White matter hyperintensities and cognition in Alzheimer's and Lewy body dementia- does *APOE*-ε4 modulate the association?

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Nothing to disclose

WMH and cognition

- White matter hyperintensities (WMH):
  - A marker of cerebral small vessel disease (SVD) in most cases
  - Also prevalent in cognitively healthy individuals
  - Are associated with worse(ning) cognitive abilities

Cognitive performance clinically ≠ severity of the WMH burden

Pantoni et al., 2010; Sandeman et el., 2013; Prins et al., 2015; Sarro et al., 2017

Complex association of WMH and cognition

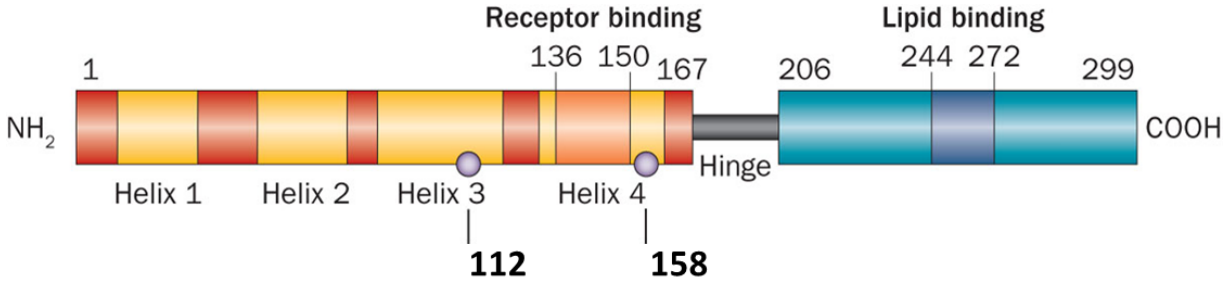
Heterogeneous etiology of WMH

- Vascular compromise and ischemia due to:
  - Cardiovascular risk factors
  - Venous collagenosis, leading to vasogenic edema
  - Cerebral Amyloid Angiopathy (CAA)
  - A combination of these

- Genetic vulnerability to neurodegeneration:
  - *APOE*-ε4

Black et al., 2009; Wardlaw et al., 2016; Keith et al., 2017

APOE-ε4 allele



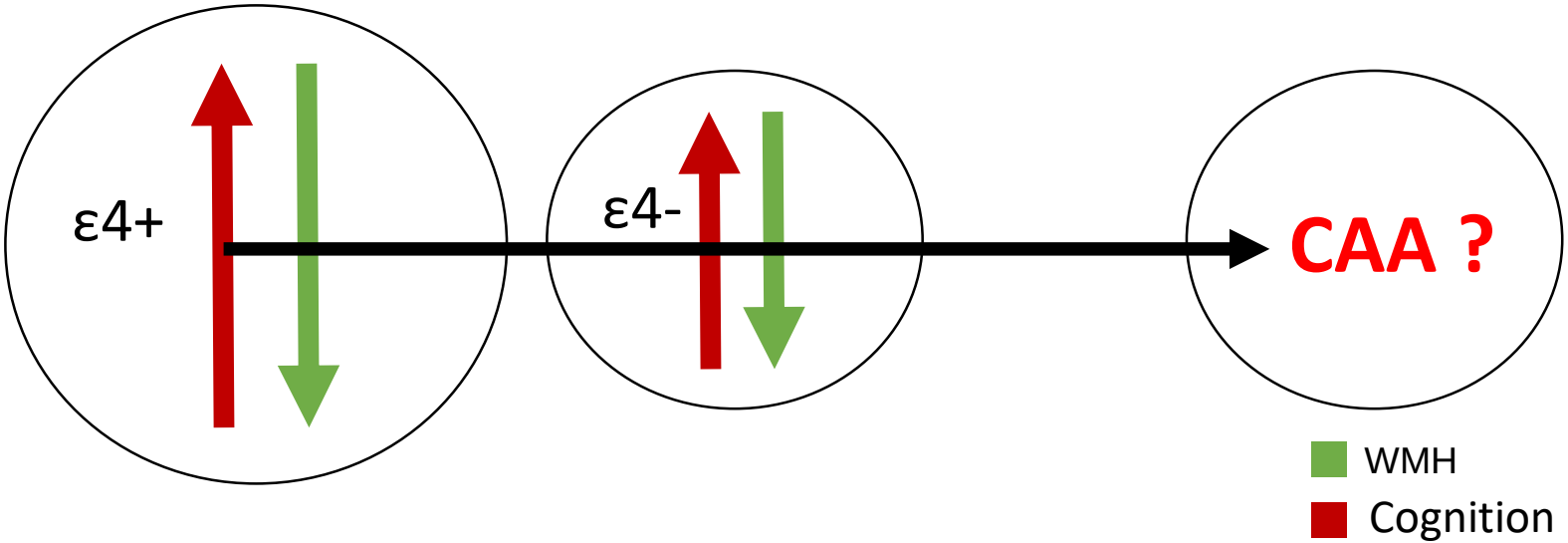
APOE ϵ2	*APOE* ϵ3	*APOE* ϵ4
Cys-112, *Cys*-158	*Cys*-112, *Arg*-158	*Arg*-112, *Arg*-158
Protective	**Neutral**	**Risk Factor**

- *APOE*-ε4 is a common risk factor for AD, DLB, mixed AD/DLB and CAA
- Role of *APOE*-ε4 as an effect modifier in the association of WMH and cognitive functions?

Schmidt et al., 1997; Tsuang et al., 2013; Schilling et al., 2013

Objective and hypotheses

- To determine if *APOE*-ε4 modulates the association between WMH and cognitive impairment in patients with Alzheimer's disease (AD) and dementia with Lewy bodies (DLB).



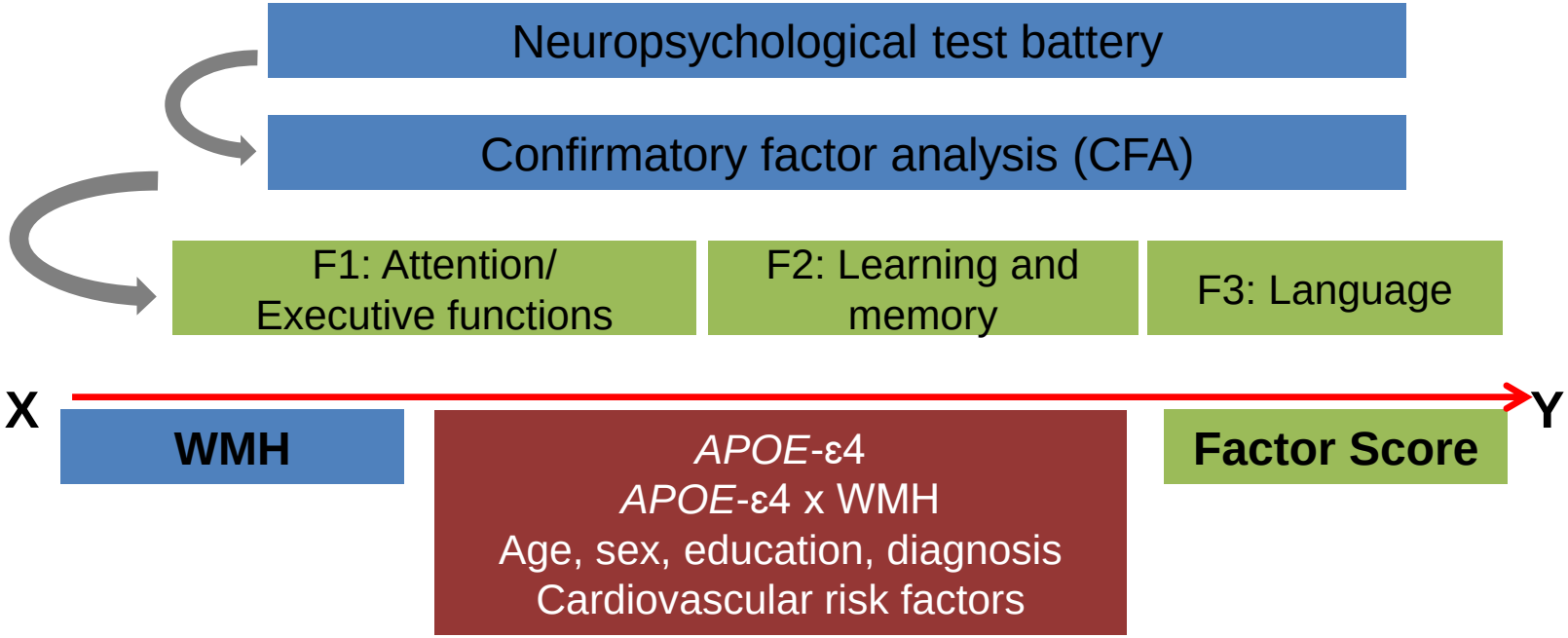
Study setting and population

- **Sunnybrook Dementia Study - SDS**
- 289 (AD=239; DLB=50) stroke-free dementia patients
- Significant WMH burden
- 34 had autopsy data

- **Alzheimer's Disease Neuroimaging Initiative - (ADNI)**
- 198 stroke-free AD patients
- Minimal WMH burden

Imaging (WMH), neuropsychological, *APOE*-ε4, and CV risk factors

Statistical analyses



Analysis repeated in:

1. *APOE*-ε4 non-carriers and carriers
2. *APOE*-ε4 heterozygotes and homozygotes
3. Excluding DLB cases, i.e. in the AD group only

Statistical analyses

- All analyses repeated in the ADNI-I sample
  - *N*=198
- Meta-analysis of estimates from SDS and ADNI-I performed
- Comparison of prevalence of Cerebral Amyloid Angiopathy in *APOE*-ε4 carriers and non-carriers
  - *n*=34

Statistical analysis-CFA (SDS)

Attention/executive function	Learning and memory	Language
▪ Forward and backward Digit Span ▪ Trails Making test A ▪ Wisconsin Card Sorting test-perseverative errors ▪ Phonemic Fluency-FAS ▪ Digit Symbol substitution Task	▪ California Verbal Learning Test (CVLT): -Total acquisition score-trials 1-5 -long delay free recall ▪ Wechsler Memory Scale: -immediate & -delayed recall	▪ Boston Naming ▪ Semantic Fluency ▪ Phonemic Fluency-FAS

SDS sample characteristics

Characteristics	Descriptives				
	Total sample N=289 (122+167)	*APOE*-ε4 non-carriers n=122	*APOE*-ε4 carriers n=167	Carriers of 1 *APOE*-ε4 allele n=130	Carriers of 2 *APOE*-ε4 alleles n=37
Age (years)	71.1 (9.6)	71.7 (10.5)	70.7 (8.9)	71.1 (9.2)	**69.4 (7.7)**
Hypertension	101 (35.0)	50 (41.0)	51 (30.1)	44 (33.8)	**6 (16.2)**
Diabetes mellitus type 2	25 (8.6)	12 (9.8)	13 (7.8)	13 (10)	**0**
Raw WMH, cm^3	7.5 (10.4)	8.1 (10.4)	7.2 (10.4)	7.5 (10.6)	**6.1 (9.5)**
TIV adjusted WMH	6.2 (8.4)	6.7 (8.8)	5.8 (8.1)	6.0 (7.9)	**5.3 (8.8)**
TIV adjusted WMH, median [IQR]	3.1 [1.1-8.1]	3.3 [1.1-8.5]	3.0 [1.0-7.8]	3.4 [1.1-8.5]	**2.2 [0.9-5.6]**

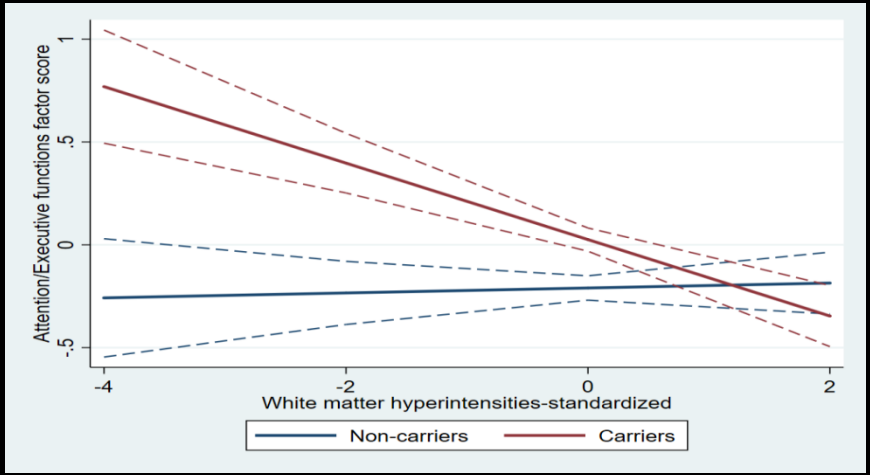
Values are means (SD), counts (percentage), or medians [inter-quartile range]

WMH and cognition by *APOE*-ε4 carrier status

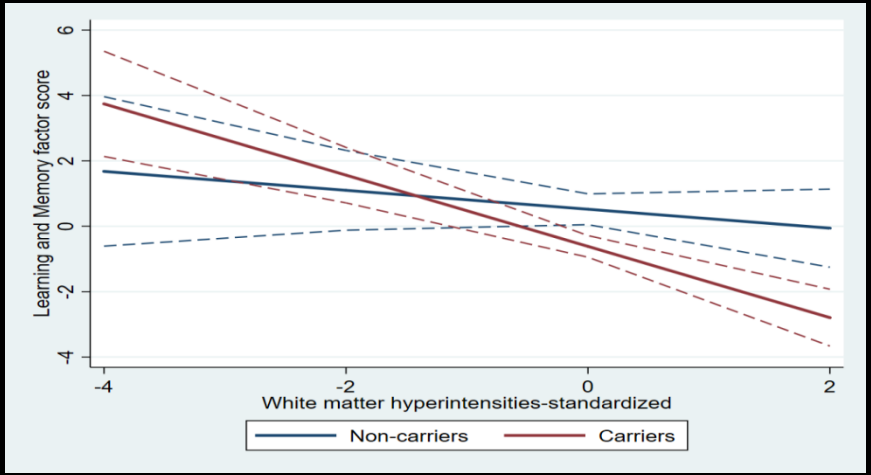
	Association between WMH and cognition			
	APOE-ε4 non-carriers, n=122		*APOE*-ε4 carriers, n=167	
Factor	Fully Adjusted Model		Fully Adjusted Model	
	Difference per SD (95% CI)	P-value	Difference per SD (95% CI)	P-value
Attention/Executive	0.01 (-0.10, 0.23)	0.895	-0.18 (-0.35, -0.01)	**0.034**
Memory	-0.28 (-1.69, 1.14)	0.699	-1.07 (-2.07, -0.08)	**0.034**
Language	0.17 (-0.53, 0.86)	0.634	-0.86 (-1.51, -0.21)	**0.009**

Models are adjusted for age, sex, education, systolic and diastolic blood pressure, diabetes mellitus type 2, smoking status, and the clinical diagnosis of dementia

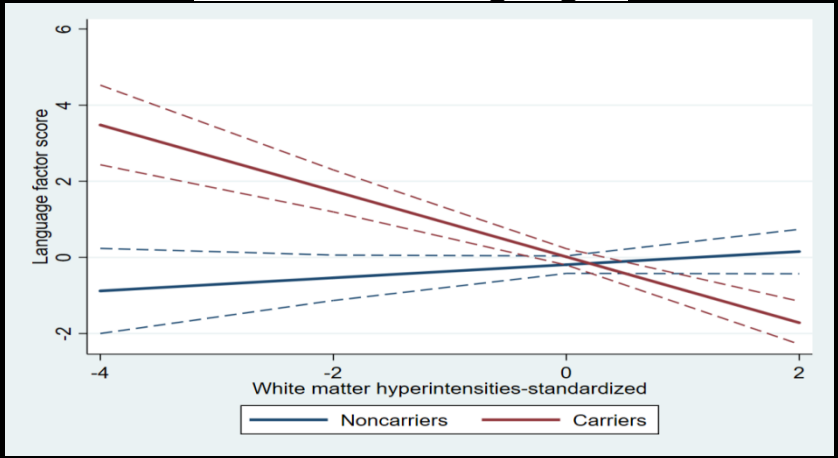
WMH and Executive functions



WMH and Memory



WMH and Language



WMH and cognition by allele dosage

	Association between WMH and cognition			
	Carriers of 1 *APOE*-ε4 allele n=130		Carriers of 2 *APOE*-ε4 alleles n=37	
Factor	Fully Adjusted Model		Fully Adjusted Model	
	Difference per SD (95% CI)	P-value	Difference per SD (95% CI)	P-value
Attention/Executive	-0.23 (-0.41, -0.04)	**0.016**	0.06 (-0.37, 0.49)	0.766
Memory	-1.39 (-2.51, -0.26)	**0.016**	0.21 (-2.21, 2.63)	0.857
Language	-0.90 (-1.59, -0.22)	**0.010**	0.34 (-2.14, 1.45)	0.698

Models are adjusted for age, sex, education, systolic and diastolic blood pressure, diabetes mellitus type 2, and smoking status

ADNI results

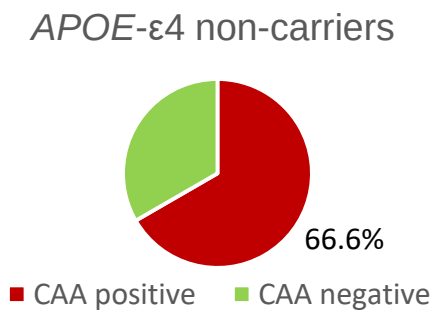
- *APOE*-ε4 carriers were younger (homozygous carriers)
- Comparable WMH in carriers and non-carriers
- Higher burden of WMH associated with worse executive function and language
- Both associations driven by heterozygous carriers

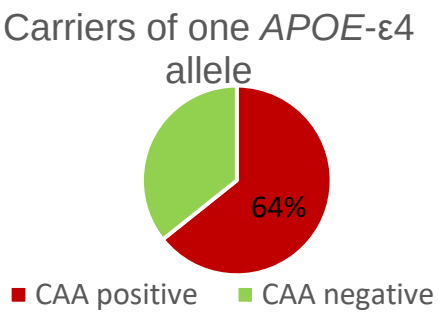
Meta-analysis of SDS and ADNI-I estimates

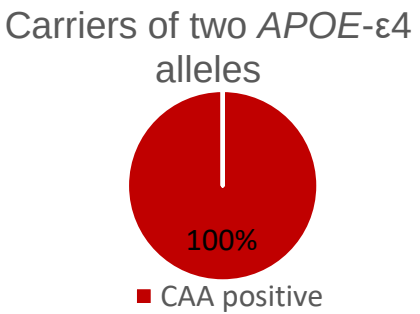
	Association between WMH and cognition			
	APOE-ε4 non-carriers, n=189		*APOE*-ε4 carriers, n=298	
Factor	Model 2		Model 2	
	Difference per SD (95% CI)	P-value	Difference per SD (95% CI)	P-value
Attention/Executive	-0.092 (-0.215, 0.031)	0.143	-0.191 (-0.271, -0.112)	**2.117×10^{-3}**
Memory	-0.626 (-1.755, 0.503)	0.277	-1.024 (-1.794, -0.254)	**0.009**
Language	-0.032 (-0.550, 0.486)	0.903	-0.749 (-1.191, -0.306)	**0.0009**

Neuropathology subsample of SDS

- WMH were indeed associated with worse cognition in *APOE*-ε4 carriers
- WMH in *APOE*-ε4 carriers might be a consequence of Cerebral Amyloid Angiopathy







Summary and comments

- *APOE*-ε4 influences the association of WMH with executive function and language in dementia patients.
- This association holds irrespective of the clinical dementia diagnosis.
- All associations were driven by the heterozygous group.
- CAA might be the likely etiology of WMH in *APOE*-ε4 carriers.
- Information on *APOE*-ε4 status may be useful to understand the relative contributions of different pathologies to an individual's unique dementia syndrome, and to guide therapy as well.

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