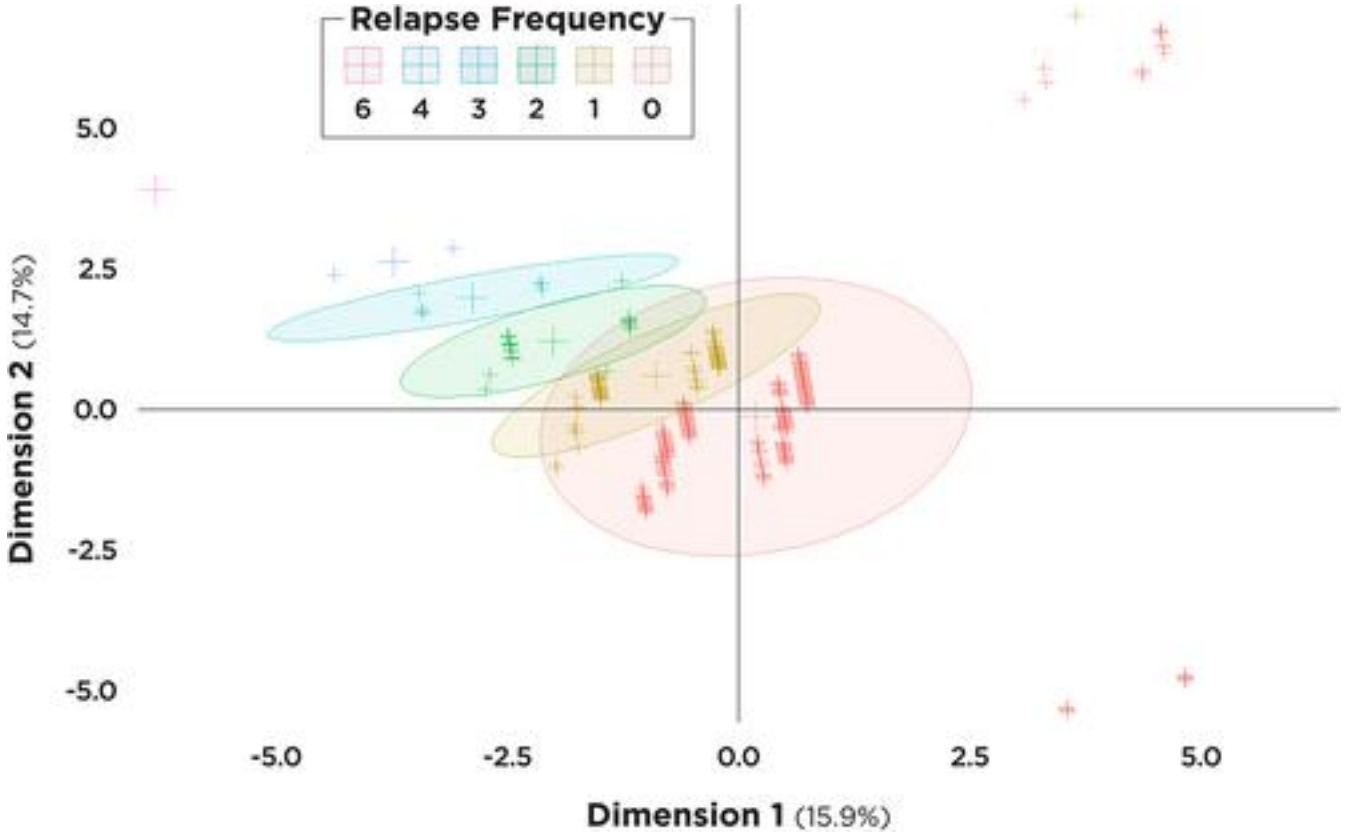
Largely independent of. . .
relapse, physical disability, and acute radiologic activity

Hypothesis: Cognitive decline is a window into progressive disease



1. Who has cognitive impairment?
2. How does cognitive decline occur?
3. **What biologically co-occurs with cognitive decline?**
4. What happens to people with cognitive decline?

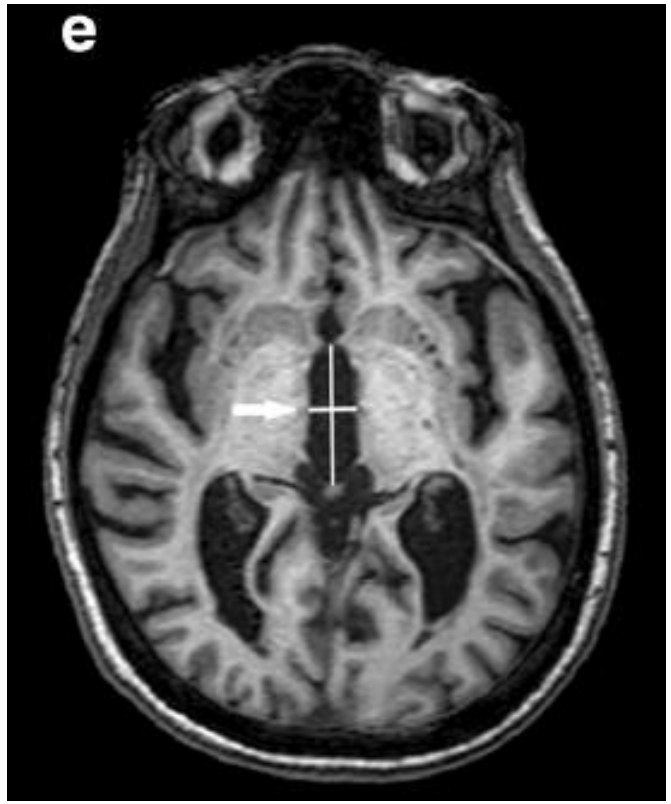
No effect of relapse



"No effect of relapses on confirmed worsening of the PASAT ($p = 0.902$) or long-term worsening ($p = 1.000$)."

"SDMT. . . no correlation between relapses. . . and confirmed worsening ($p = 0.755$)."

Third ventricular width



Third ventricular width

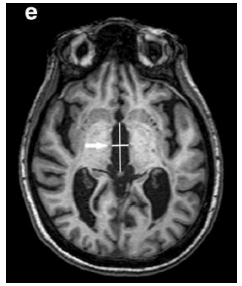


Table 4.—Partial Correlations Between Linear Computed Tomography and Neuropsychological Test Measures Controlling for Effects of Age

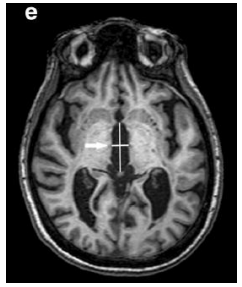
Variable*	"Bifrontal"	"Bicaudate"	"Third"
WAIS-R			
Verbal IQ (prorated)	...	...	−.27†
Vocabulary	...	...	
Comprehension	...	...	−.26†
Similarities	...	...	−.33‡
WMS			
Memory Quotient	...	−.32‡	−.37§
Information	−.25†	...	−.29†
Orientation	...	...	...
Mental Control	...	...	...
Digit Span	−.26†	−.29†	−.32†
Logical Memory	...	...	−.41§
Visual Reproduction	...	−.29†	−.35§
Associate Learning	...	−.26†	−.34‡
FVRT			
List A (total recall)	...	...	−.28†
List B	...	−.30‡	−.34‡
List A recall	...	...	−.32‡
List A delayed	...	...	−.26†
7/24 SRT			
Design A (total recall)	...	−.29†	−.32‡
Design B	...	...	−.37§
Design A recall	...	...	−.28†
Design A delayed	...	...	...

"The width of the third ventricle proved to be the best indicator of intellectual and memory dysfunction. Measures of cognition and ventricular size did not correlate with length of illness or overall disability as rated by the Kurtzke Disability Status Score."

Ventricular Size, Cognitive Function and Depression in Patients with Multiple Sclerosis

Campbell M. Clark, Gerald James, David Li, Joel Oger, Donald Paty and Harry Klonoff

Third ventricular width



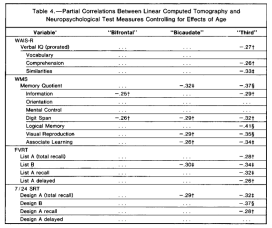


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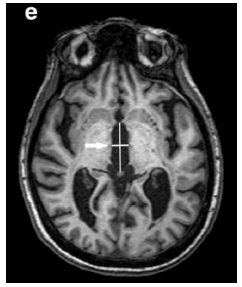
Table 3. Results of Significant Linear Regression Analyses

Neuropsychological Test	Block 1 Covariates	Retained MRI Variables	Partial *r* for Primary Predictor	Multiple R^2	Change in R^2 From Block 1	*P* Value
Series 1: all MRI predictors						
CVLT-II Learning	Age, NAART score	Third ventricle width	−0.45	0.42	0.14	<.001
	Age, NAART and CES-D-10 scores	Third ventricle width	−0.44	0.26	0.15	.02
CVLT-II Delayed Recall	Age, NAART score	Third ventricle width	−0.45	0.44	0.14	<.001
	Age, NAART and CES-D-10 scores	Third ventricle width	−0.45	0.44	0.14	<.01
BVMT-R Delayed Recall	Age, NAART score	Third ventricle width	−0.47	0.42	0.17	<.001
	Age, NAART and CES-D-10 scores	Third ventricle width	−0.47	0.42	0.17	<.01
PASAT	Age, NAART score	Third ventricle width	−0.57	0.43	0.16	<.01
	Age, NAART and CES-D-10 scores	Third ventricle width	−0.57	0.44	0.26	<.001
SDMT	Age, NAART score	Third ventricle width	−0.71	0.57	0.43	<.001
	Age, NAART and CES-D-10 scores	Third ventricle width	−0.71	0.57	0.43	<.001

Third ventricular width



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Variable*	"Bifrontal"	"Bicaudate"	"Third"
WAIS-R			
Verbal IQ (prorated)	. . .	. . .	−.271
Vocabulary	. . .	. . .	. . .
Comprehension	. . .	. . .	−.261
Similarities	. . .	. . .	−.338
WMS			
Memory Quotient	. . .	−.324	−.375
Information	−.291	. . .	−.291
Orientation	. . .	. . .	. . .
Mental Control	. . .	. . .	. . .
Digit Span	−.261	−.291	−.321
Logical Memory	. . .	. . .	−.415
Visual Reproduction	. . .	−.299	−.305
Associate Learning	. . .	−.261	−.348
FVRT			
List A (total recall)	. . .	. . .	−.281
List B	. . .	−.309	−.348
List A recall	. . .	. . .	−.329
List A delayed	. . .	. . .	−.261
T-24 SRT			
Design A (total recall)	. . .	−.291	−.321
Design B	. . .	. . .	−.275
Design A recall	. . .	. . .	−.281
Design A delayed	. . .	. . .	. . .

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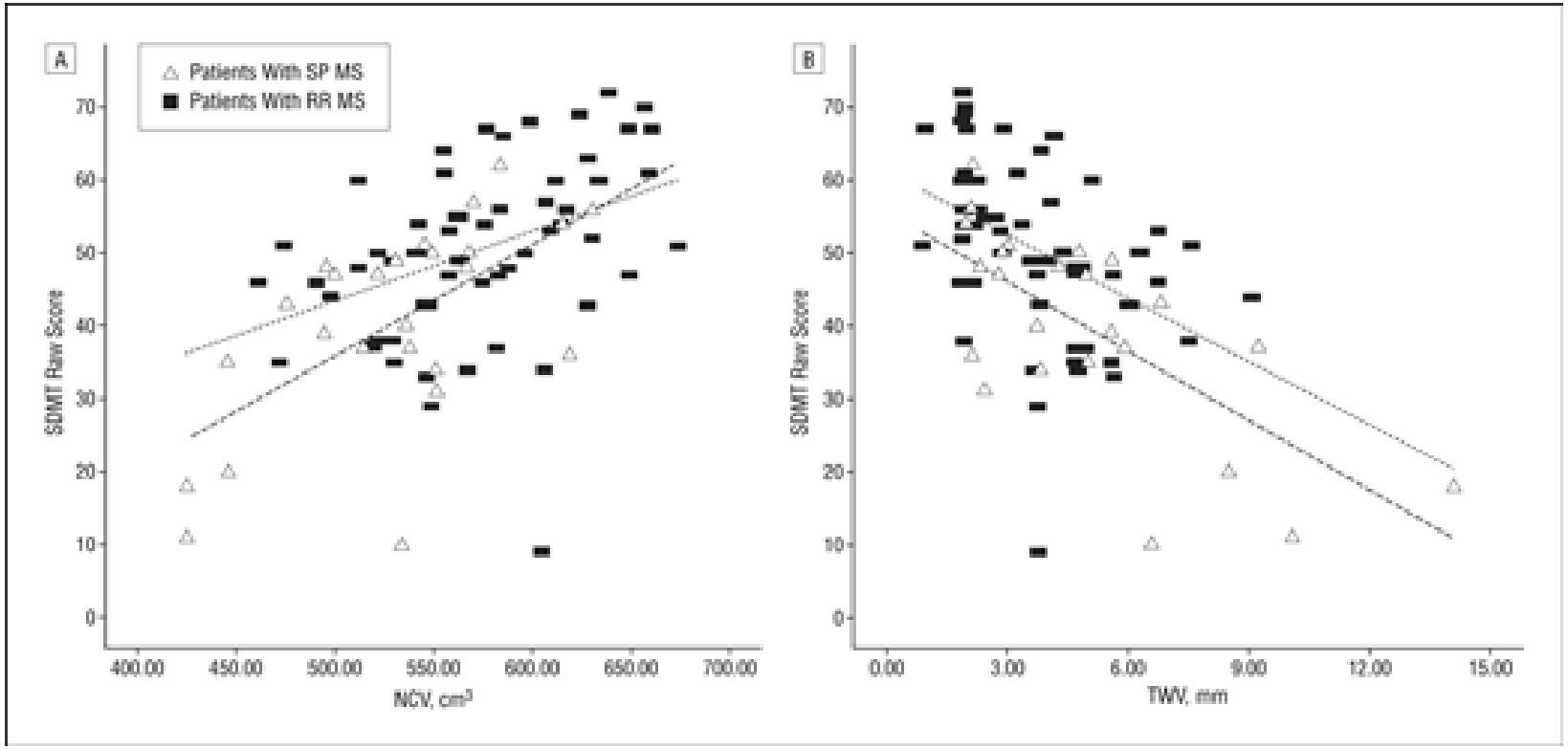
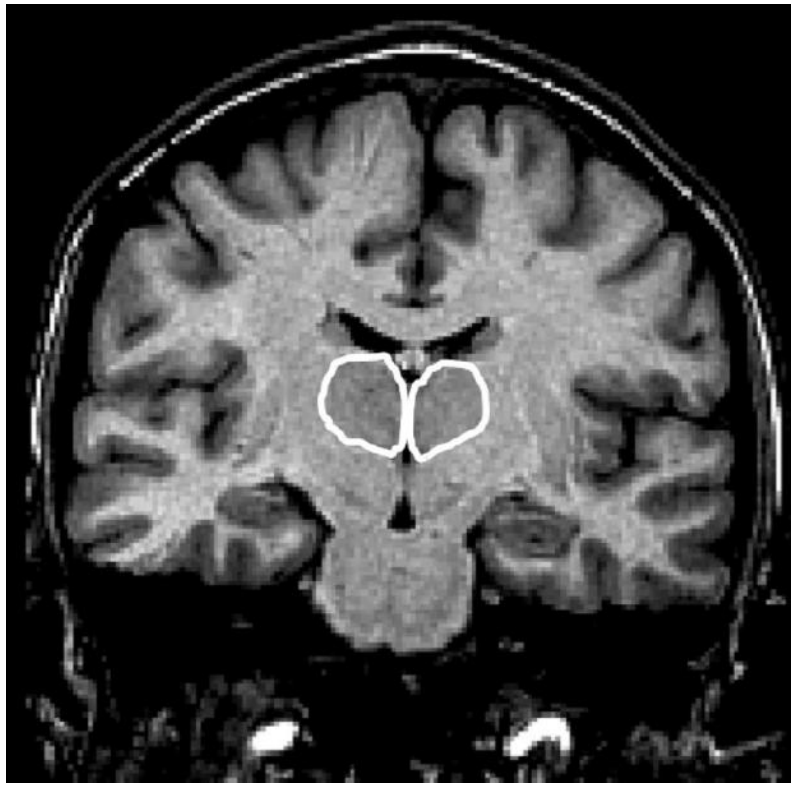


Benedict, JAMA Neurology, 2006

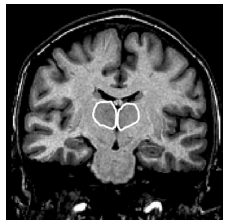
MS Center Amsterdam

Thalamus!



Cognitive test	Variables remaining in model after adjusting for age and sex	Partial *r* for variable remaining in final model
COWAT	Thalamic fraction	0.47
JLO	Thalamic fraction	0.74
	Third ventricle width	−0.77
CVLT-II-TR	Thalamic fraction	0.55
CVLT-II-D	Thalamic fraction	0.68
BVMT-R TR	Thalamic fraction	0.67
BVMT-R-D	Thalamic fraction	0.74
PASAT	Thalamic fraction	0.74
SDMT	Thalamic fraction	0.69

Thalamus!



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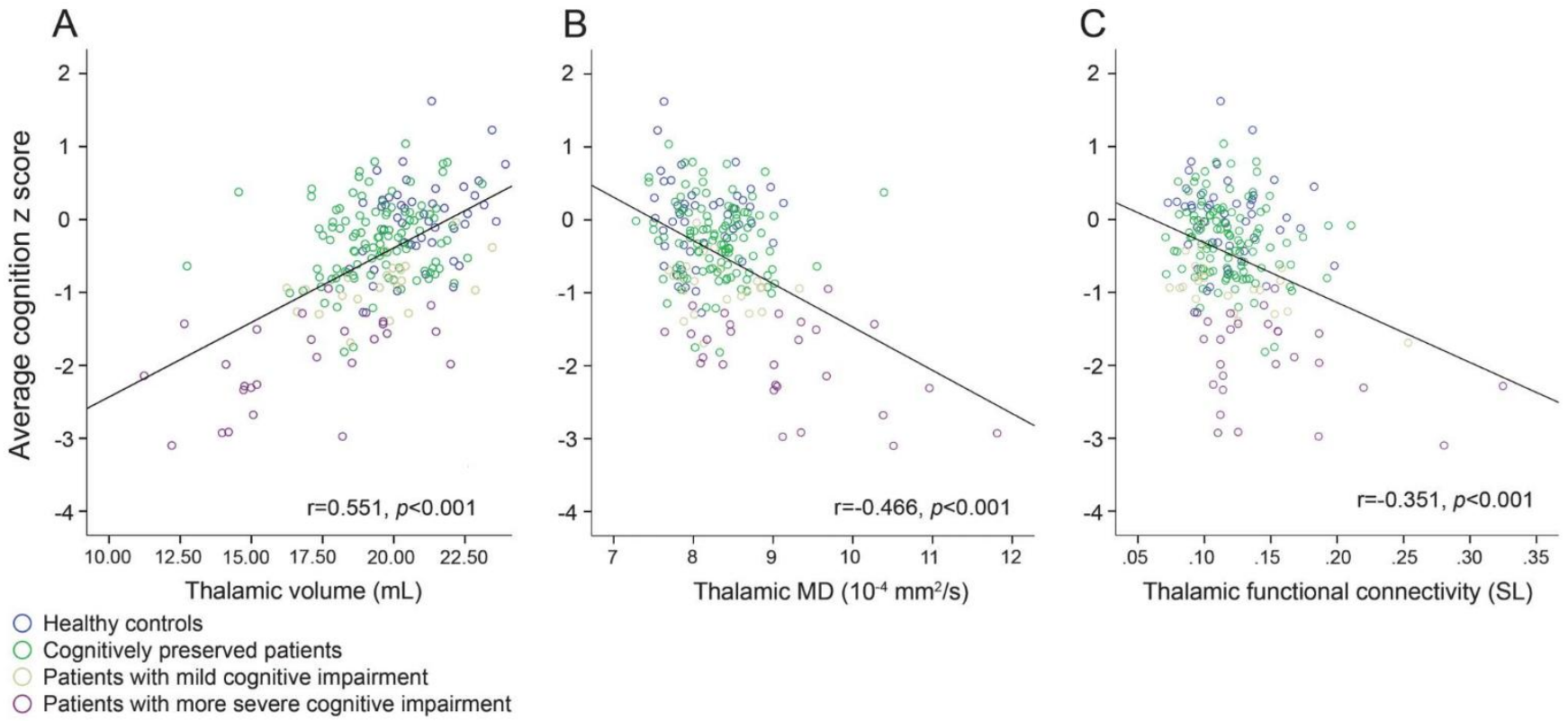
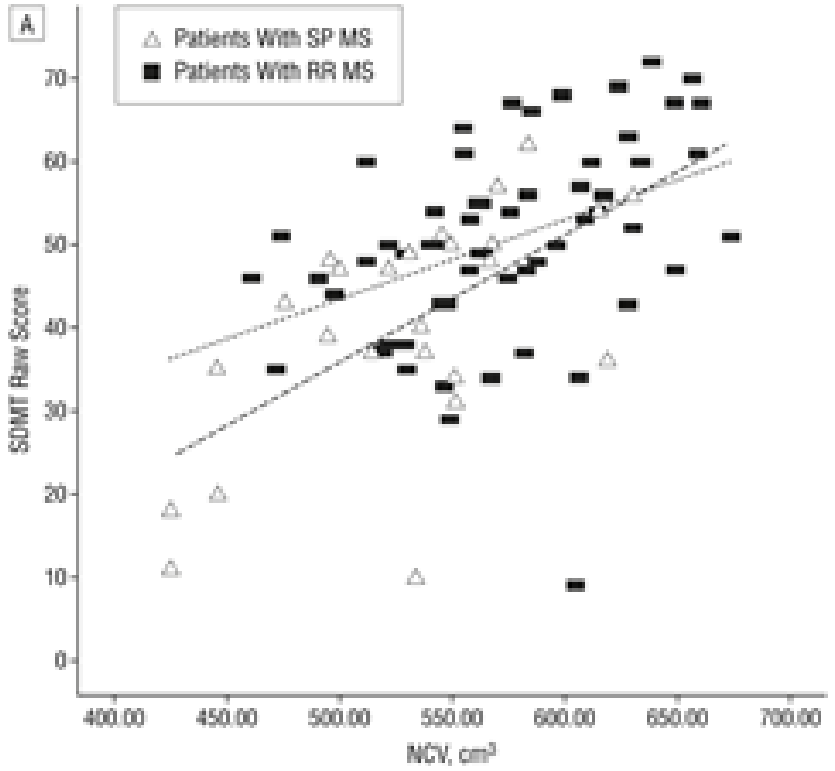
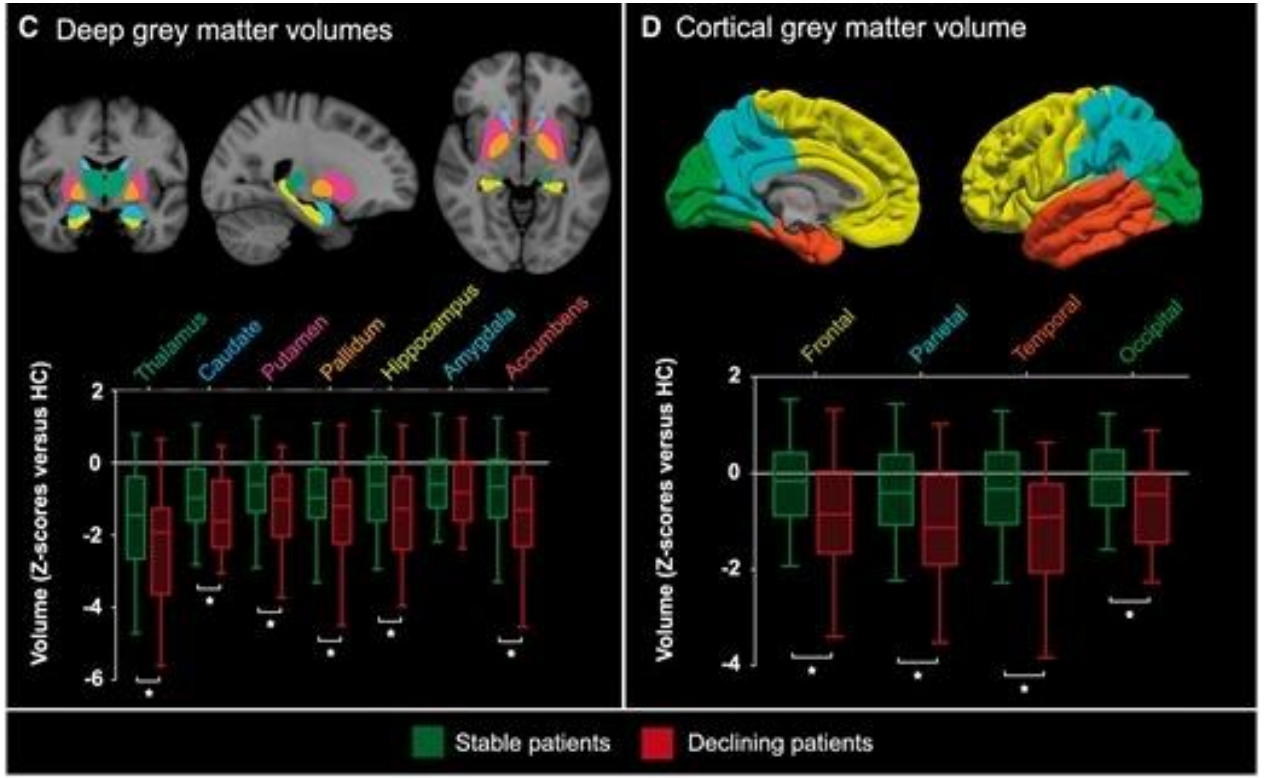
PASAT	Thalamic fraction	0.74
SDMT	Thalamic fraction	0.69

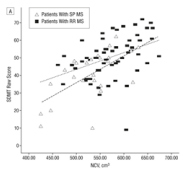


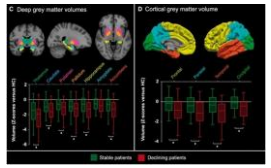
Neocortical atrophy

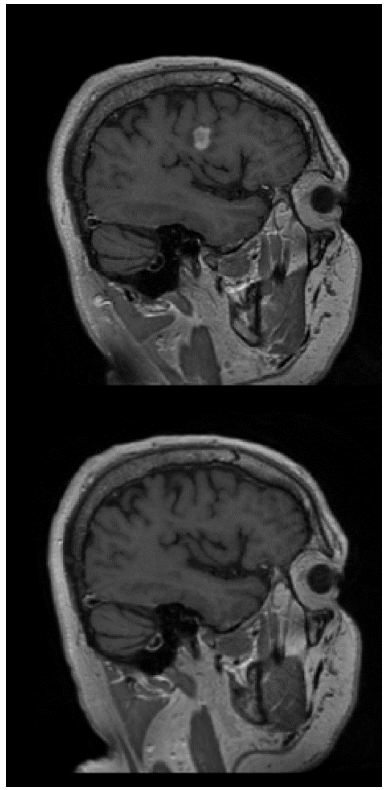


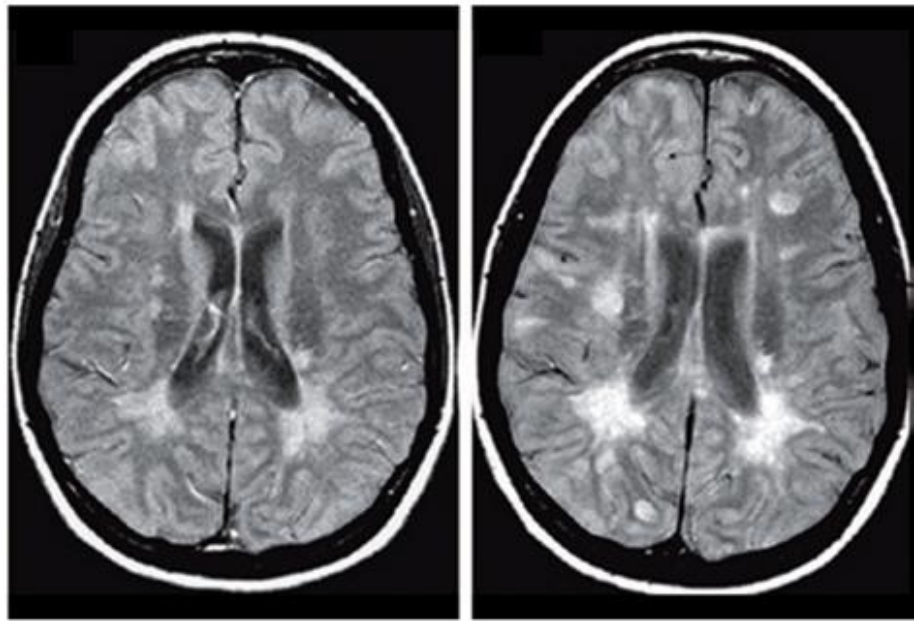


Neocortical atrophy

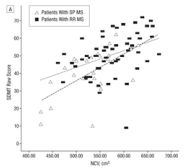


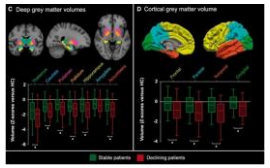


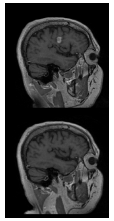


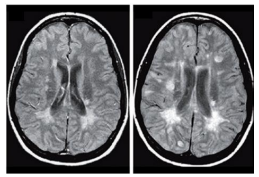


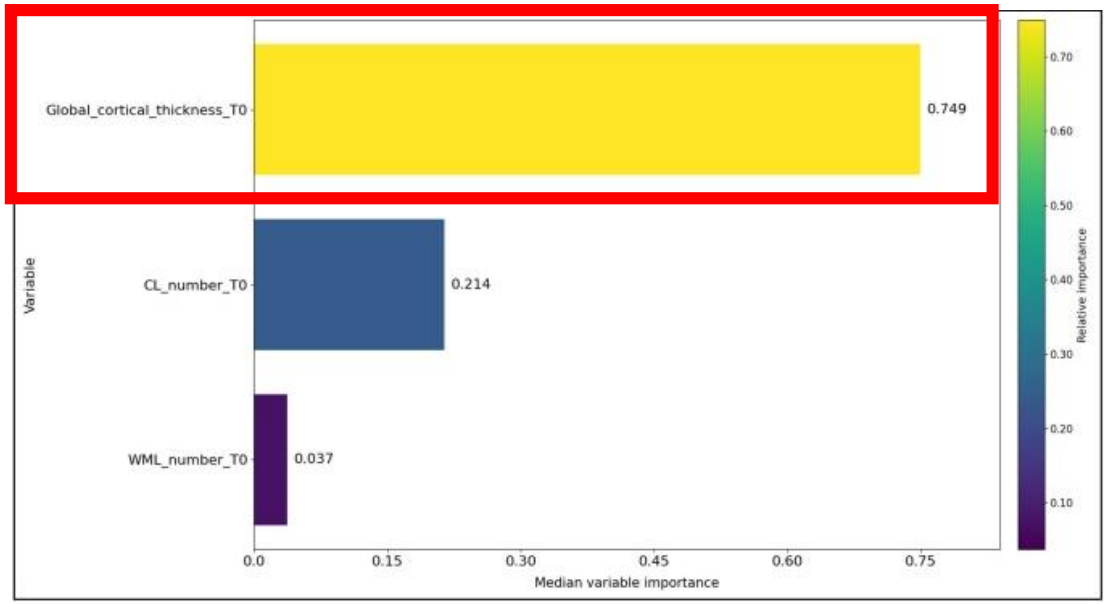
Neocortical atrophy

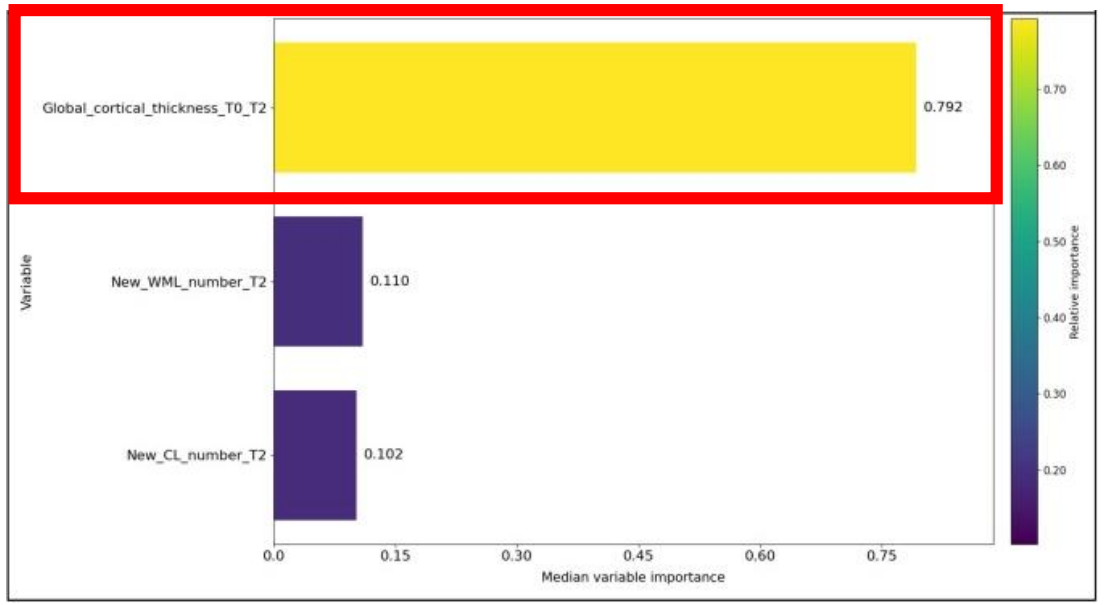




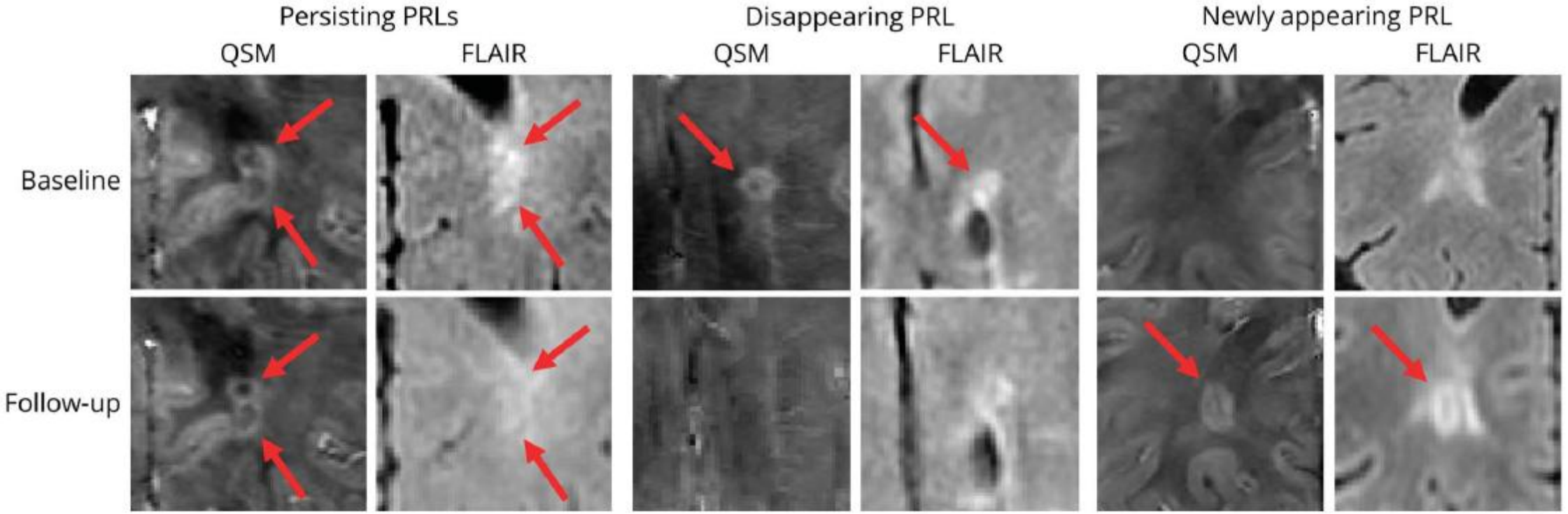








Paramagnetic rim lesions



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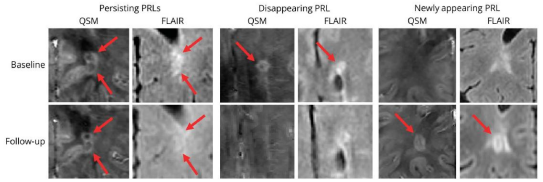

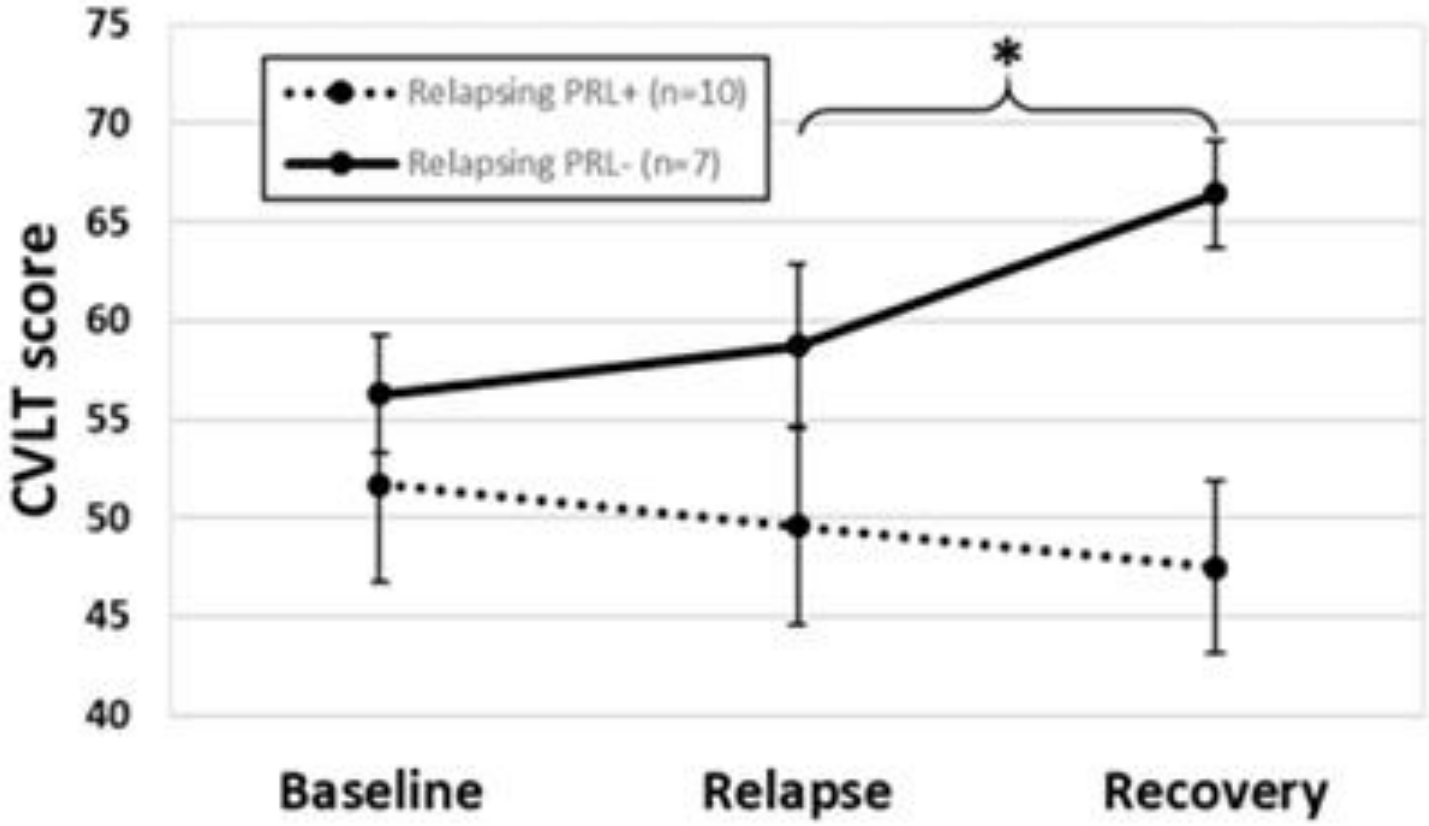

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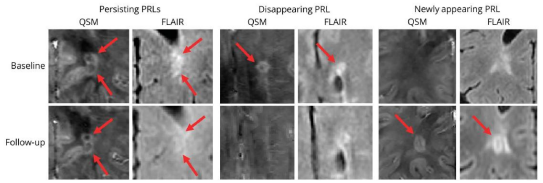
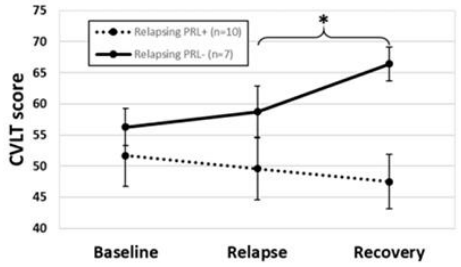
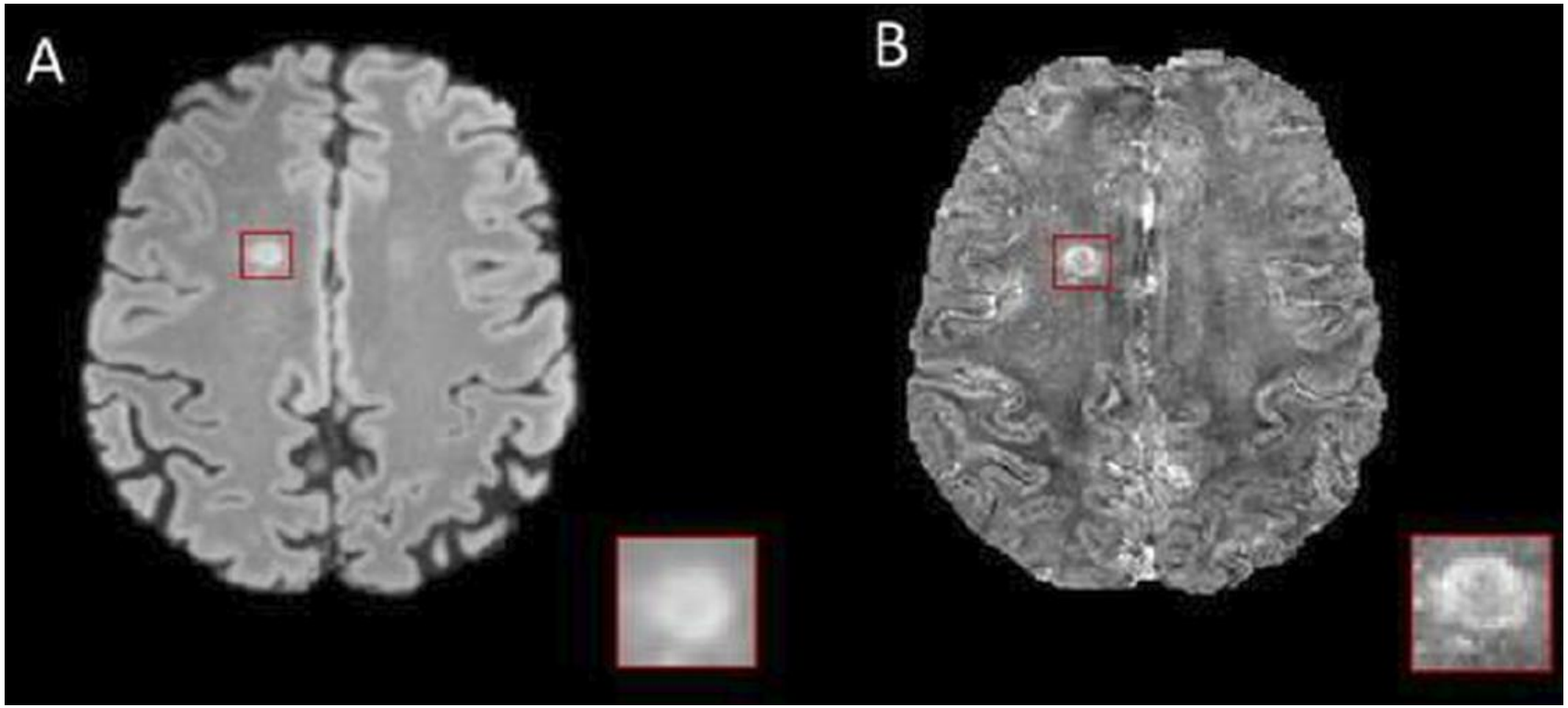
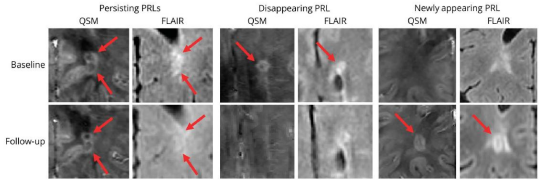
Paramagnetic rim lesions

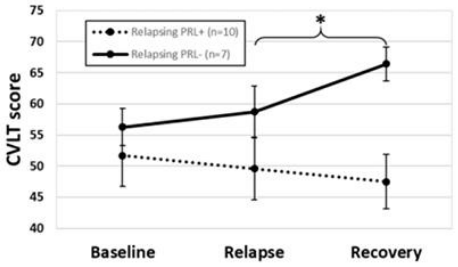


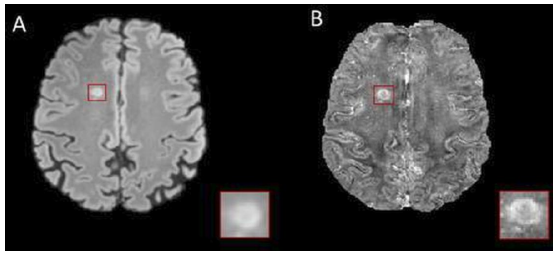


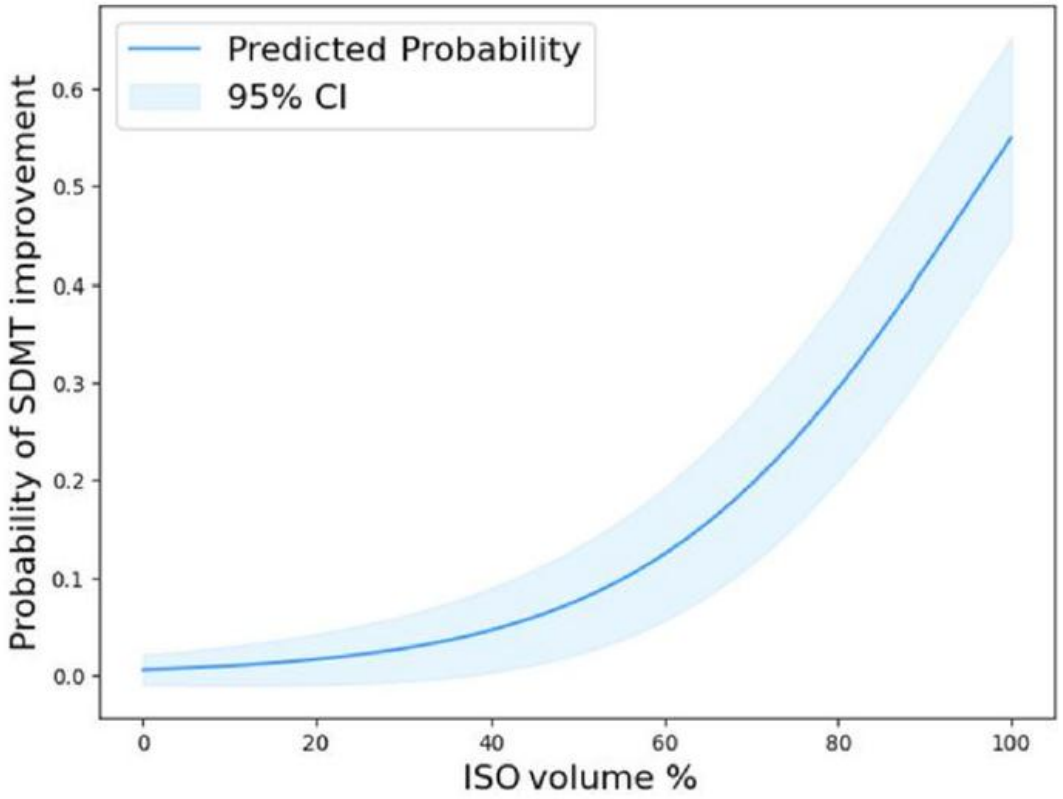


Paramagnetic rim lesions



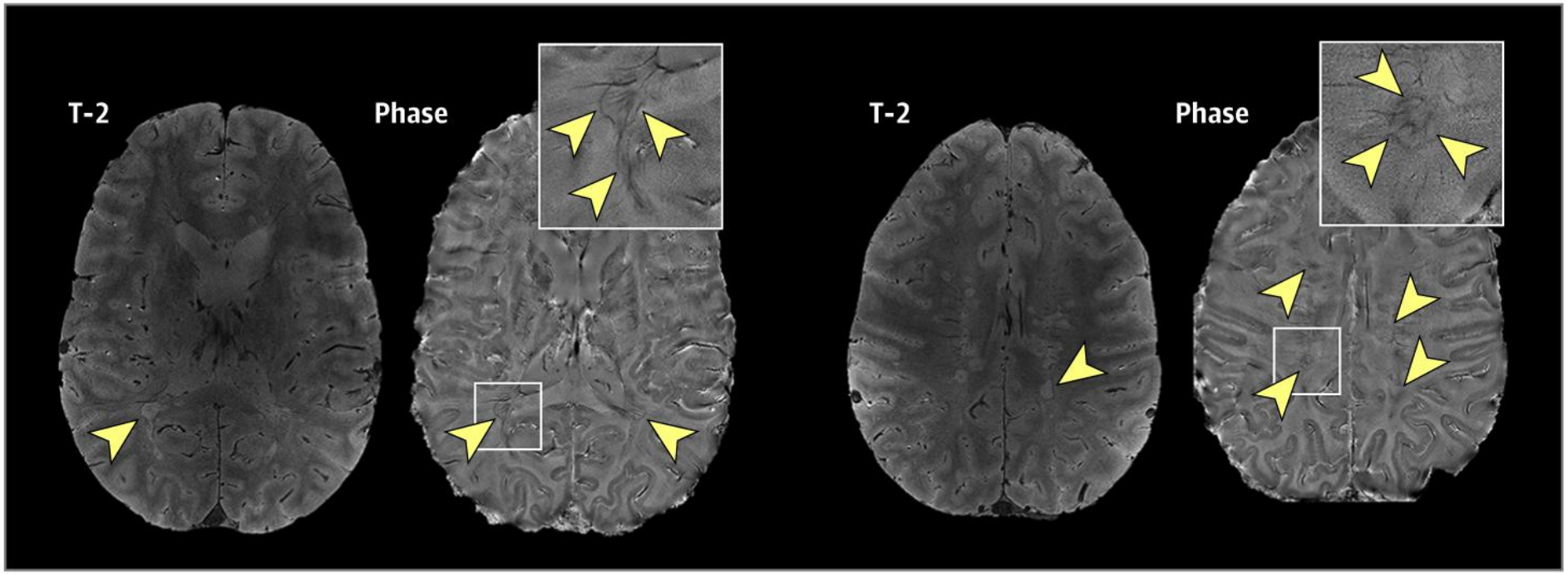




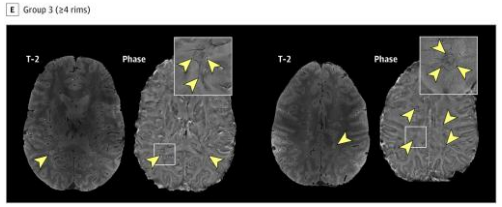


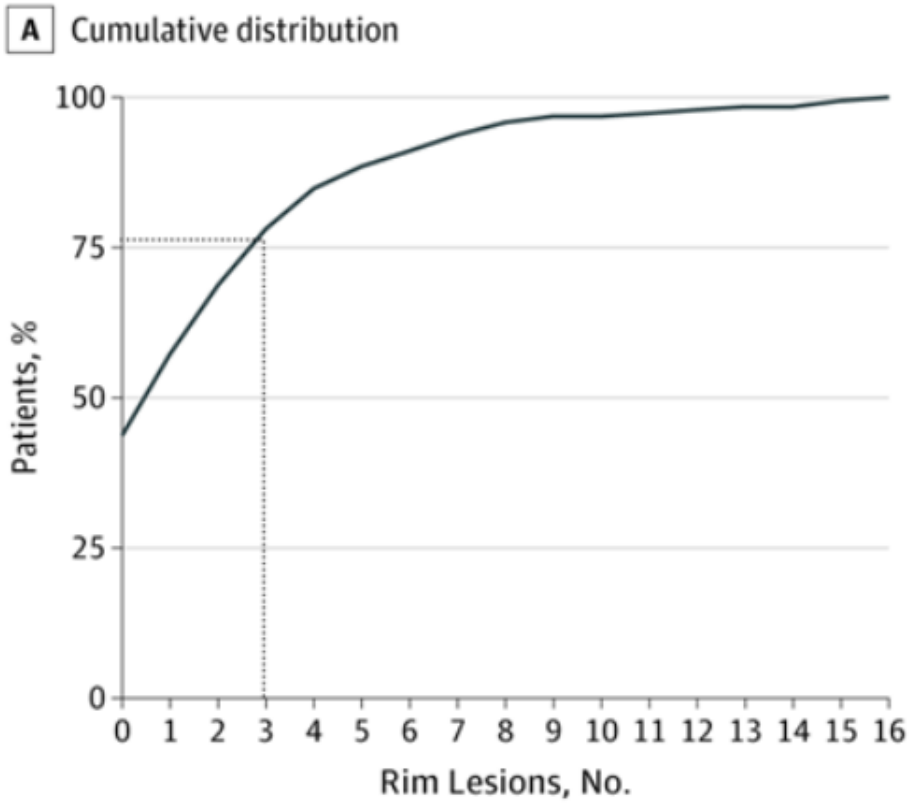
Paramagnetic rim lesions

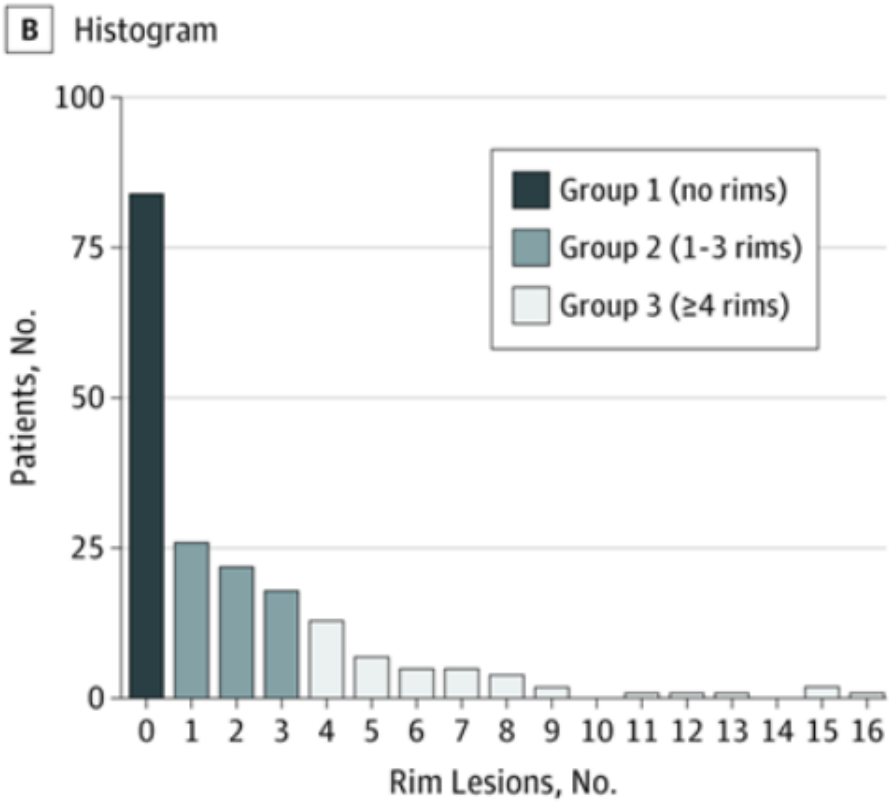
E Group 3 (≥4 rims)



Paramagnetic rim lesions

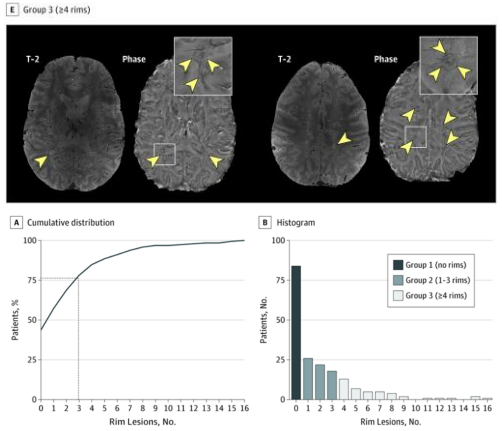


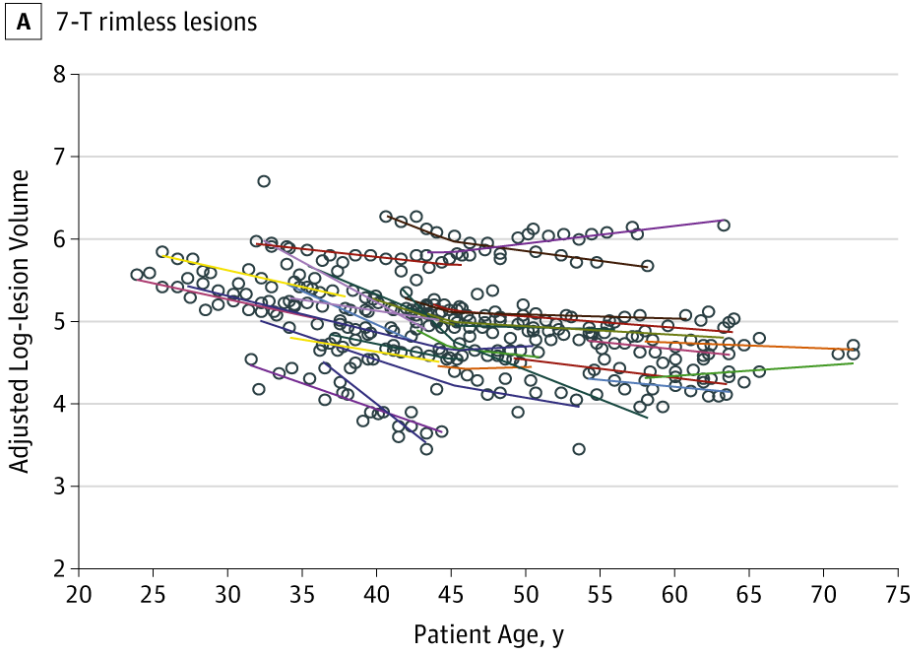


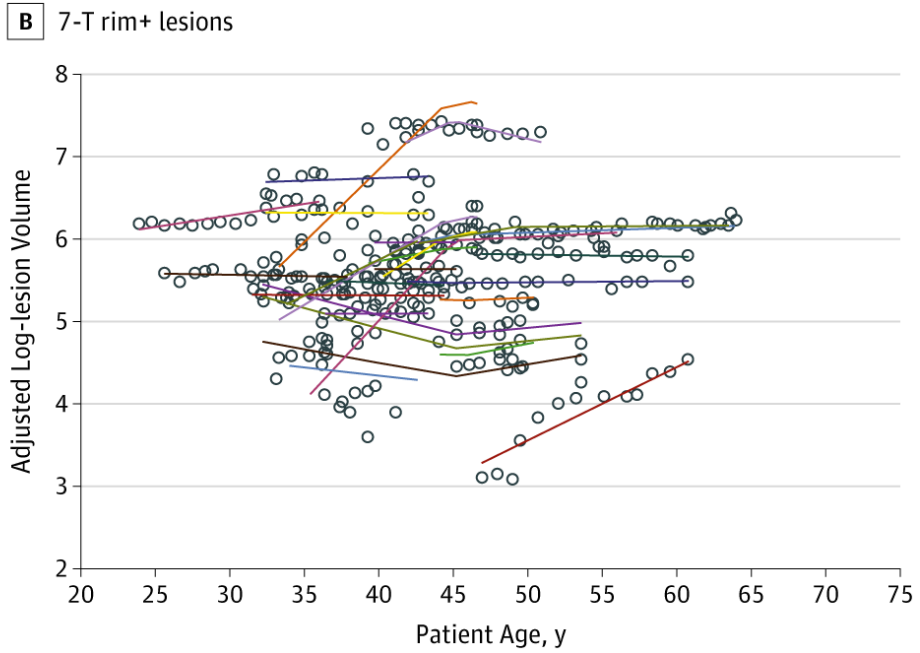


Absinta, JAMA Neurology, 2019

Paramagnetic rim lesions







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Paramagnetic rim lesions

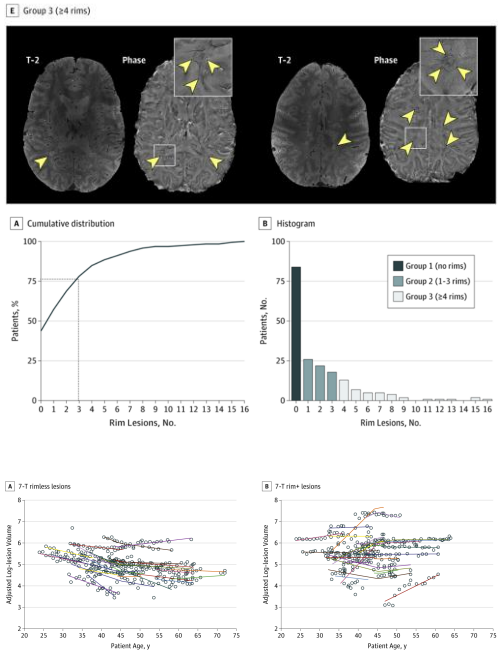
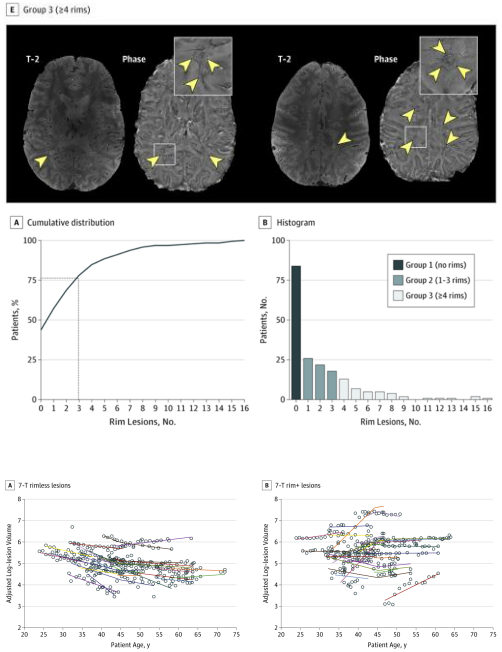


Table. Cohort Characteristics of 192 Patients With Multiple Sclerosis in the Cross-Sectional Cohort

Rim Category	No Detected Rims	1-3 Rims	≥4 Rims	Statistical Analysis[a]
Demographic and Clinical Data				
No. (%)	84 (44)	66 (34)	42 (22)	NA
Clinical phenotype, No. (%)				
CIS/RR	61 (73)	46 (70)	24 (57)	Fisher 2 × 3 *P* = .20, NS
SP	16 (19)	14 (21)	10 (24)	
PP	7 (8)	6 (9)	8 (19)	
Sex, Female, No. (%)	59 (70)	45 (68)	28 (67)	Fisher 2 × 3 *P* = .90, NS
Age, mean (SD), y	47.3 (14.5)	47.2 (11.4)	44.3 (11.1)	ANOVA *P* = .40, NS
Disease duration, mean (SD), y	13.4 (12.5)	12.9 (9.9)	12.2 (8.3)	ANOVA *P* = .80, NS
PASAT score, mean (SD)	49.9 (8.6)*	48.4 (9.9)	44.6 (11.9)*	ANOVA *P* = .03
SDMT score, mean (SD)	53.4 (12.3)*	48.3 (13.4)	43.7 (17.8)*	ANOVA *P* = .001

Paramagnetic rim lesions



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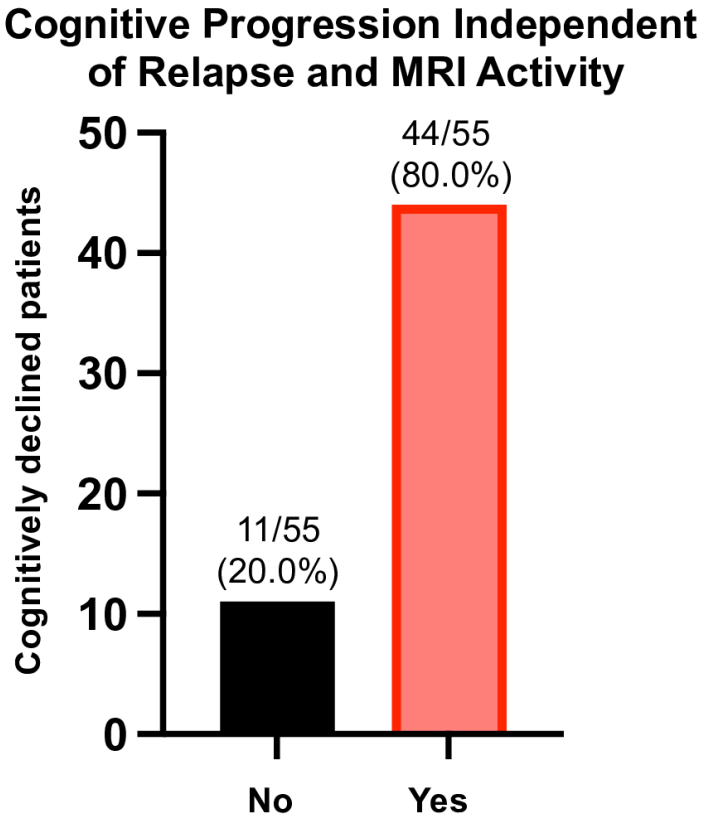
Patients never treated, No. (%)	27/84 (32)	11/66 (17)	5/42 (12)	Fisher 2 × 3 P = .01
African American, No. (%)	10 (12)	12 (18)	10 (24)	Fisher 2 × 3 P = .20, NS



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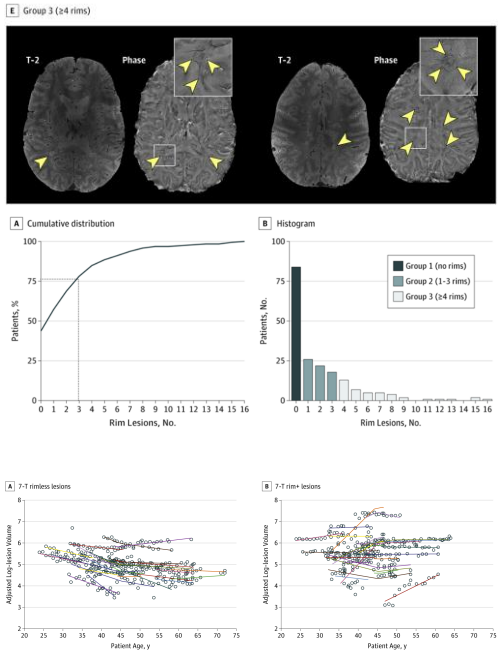

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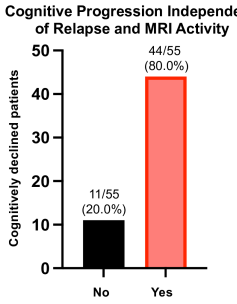
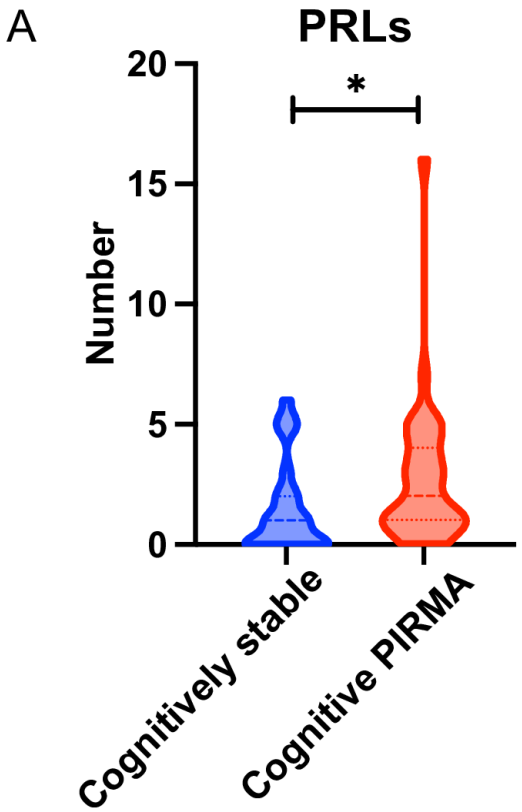
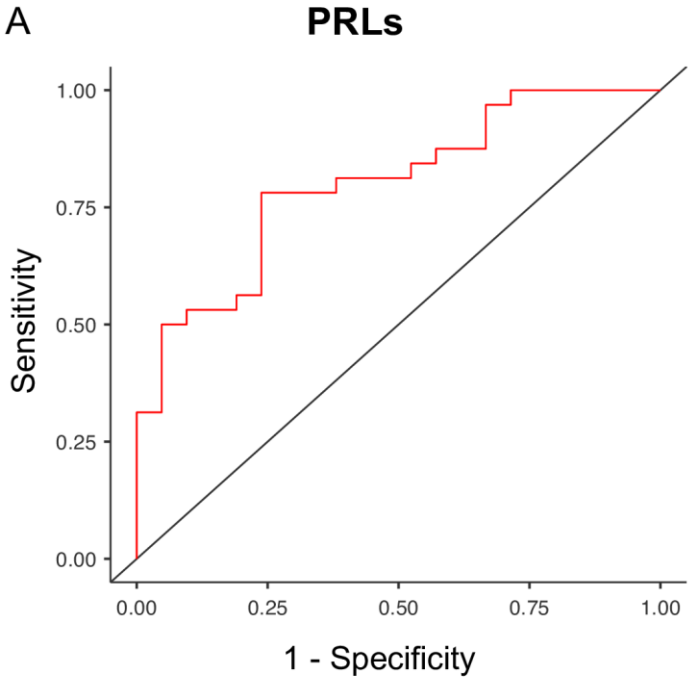
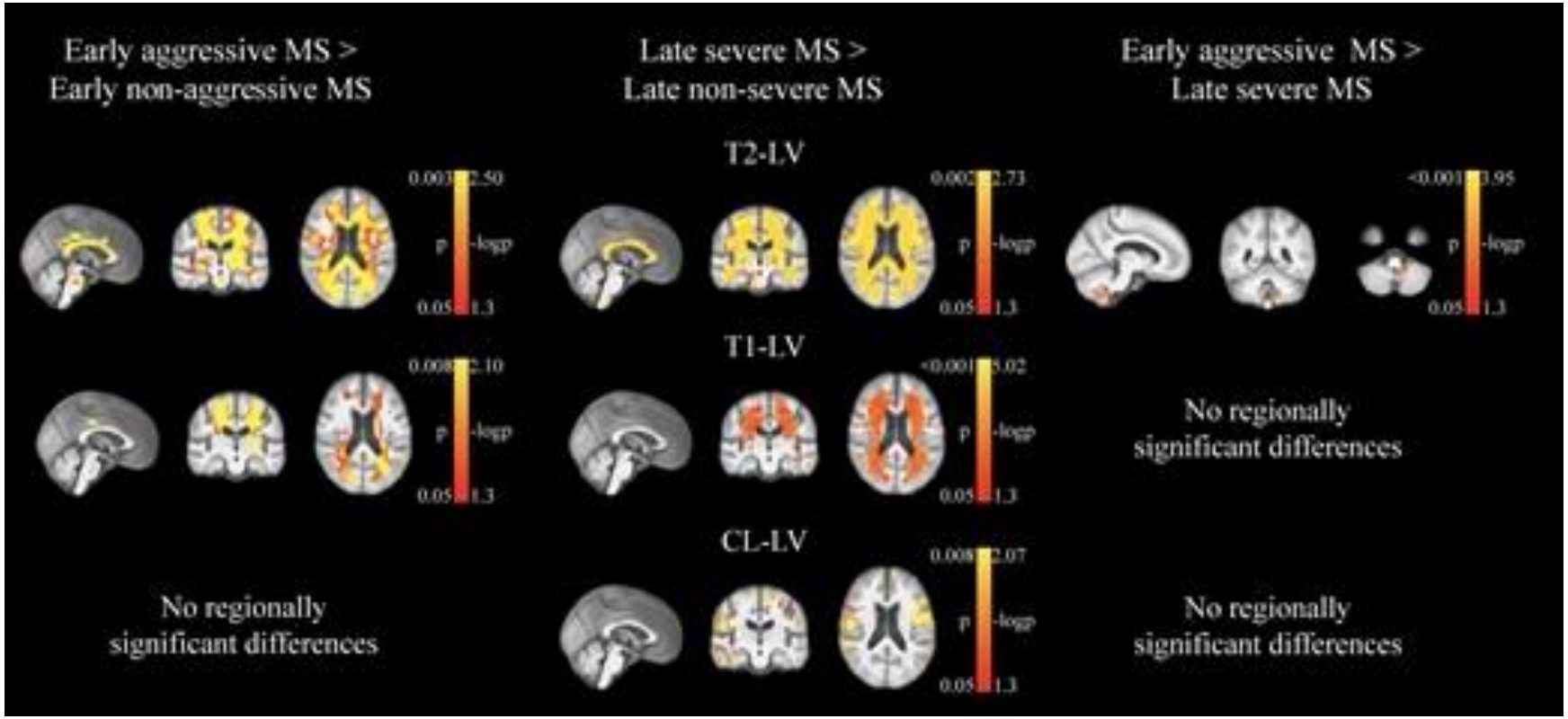


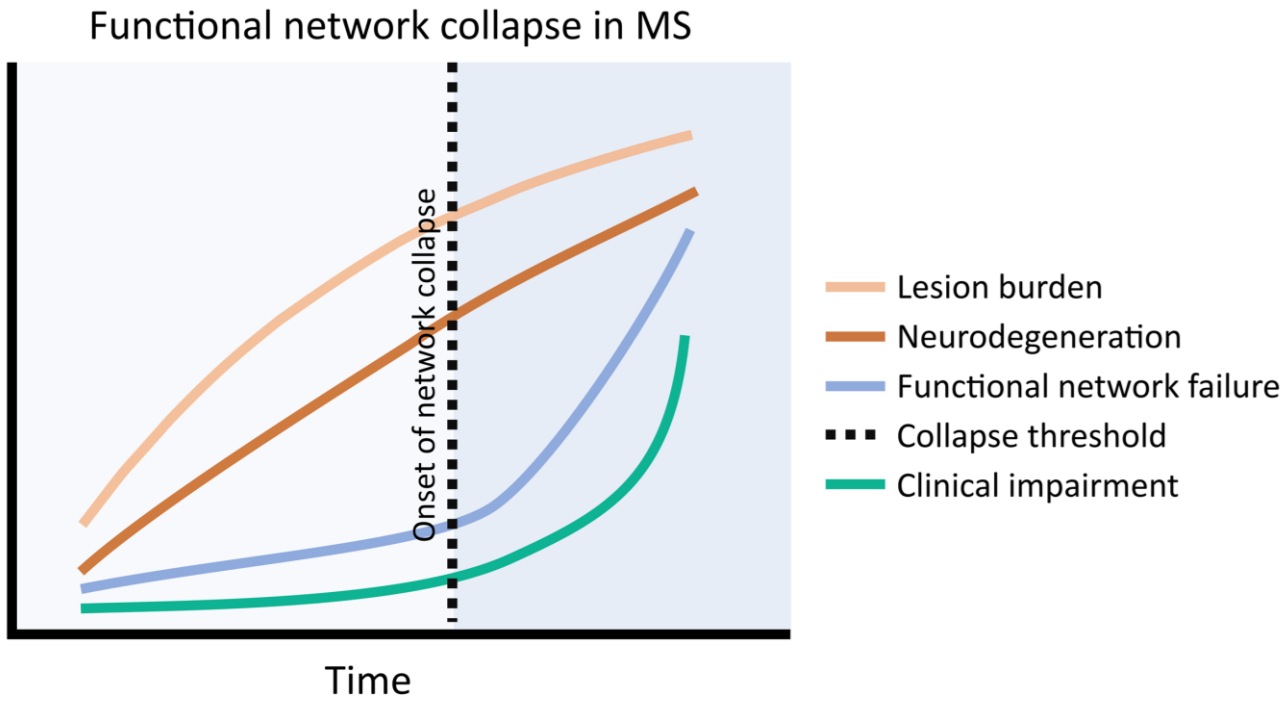


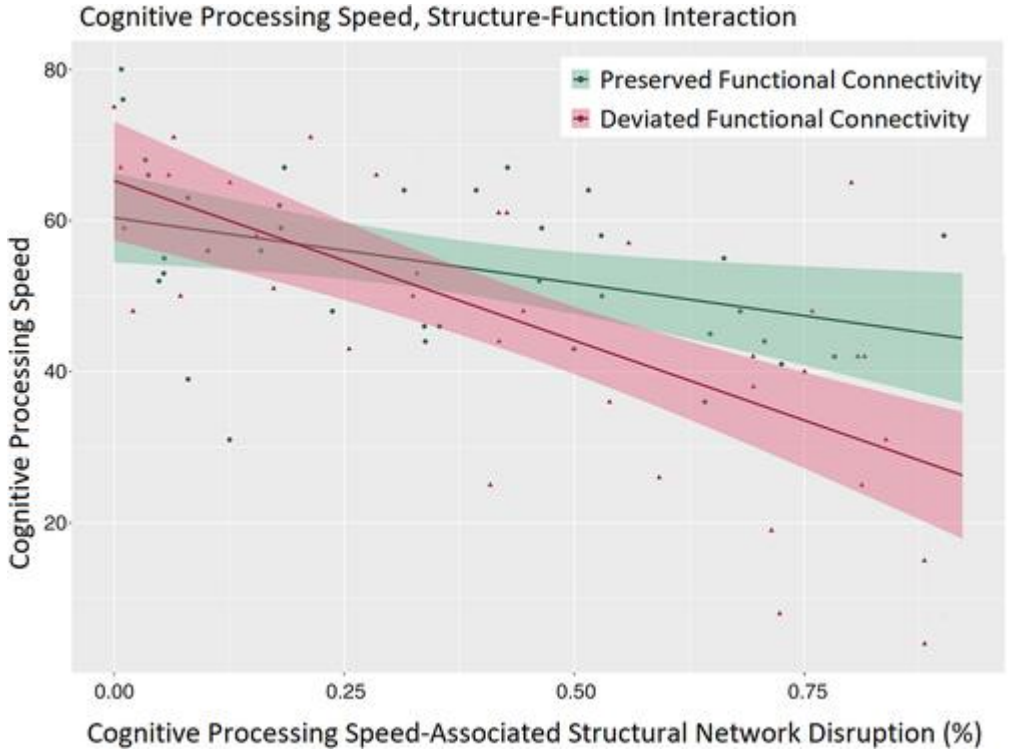


Aggressive MS



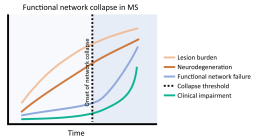
Functional network collapse

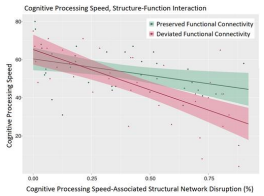


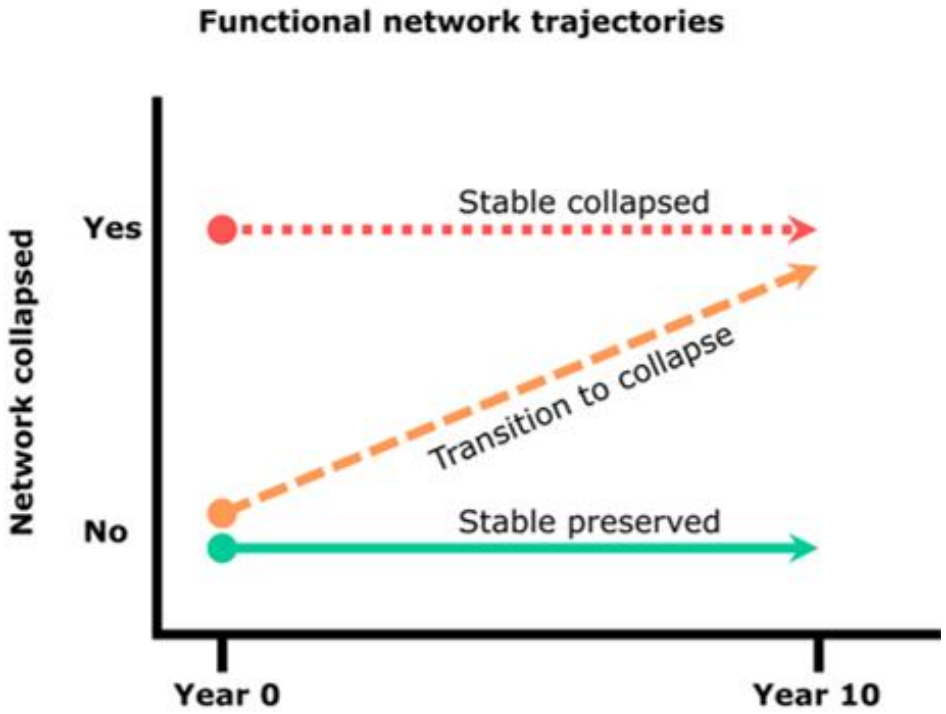


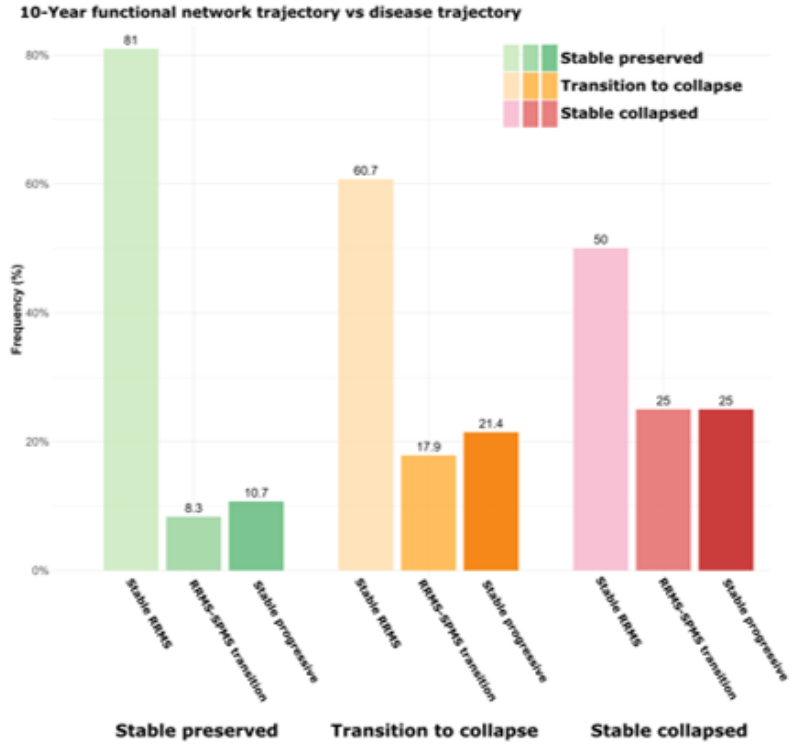
Schoonheim, Frontiers in Neurology, 2015; Fuchs, HBM, 2018

Functional network collapse









Fuchs, Neurology, in press

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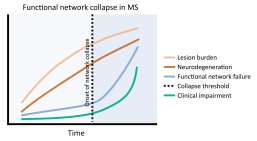
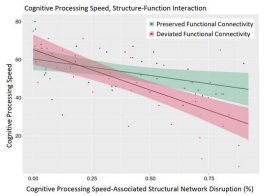
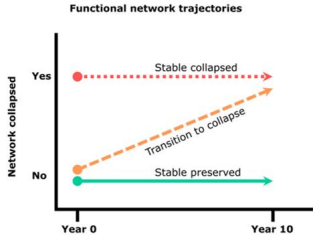
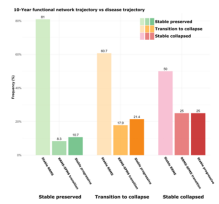
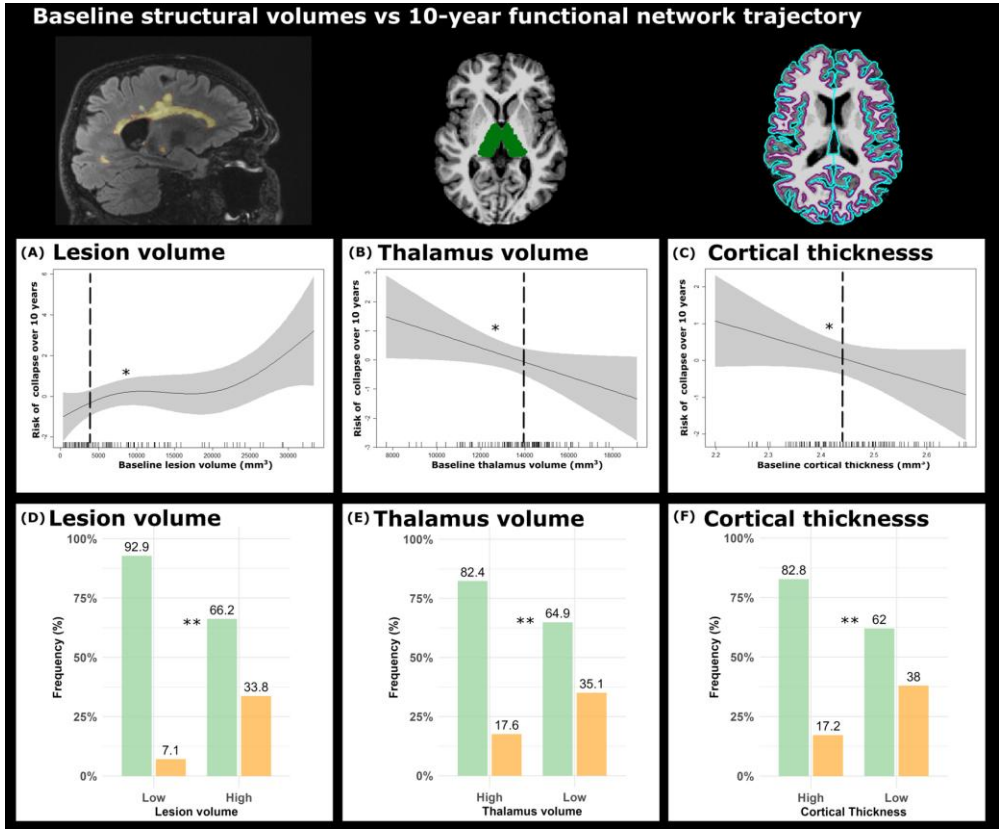
Functional network collapse

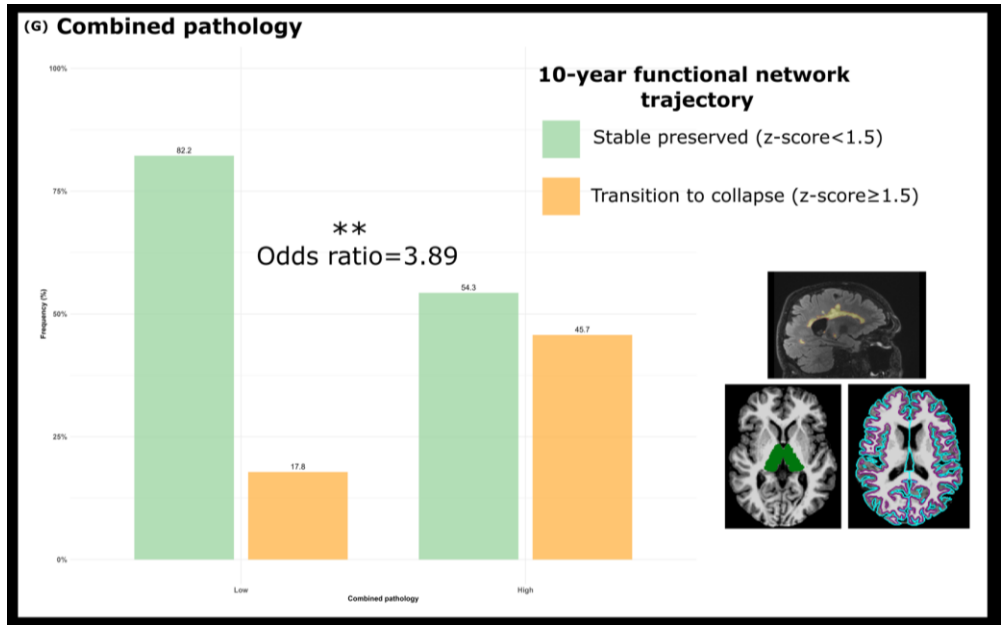












Fuchs, Neurology, in press

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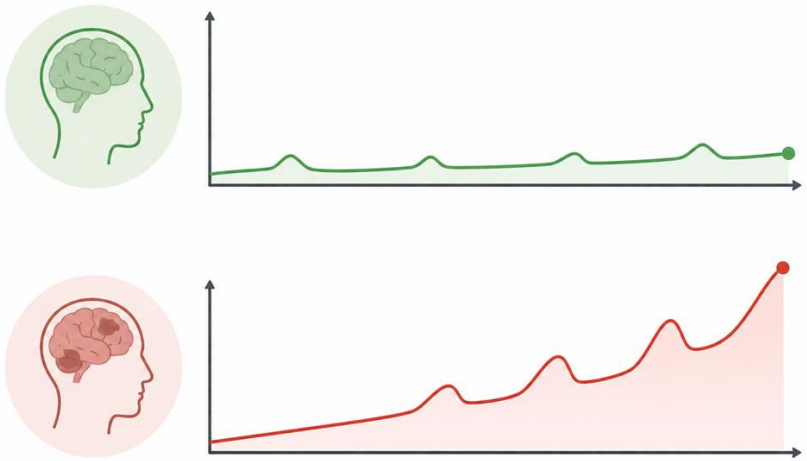
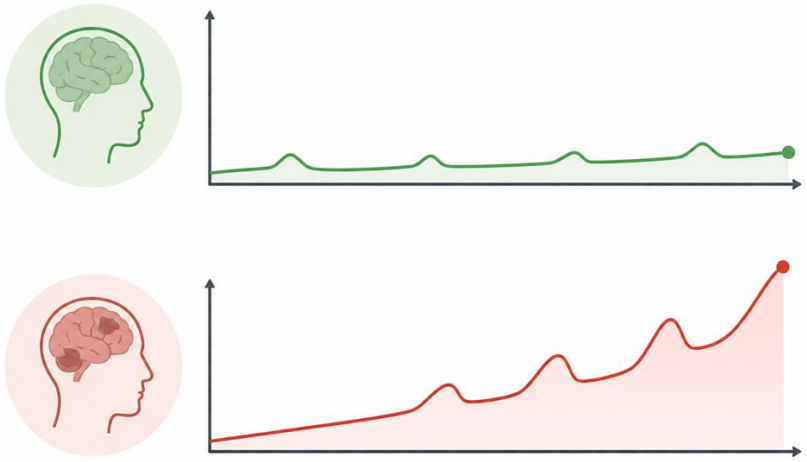
Hypothesis: Cognitive decline is a window into progressive disease



What biologically co-occurs with cognitive decline?

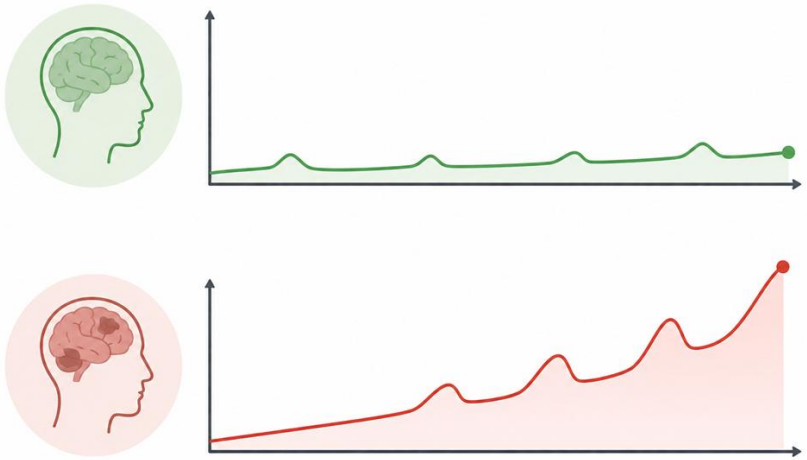
Hypothesis: Cognitive decline is a window into progressive disease



What biologically co-occurs with cognitive decline?

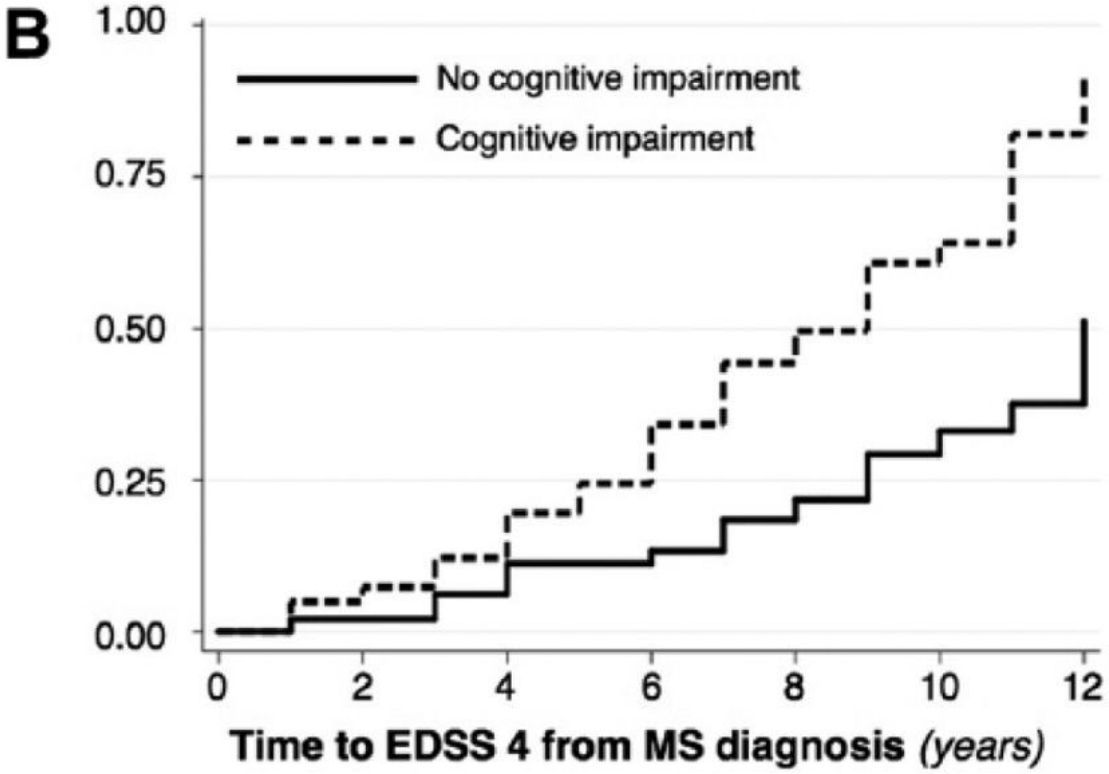
Thalamic and cortical atrophy, chronic active lesions, and functional network failure

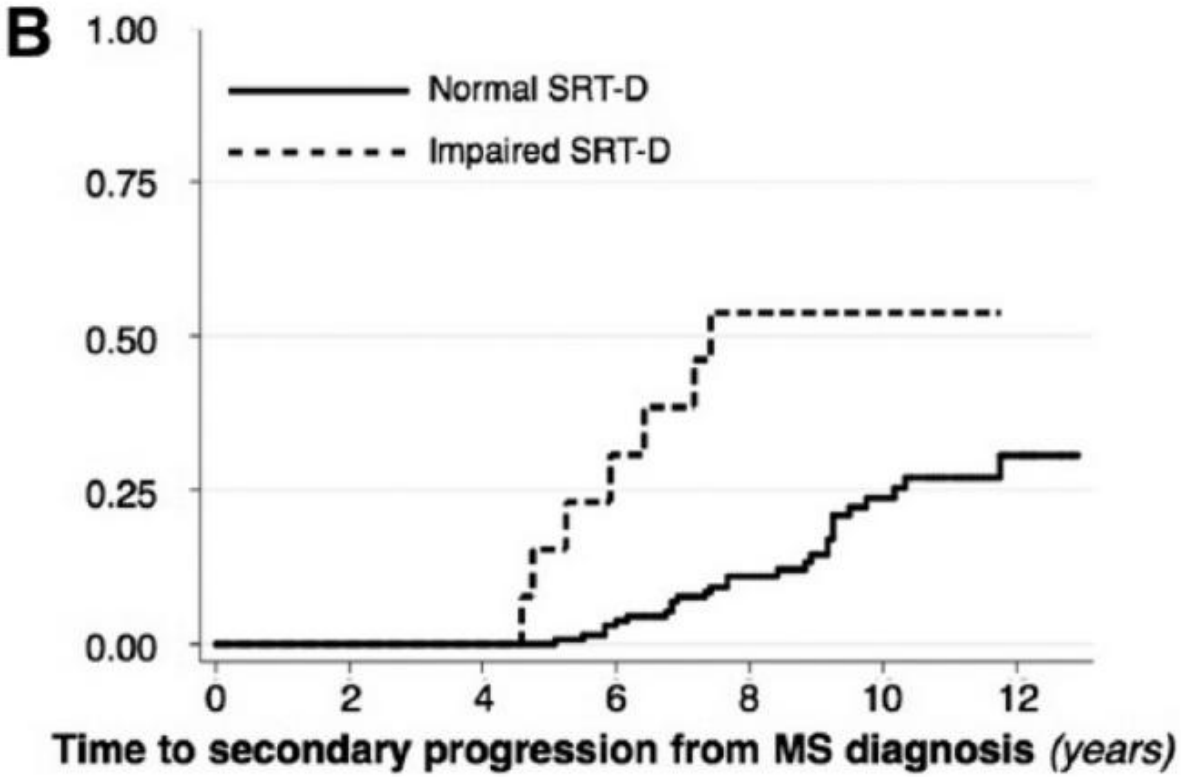
Hypothesis: Cognitive decline is a window into progressive disease



1. Who has cognitive impairment?
2. How does cognitive decline occur?
3. What biologically co-occurs with cognitive decline?
4. **What happens to people with cognitive decline?**

Early CI and future disease worsening





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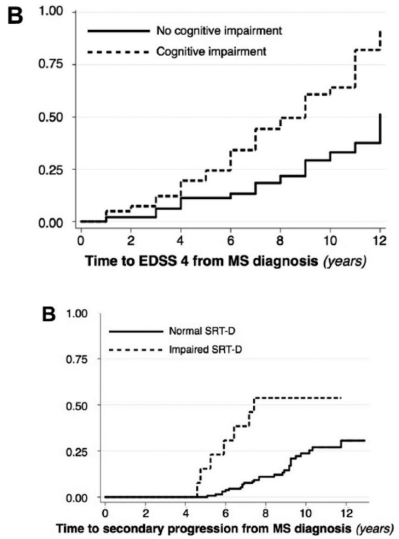

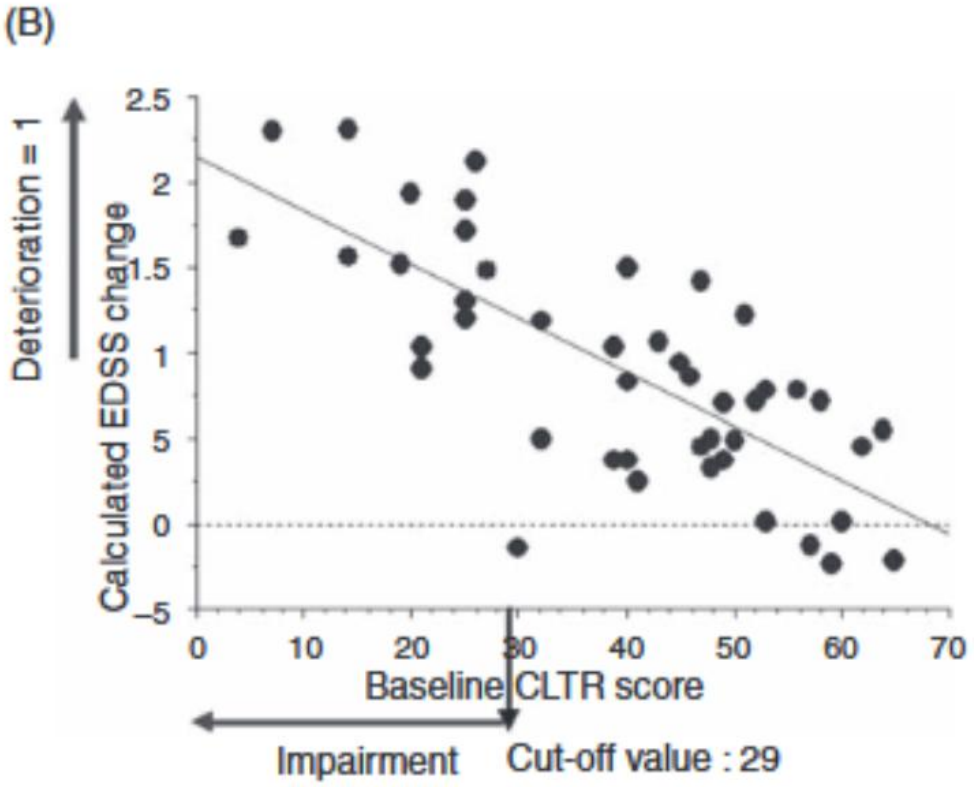

Deloire, 2010, *MSJ*

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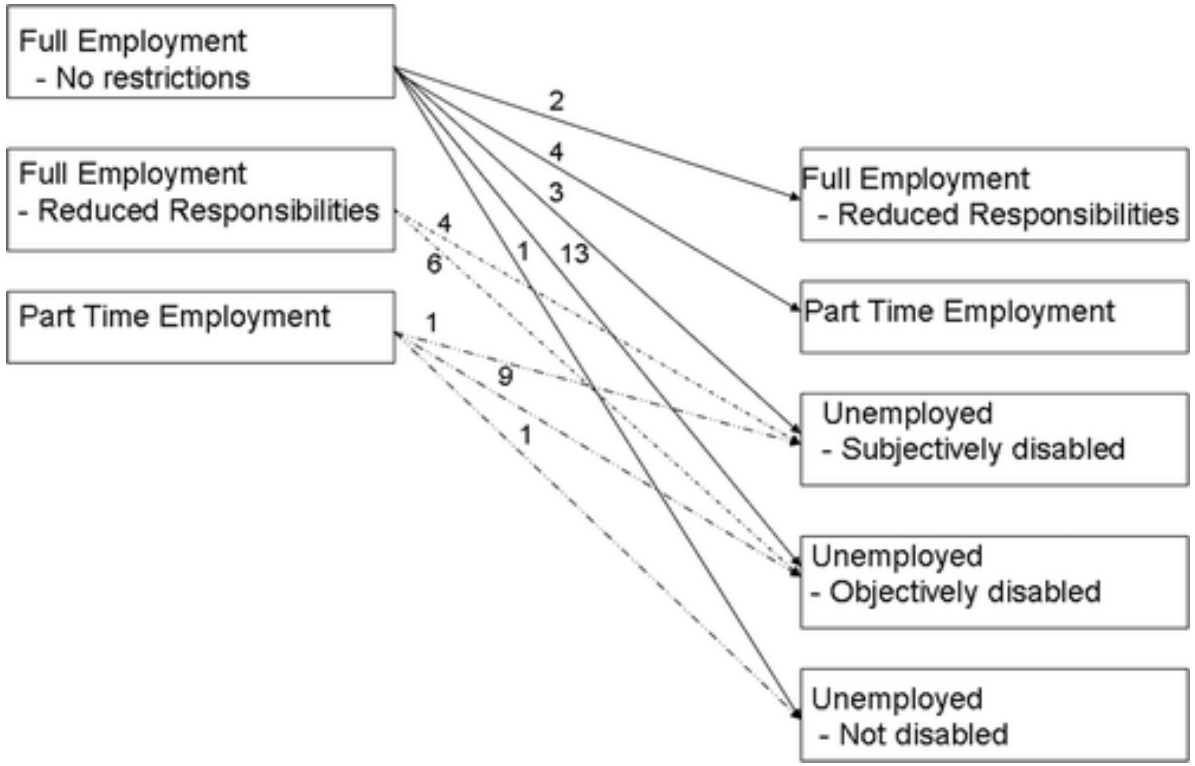
Quality of life

TABLE 4 Correlations between Mental Component Summary (MCS) and Physical Component Summary (PCS)

	MCS	PCS
EDSS	0.14 (p = .235)	−0.27 (p = .325)
9HPT	−0.06 (p = .658)	−0.07 (p = .642)
T25FW	0.14 (p = .308)	−0.51 (p < .001)*
PASAT	0.43 (p = .001)	0.17 (p = .239)
TRAIL-B	−0.40 (p = .003)	−0.07 (p = .641)
SDMT	0.46 (p = .001)	0.12 (p = .406)

*Statistically significant after Bonferroni correction (p < .001).

Employment loss



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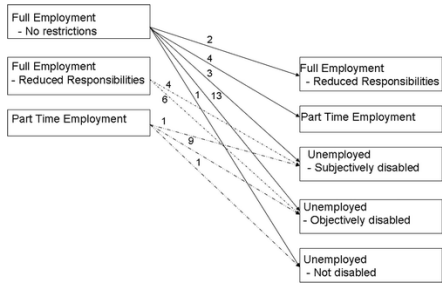


Neuropsychological test	Block 1 covariates	R^2
(*a*) CVLT2-TL	MS course$^+$, sex, age, EDSS category, number of months between assessments	41.5
SDMT	MS course$^+$, sex, age, EDSS category, number of months between assessments	50.0
(*b*) CVLT2-TL	MS course$^+$, sex, age, EDSS category, number of months between assessments	31.2
SDMT	MS course$^+$, sex, age, EDSS category, number of months between assessments	39.6

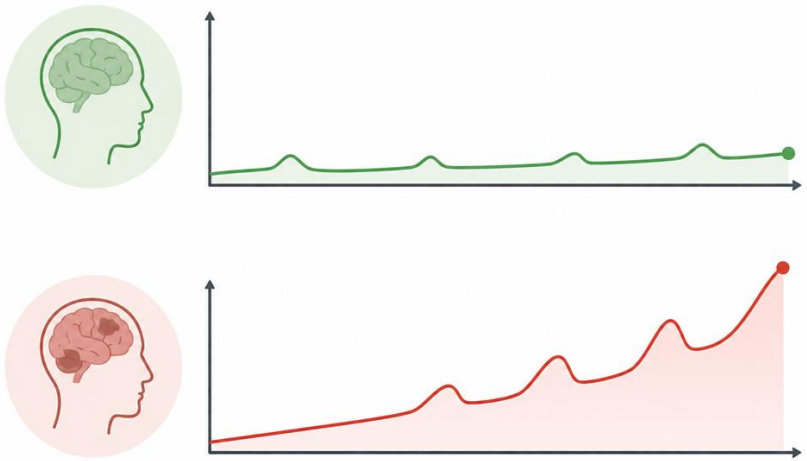
Employment loss

Table 5 Logistic regression model of stable or deteriorated employment after 2 years

From: Cognitive functioning as a predictor of employment status in relapsing-remitting multiple sclerosis: a 2-year longitudinal study

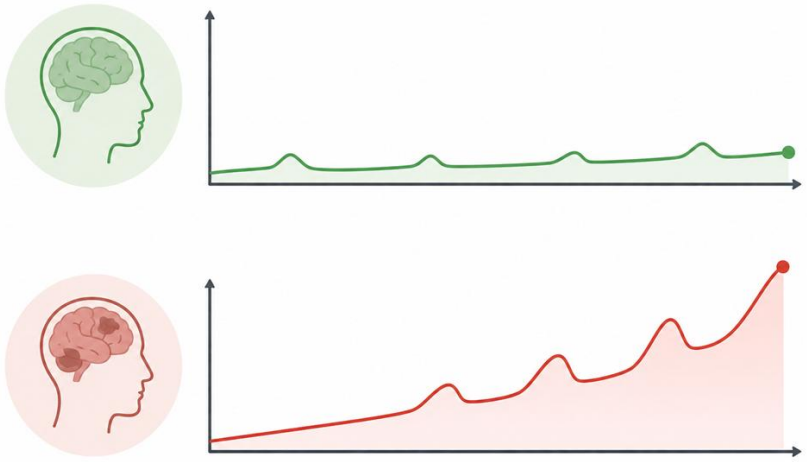
Included	*B*	S.E.	OR	[95% CI OR]	*p* value
Constant	- 3.70	0.78			$p \leq 0.001$*
Complex attention	- 0.14	0.27	0.87	[0.51–1.47]	$p = 0.60$
Executive functioning	- 1.20	0.55	0.30	[0.10–0.88]	$p = 0.03$*
Self-reported cognitive functioning	- 0.18	0.32	0.84	[0.45–1.57]	$p = 0.58$
Self-reported depression	0.36	0.29	1.43	[0.81–2.51]	$p = 0.22$
Self-reported fatigue	- 0.58	0.38	0.56	[0.27–1.18]	$p = 0.13$
Expanded Disability Status Scale	0.64	0.25	1.90	[1.16–3.10]	$p = 0.01$*

Hypothesis: Cognitive decline is a window into progressive disease



What happens to people with cognitive decline?

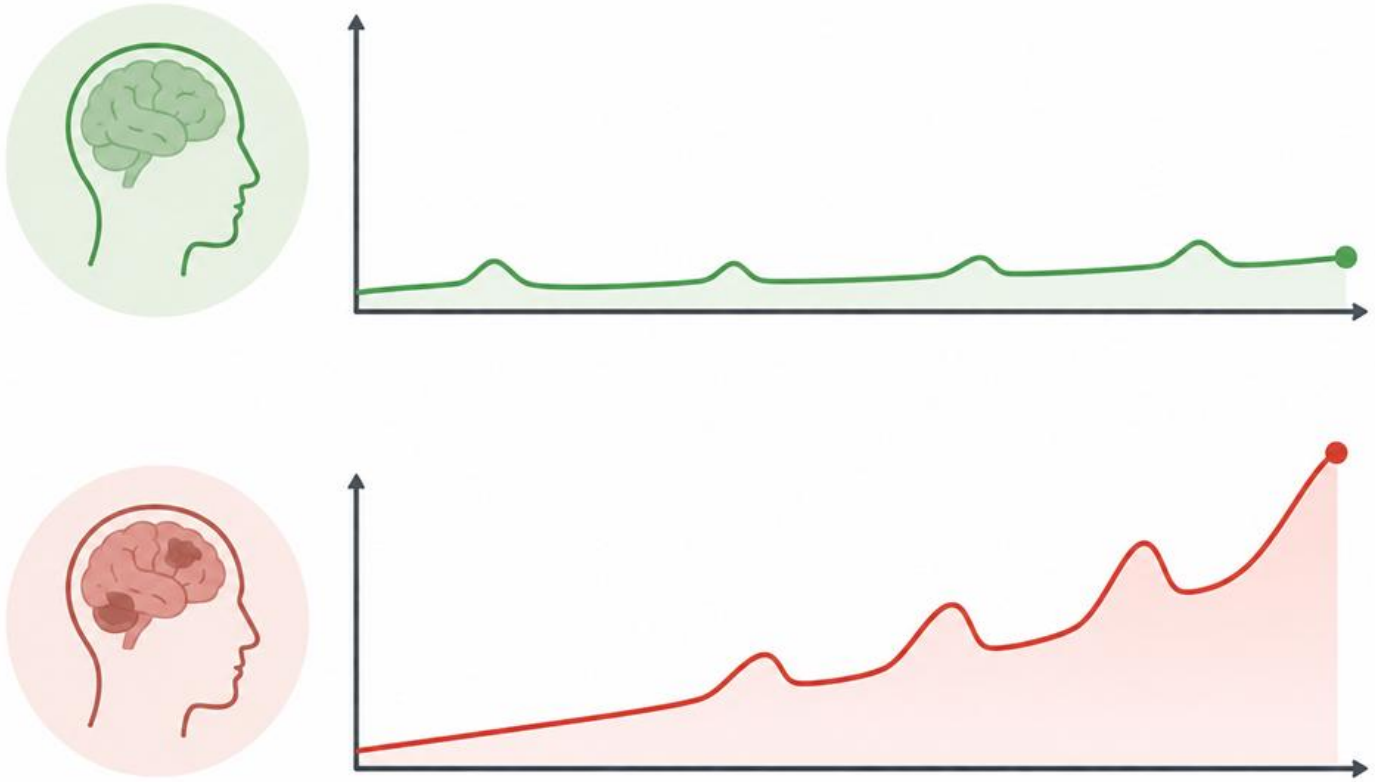
Hypothesis: Cognitive decline is a window into progressive disease



What happens to people with cognitive decline?

Faster time to disability, faster transition to SPMS, lower quality of life, loss of employment

Hypothesis: Cognitive decline is a window into progressive disease



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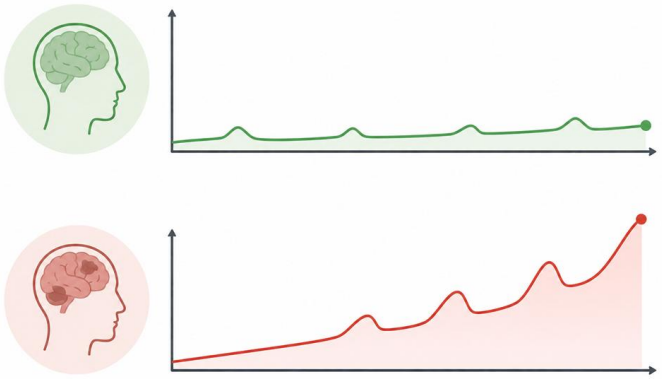

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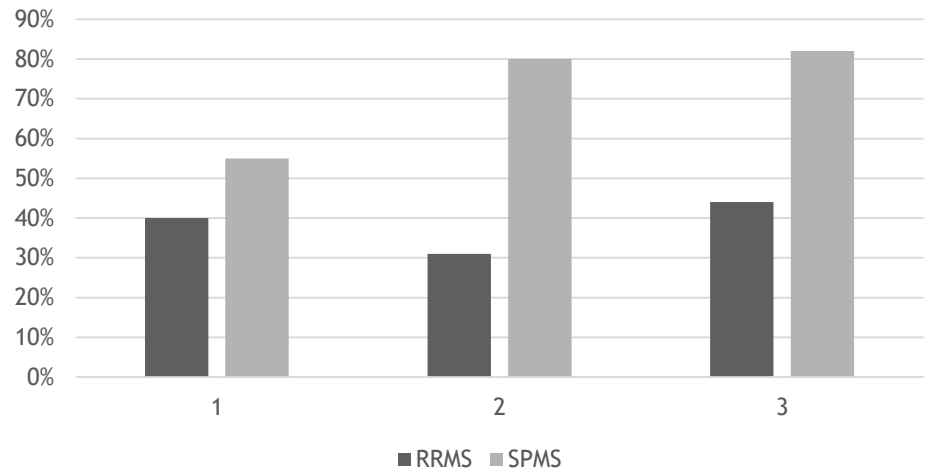

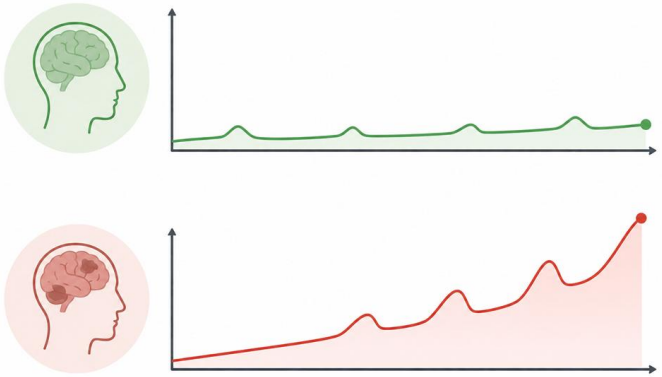

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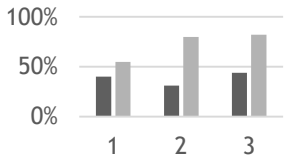

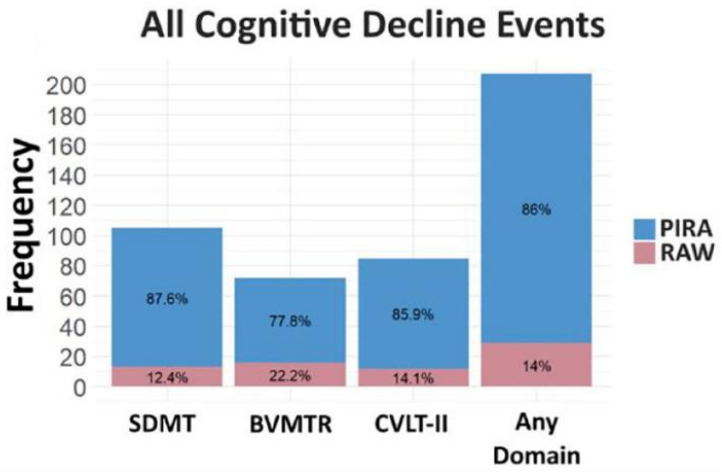

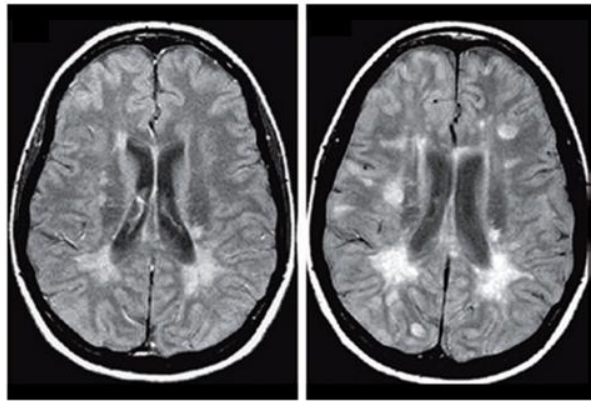

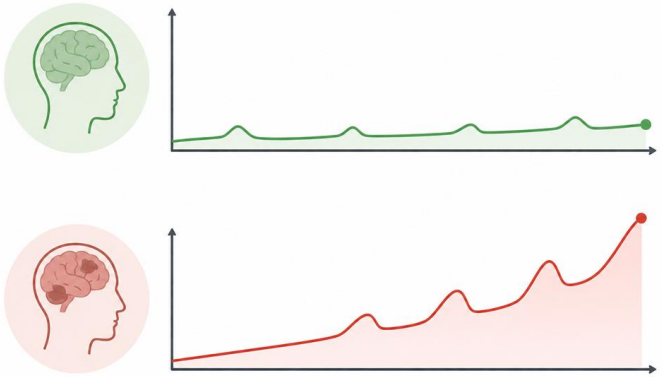

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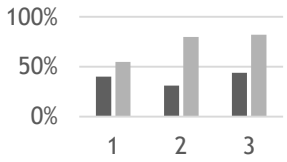

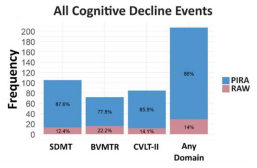

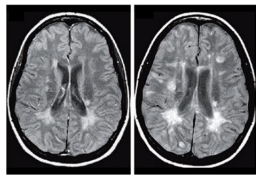

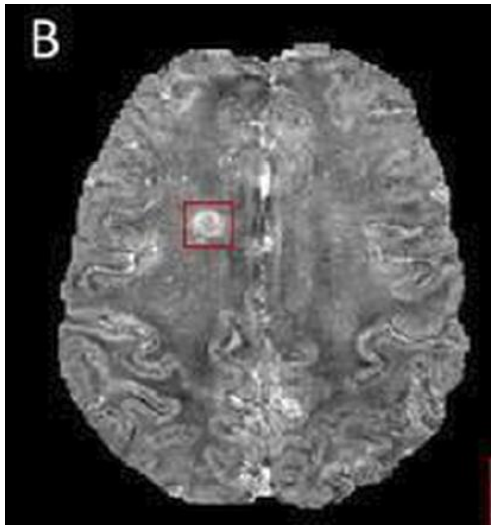

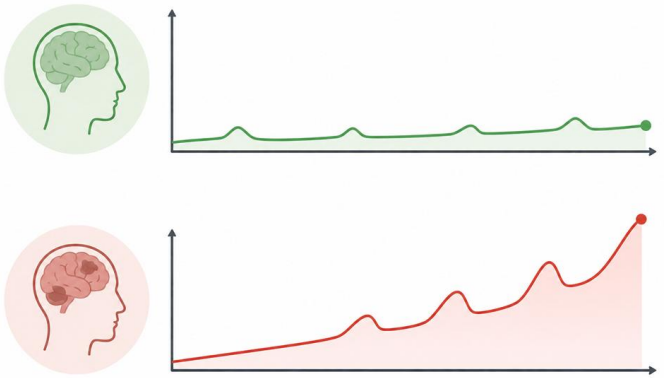

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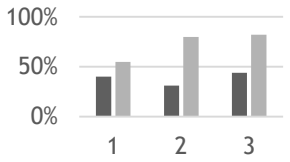

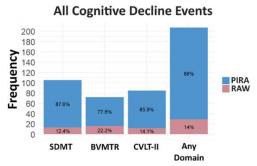

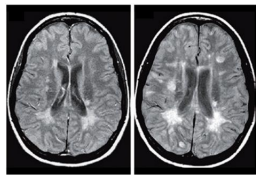

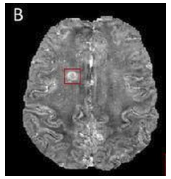

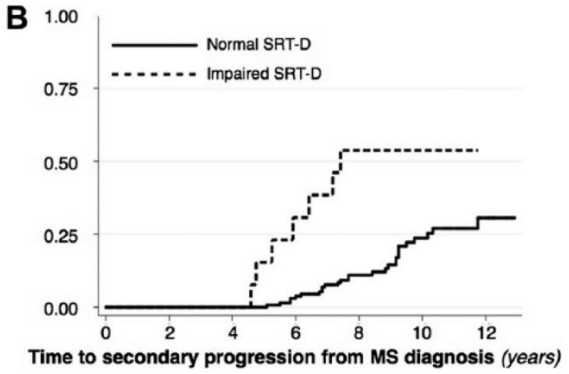

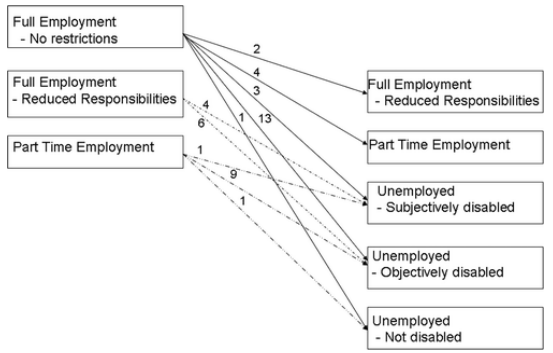

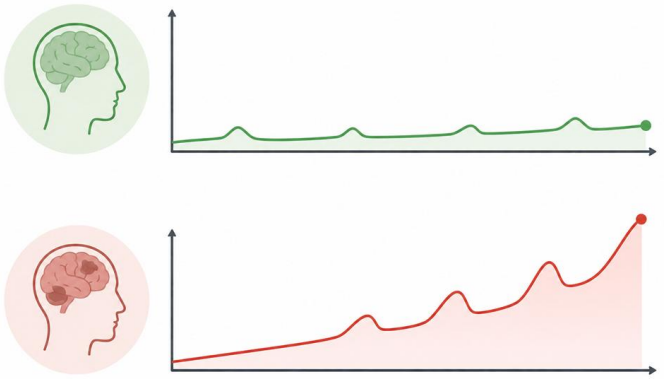

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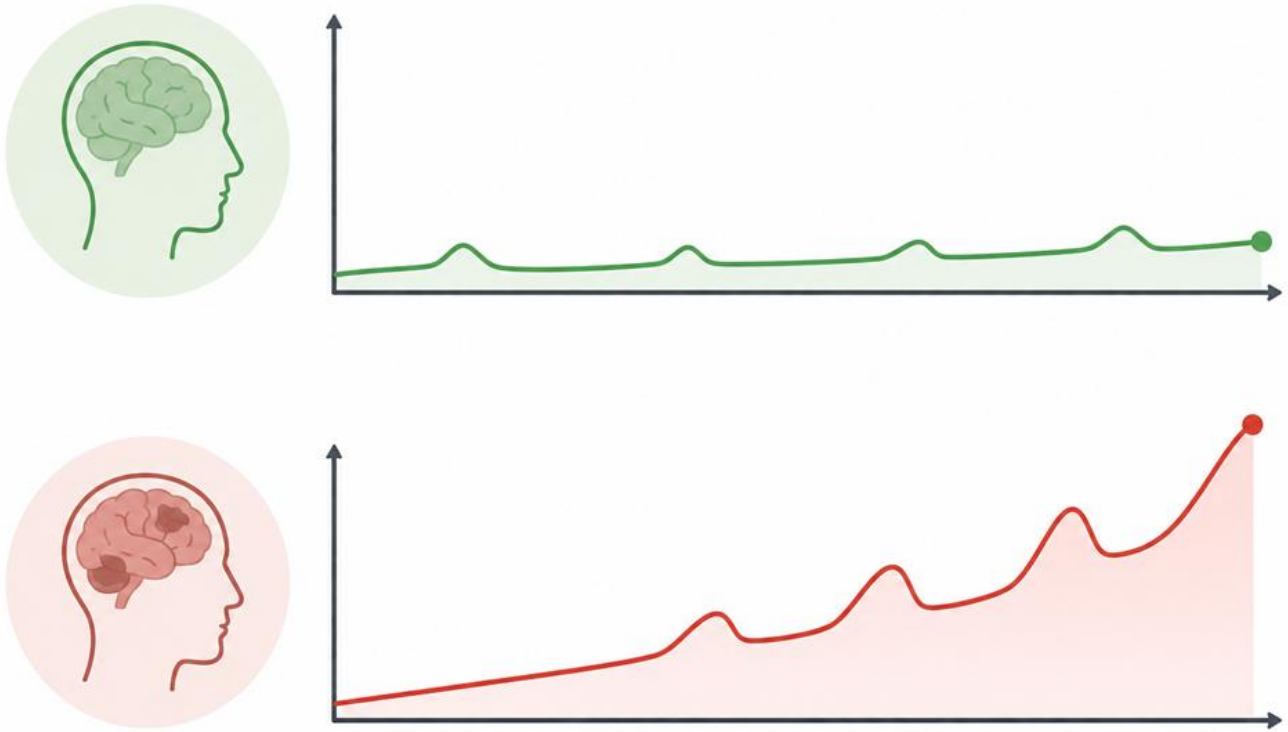

Thank you!

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Amsterdam Clinical Neuroscience

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BUFFALO NEUROIMAGING ANALYSIS CENTER

Jacobs School of Medicine and Biomedical Sciences
University at Buffalo

Slides & citations

Thoughts or questions?
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