

Sex Differences in White Matter and Cognition in CADASIL

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Background

- CADASIL is caused by mutations in the *NOTCH3* gene, leading to progressive degeneration of vascular smooth muscle cells and disruption of cerebral small vessels
- Clinical presentation includes recurrent subcortical ischemic strokes, migraine with aura, mood disturbance, and progressive cognitive decline, often culminating in vascular dementia

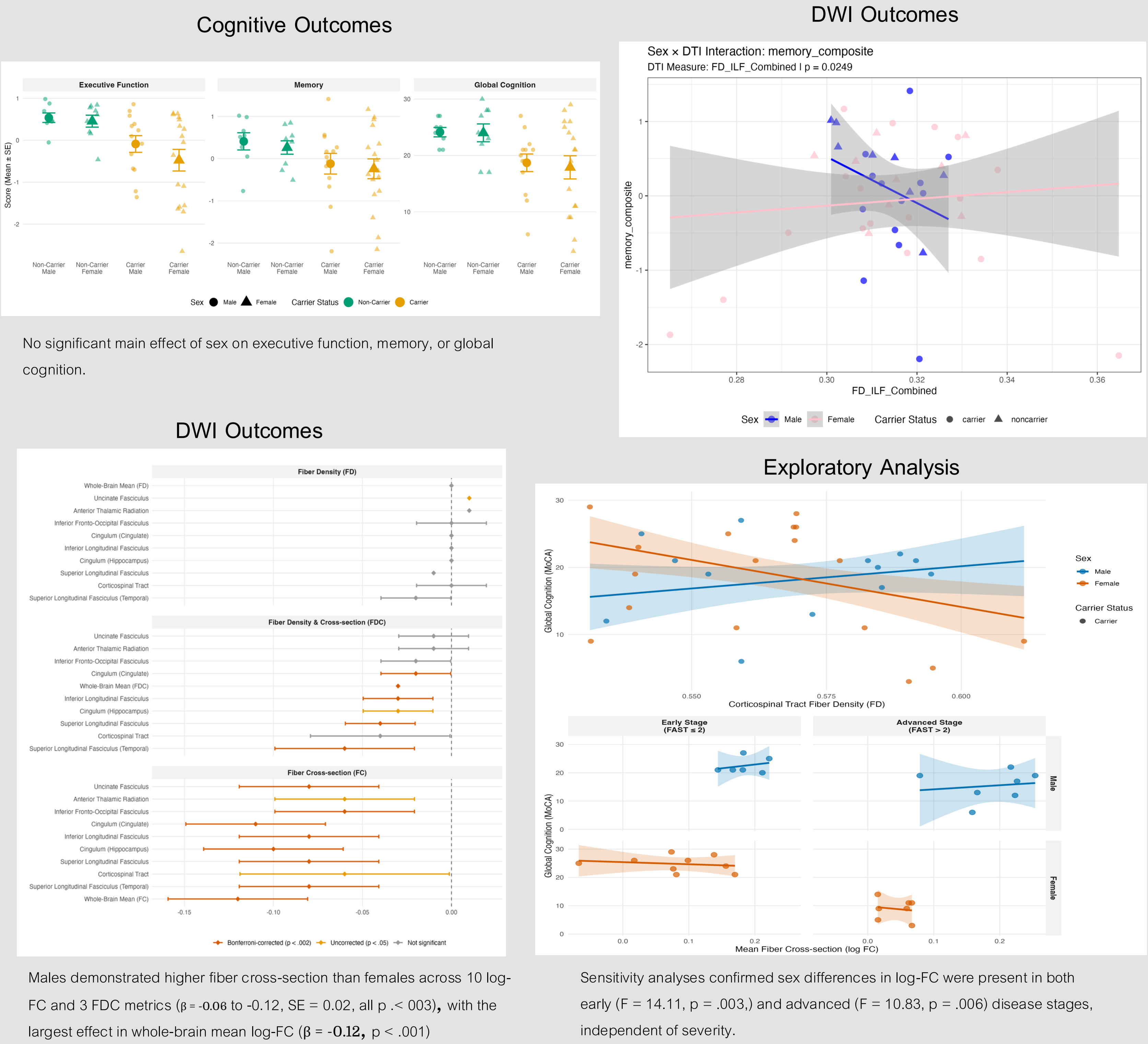
Objective

The objective of this study was to investigate whether biological sex modulates the relationship between white matter microstructure and cognition in individuals with CADASIL

Methods

- 47 participants — 30 *NOTCH3* mutation carriers, 17 non-carriers
- Fixel-based analysis quantified fiber density (FD), fiber cross-section (log-FC), and combined fiber density & cross-section (FDC) across 10 white matter tracts
- Regression models** with robust standard errors examined sex differences in white matter microstructure and cognition.
- Models adjusted for carrier status, age, and education
- Exploratory analyses:** Tested whether white matter–cognition associations were sex-dependent and varied by disease stage

Results



Sample Characteristics

	Female Carriers N = 17	Female Non-carriers N = 9	Male Carriers N = 13	Male Non-carriers N = 8	p-value
Age (years)	51.24 (11.27)	49.44 (11.48)	48.00 (7.07)	45.88 (11.14)	0.6
Education (years)	9.82 (5.46)	12.33 (4.72)	10.00 (3.11)	11.00 (3.07)	0.5
FAST score	3.12 (2.23)	1.67 (0.71)	2.92 (1.85)	1.50 (0.53)	0.064
Executive function composite	-0.47 (1.06)	0.46 (0.43)	-0.09 (0.72)	0.54 (0.32)	0.009
Memory Composite	-0.24 (0.97)	0.26 (0.48)	-0.12 (0.88)	0.41 (0.58)	0.2

Conclusions

- Males demonstrate consistently higher white matter fiber cross-section than females across multiple tract systems in CADASIL
- Findings suggest sex-specific compensatory mechanisms that may confer greater cognitive resilience in females, despite their increased structural vulnerability
- Future work should examine the biological mechanisms underlying sex-specific compensatory processes

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