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BIOMARKERS

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NEUROIMAGING

# Simvastatin restores neurovascular coupling and cognition in APP mice

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## Abstract

**Background:** Alzheimer's disease (AD) is the leading cause of dementia worldwide and vascular dysfunction represents one of the first abnormalities in AD spectrum. Brain imaging techniques that use changes in hemodynamic signals to measure alterations in neurovascular coupling (NVC) have proven useful for early detection of cognitive deterioration. Pharmacological interventions targeting vascular risk factors, including simvastatin (SV), show promise in preventing dementia. To better understand the changes in brain NVC through the AD progression, we measured whisker-evoked changes in hemodynamics signals and cognition longitudinally in a transgenic mouse model of AD (APP-J20 mice) and wild-type (WT) mice treated or not with SV.

**Method:** Hemodynamic signals following whisker stimulation (8Hz, 10 sec) were recorded longitudinally (3-8 months) in anesthetized (ketamine/xylazine) and awake WT and APP mice, implanted with full cranial window, using optical imaging of intrinsic signals (OIS) (525, 590, and 625 nm), together with cognitive testing. The effects of SV treatment were evaluated after 2.5 and 5 months.

**Result:** APP mice displayed significant NVC deficits compared to WT littermates in both awake and anesthetized conditions. The anesthesia worsened the whisker-evoked hemodynamic responses in APP mice. These changes were detected at early stage of the disease (3 months-old), before the appearance of cognitive impairment (5.5 months-old). SV treatment totally restored NVC and cognitive function after 5 months of treatment in APP mice.

**Conclusion:** The longitudinal analysis of NVC supports their relevance as translational measures for early diagnosis. Our data with SV indicate that preventive cardiovascular strategy for individuals at risk of developing AD may bear promise in protecting brain function.

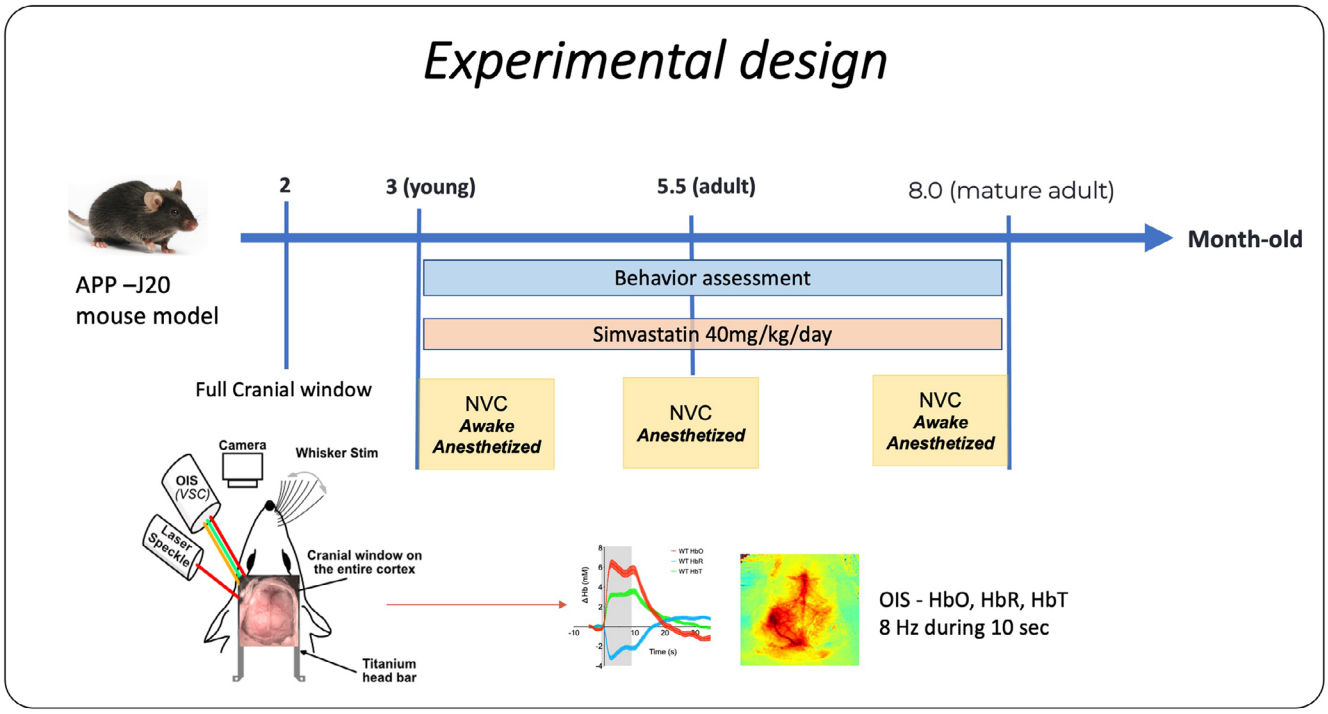


**Figure 1:** Representation of whisker-evoked NVC assessment using optical intrinsic imaging (OIS): Two months-old mice were chronically implanted with a full cranial window on an intact skull overlaying the entire cerebral cortex and covered with a glass coverslip, and a titanium head bar was fixed with dental cement. Awake or anesthetized mice were fixed through head bars and placed parallel to a charge-coupled device (CCD) camera with a full resolution of 1024 × 1024 pixels to the imaging system (OIS200 from LabeoTech, Montreal, QC, Canada). Whisker-evoked (NVC) changes in oxy-, deoxy- and total hemoglobin (HbO, HbR and HbT, respectively) were measured with light-emitting diodes (LEDs, 525, 590, and 625 nm). Each recording session consisted of 1 acquisition of whisker-evoked stimulation (8 Hz, 10 s right whisker stimulation followed by an inter-stimulation period of 40 s, repeated 7 times), using a piezo actuator (Q220-A4-303YB, MA, USA). **O**ne month after window implantation, WT and APP-J20 mice were submitted to behavioral tests and exposed to the first imaging recording session. OIS recordings were performed longitudinally first in awake mice (3 and 8 months-old) and, the following week, in anesthetized mice (ketamine/xylazine, 85/15 mg/kg, i.m.) (3, 5.5 and 8.0 months-old). SV administration began at 3.0 months of age and continued for 5.0 months (endpoint at 8.0 months-old). The behavioral tests were performed at baseline (3 months-old), and after 2.5 and 5 months of SV treatment (5.5 and 8 months-old mice, respectively).

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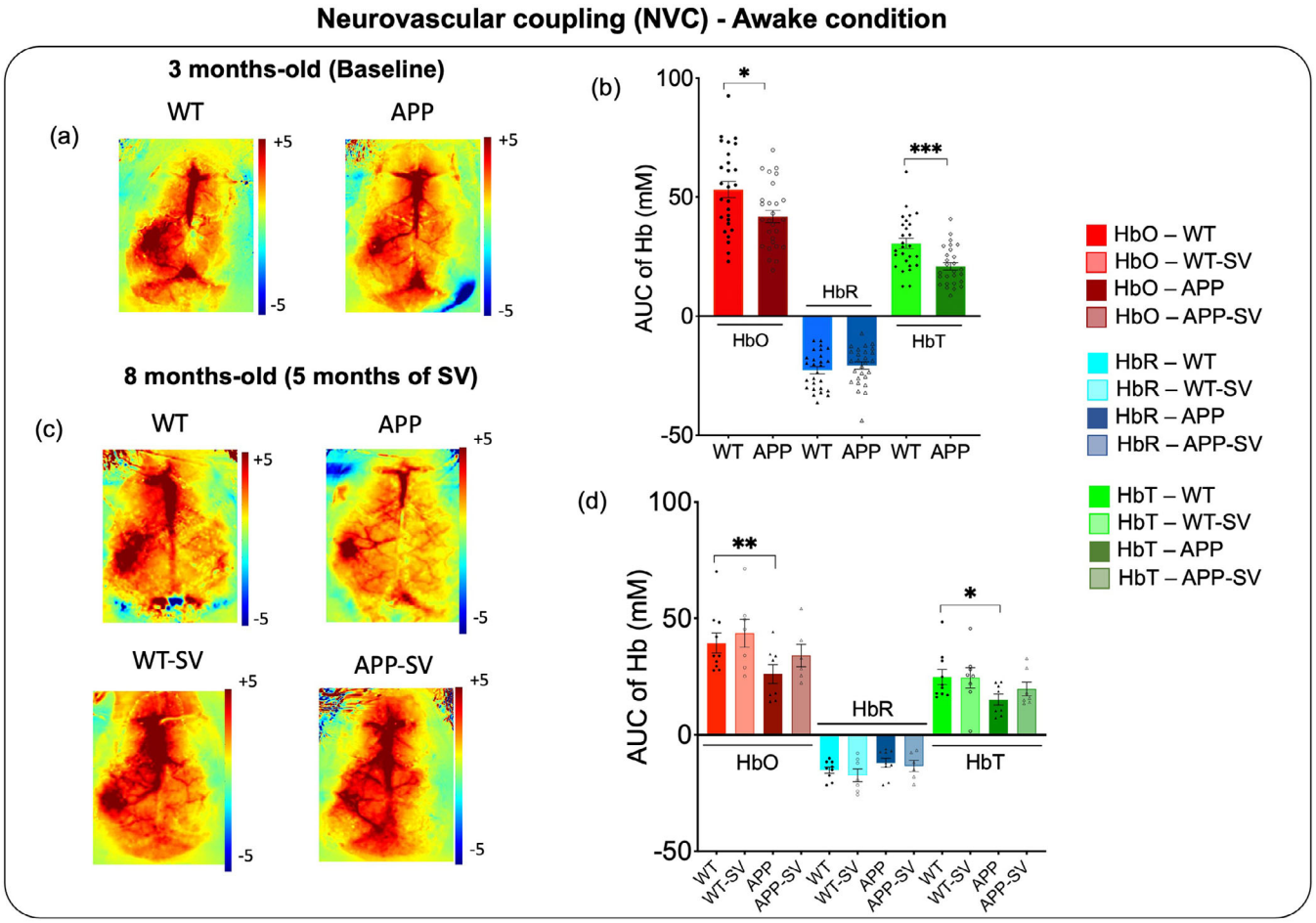


**Figure 2:** Whisker-evoked NVC response in WT and APP mice (3 (a) and 8 months-old (c)). Representative changes in oxy-, deoxy- and total hemoglobin (red, HbO; blue HbR; green, HBT, respectively; 3 (b) and 8 months-old (d)) after whisker in WT and APP mice, treated or not with SV. APP mice displayed significant decreases in HbO and HbT responses (b and d), and the impaired response was rescued by 5 months of SV treatment (d). Student's t-test was used for two groups comparison (WT and APP, 3 months-old), and two-way ANOVA (genotype and treatment as factors) was performed to compare multiple groups followed by a Tukey post-hoc multiple comparison test. *p<0.05, **p<0.01, ***p<0.001.