

# Microstructural white matter alterations correlate with cerebral amyloid angiopathy burden and cognition

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## Background

Cerebral amyloid angiopathy (CAA) is a common small vessel disease characterized by amyloid deposition in the cortical blood vessels. Epidemiological and autopsy studies show that CAA is an independent contributor to dementia. We do not know through which mechanisms CAA affects cognition. Autopsy studies show small ischemic and hemorrhagic tissue injury in the white matter of patients with CAA. These microstructural white matter alterations may hamper the communication between brain regions and thereby impact cognitive functioning.

Hypotheses: 1) Patients with CAA show microstructural alterations in white matter connections compared to controls.

2) CAA-related white matter alterations mediate the association between vascular amyloid burden and cognitive impairment.

## Methods

**Subjects:** 20 non-demented patients with probable CAA without ICH (mean age:  $71\pm6$ ) and 25 agematched non-demented control participants.

**MRI processing:** All subjects underwent a 1.5T MRI scan, including a T1, FLAIR, and diffusion weighted sequence. Whole-brain fiber tractography reconstructions were registered to a standard gray matter template (AAL) and parcellated into tracts projecting onto the frontal, parietal, occipital, and temporal lobes. The mean fractional anisotropy (FA) and mean diffusivity (MD) were averaged across all tracts of each lobe (Figure 1).

**PET:** 14 patients also had a Pittsburg compound B (PiB) PET scan. PiB retention was expressed as the standardized uptake value (SUV) within each lobe, with the cerebellum as reference region.

**Cognition:** Tests of memory, executive functioning and information processing speed were obtained for all CAA patients.



Analyses: correlations were adjusted for age, sex, education, and secondarily for white matter hyperintensity (WMH) volume.

## Results



White Matter FA - Cognition



Figure 2. Correlation between microstructural white matter tract alterations in the occipital lobe (FA occipitalto-global ratio) and a) executive functioning, b) memory, adjusted for age and education. No relationship was observed with processing speed (p=0.677).

#### Table 1. Between-group difference in FA and MD between patients with CAA and controls

#### FA Frontal Occipita Tempor Parietal

### MD

Frontal Occipita Tempora Parietal

Mean  $\pm$  SD. MD = 10<sup>-3</sup> \*p<0.001





low occipital FA (right).

Figure 1. a) Whole brain fiber tract reconstructions are parcellated into 90 regions based on a standard gray matter template. b) The mean FA of tracts projecting onto each lobe are averaged in order to obtain one value per lobe. Green=frontal, red=occipital, purple=temporal, yellow=parietal.

	CAA	Controls
	$0.28 \pm 0.02$	0.30 ±0.02*
al	$0.29 \pm 0.02$	0.33 ±0.02*
al	$0.28 \pm 0.01$	$0.30 \pm 0.02^{*}$
	$0.31 \pm 0.01$	$0.32 \pm 0.02^{*}$
	CAA	Controls
	$1.01 \pm 0.05$	0.96 ±0.05*
al	$1.01 \pm 0.05$ $0.29 \pm 0.02$	0.96 ±0.05* 0.33 ±0.02*
al al	$1.01 \pm 0.05$ $0.29 \pm 0.02$ $1.03 \pm 0.06$	0.96 ±0.05* 0.33 ±0.02* 0.97 ±0.05*
al al	$1.01 \pm 0.05$ $0.29 \pm 0.02$ $1.03 \pm 0.06$ $1.02 \pm 0.05$	$0.96 \pm 0.05^{*}$ $0.33 \pm 0.02^{*}$ $0.97 \pm 0.05^{*}$ $0.96 \pm 0.05^{*}$

### White Matter FA – Amyloid Load

Occipital PiB retention (SUV)

Figure 3. A) Correlation between occipital FA ratio and Occipital PiB retention. B) PiB retention maps indicating low occipital amyloid load in a patient with relatively high occipital FA (left) and a patient with high occipital amyloid load in a patient with relatively

## Results

1) Patients with CAA show microstructural by a decrease in FA and increase in MD compared to controls (p < 0.01). occipital lobe, in line with the known posterior predominance of CAA pathology (Table 1).

2) Microstructural white matter alterations in the occipital lobe are correlated with poor executive functioning (p=0.007; Figure 2) and increased occipital amyloid load (p=0.037; Figure 3), independent of WMH load.

3) The association between occipital amyloid load and executive functioning (Beta (95% CI): -0.48 (-2.77 to -0.07)) was significantly attenuated after adjusting for occipital white matter alterations (adjusted Beta: -0.29 (-2.48 to 0.76); Figure 4).



## Conclusions

- widespread loss of white matter connectivity.
- the relationship between vascular amyloid burden and executive functioning in patients with CAA.
- Vascular amyloid may contribute to cognitive impairment through even in patients without ICH.



# alterations in white matter connections, reflected The alterations in FA were most pronounced in the

## Patients with CAA (without ICH) show

White matter connectivity loss mediated

microstructural white matter alterations

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