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# **Dissecting Neurocognitive Aging:**

*Dopaminergic Decline, Cerebral Small Vessel  
Disease, and Inflammation*

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## **Academic dissertation**

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## Abstract

**Background:** Life expectancy is increasing, leading to a growing number of individuals affected by cognitive impairments. However, cognitive aging varies greatly: some individuals experience substantial decline, while others retain their cognitive abilities well into old age. Three early brain changes associated with cognitive decline are reduced dopamine function, cerebral small vessel disease (CSVD), and inflammation. Key knowledge gaps remain regarding how these processes are intertwined in healthy cognitive aging and whether some of these play a particularly important role in driving individual differences in cognition.

**Aim:** To examine the associations among dopamine decline, CSVD, and inflammation in healthy older adults, and the respective links between these processes and cognition. Sex differences are considered.

**Methods:** Data were drawn from two studies, referred to as COBRA and InflammAge. The COBRA study included data from 81 healthy adults (45% women) aged 64–68 years. Of these, 129 underwent a five-year follow-up. Dopamine D<sub>2</sub>-like receptors (DRD<sub>2</sub>) in the brain were measured using <sup>11</sup>C-raclopride and positron emission tomography (PET). Peripheral inflammation was estimated via two DNA methylation-based inflammation scores. The InflammAge study has a cross-sectional design and included 55 older adults (60–79 years, 51% women). Dopamine transporter (DAT) availability was estimated with <sup>18</sup>F-FE-PE<sub>2</sub>I/PET, and inflammation (specifically astrocyte reactivity) via <sup>11</sup>C-L-deprenyl-D<sub>2</sub>/PET. The same cognitive test battery, magnetic resonance imaging (MRI) scanner, and protocols were used in the two studies. MRI was employed to evaluate markers of CSVD (lesions, lacunes, and perivascular space enlargement), brain volumes, and cerebral perfusion. Health-related factors (hypertension, BMI, and hyperlipidaemia) were also mapped.

**Results:** CSVD was a stable predictor of individual differences in dopaminergic integrity and emerged as a potential predictor of within-person dopamine decline rate over time. Cross-sectional analyses in both samples showed that higher white-matter lesion volumes were associated with reduced DRD<sub>2</sub> and DAT availability. Longitudinal analyses in COBRA demonstrated that individuals with a higher burden of white matter lesions and lacunes showed the fastest DRD<sub>2</sub> decline, while those spared of these manifestations were also spared of DRD<sub>2</sub> decline. Hypertension was associated with lower DAT availability as well as faster DRD<sub>2</sub> decline. Peripheral inflammation was also associated with individual differences in DRD<sub>2</sub> availability, but only in men. As opposed to CSVD, peripheral inflammation did not predict the degree of prospective DRD<sub>2</sub> decline over 5 years. Astrocyte reactivity (generally considered a marker of neuroinflammation) was higher at older ages. Contrary to expectations, it was positively associated with DAT availability and negatively with CSVD. Regarding cognition, higher CSVD severity was associated with a trend for faster declining processing speed. When modelled together, DAT availability was the strongest and most significant predictor of general cognition. Sex differences were found for links between DRD<sub>2</sub> and peripheral inflammation scores, but overall, findings were similar for men and women.

**Conclusion:** Dopaminergic integrity is key for several cognitive functions and is important to preserve in aging. Reduction of CSVD severity may serve as one viable intervention approach. The relationship between chronic inflammation and dopamine integrity remains inconclusive and should be further investigated in future work.

**Keywords:** aging, cognition, positron emission tomography, dopamine, cerebral small-vessel disease,, inflammation

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