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Functional connectivity changes through Alzheimer's disease continuum: disease onset, progression, and response to therapy

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Abstract

Background: Hemodynamic signals are the basis of functional brain imaging techniques, such as fMRI and NIRS, and are often used to infer changes in resting-state functional connectivity (RSFC) in Alzheimer's disease (AD) and other dementias. Increasing evidence suggests that disruption of neuronal circuits has been associated with the AD continuum and may precede changes in Ab and tau biomarkers, neurodegeneration, and cognitive impairment. To better understand the changes in brain RSFC through the AD spectrum, we use hemodynamic signals to detect disease onset, progression, and response to therapy in a mouse model of AD.

Method: Hemodynamic signals were recorded longitudinally (3-8 months) in anesthetized (ketamine/xylazine) and awake WT and APP (J20) mice, implanted with full cranial window, using optical imaging of intrinsic signals (OIS), together with cognitive testing. Seed-based functional connectivity maps were generated for the bilateral connectivity (BC) and RSFC analyses. The effects of simvastatin (SV), a cardiovascular medicine that has shown promise in preventing dementia, were evaluated after 2.5 and 5 months.

Result: Alterations in RSFC in brain regions associated with the sensory-motor (SM) and default-mode (DMN) networks were detected before the appearance of cognitive impairment. 3-month-old APP mice showed consistent decrease in bilateral functional connectivity (BC) in motor (M) and cingulate (C) cortical regions and a severe hypoconnectivity within the SM network in the RSFC analysis. Throughout the course of the disease, RSFC analysis in APP mice uncovered an early hyperconnectivity within the DMN, mainly driven by the frontal (F) cortex, followed by a later hypoconnectivity stage. At late stage of the disease (8-months-old), a decreased BC in somatosensory (S) cortex was detected. SV treatment prevented the aberrant increases in DMN FC in midlife APP mice, improved the BC of S cortex, while concurrently sparing cognitive function.

Conclusion: Our results demonstrated that hemodynamic signals measured by OIS at the cortical level successfully detected RSFC disruptions preceding dementia in APP mice and allowed to capture SV therapeutic benefits. These findings suggest that OIS,

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or its human equivalent NIRS, could contribute to effectively diagnosing the early stages of AD, leading to promising intervention opportunities.

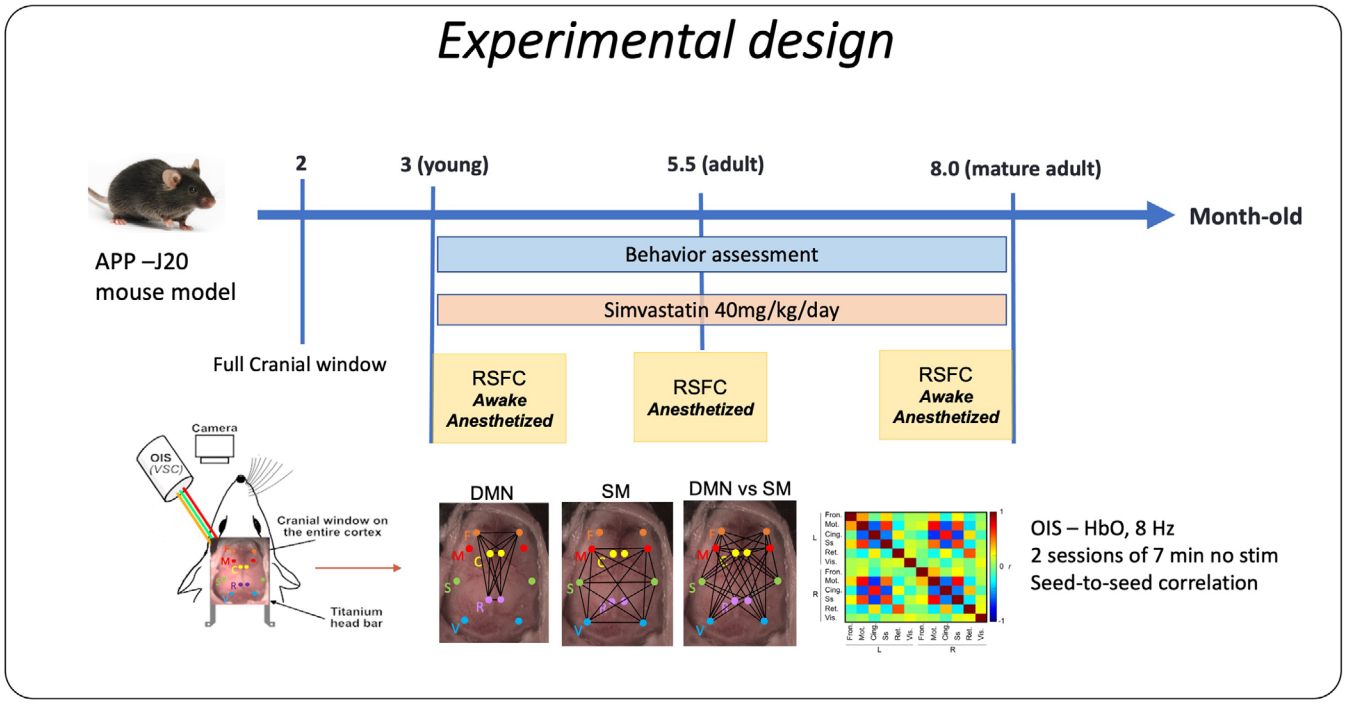

Figure 1: Representation RSFC assessment using optical intrinsic imaging (OIS): Two months-old mice were chronically implanted with a full cranial window on an intact skull overlaying the entire cerebral cortex and covered with a glass coverslip, and a titanium head bar was fixed with dental cement. 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). Spontaneous (RSFC) changes in oxyhemoglobin (HbO) were measured with light-emitting diodes (LEDs, 525, 590, and 625 nm). Each recording session consisted of 2 acquisitions of resting state of 7 min each (8 Hz). One 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.

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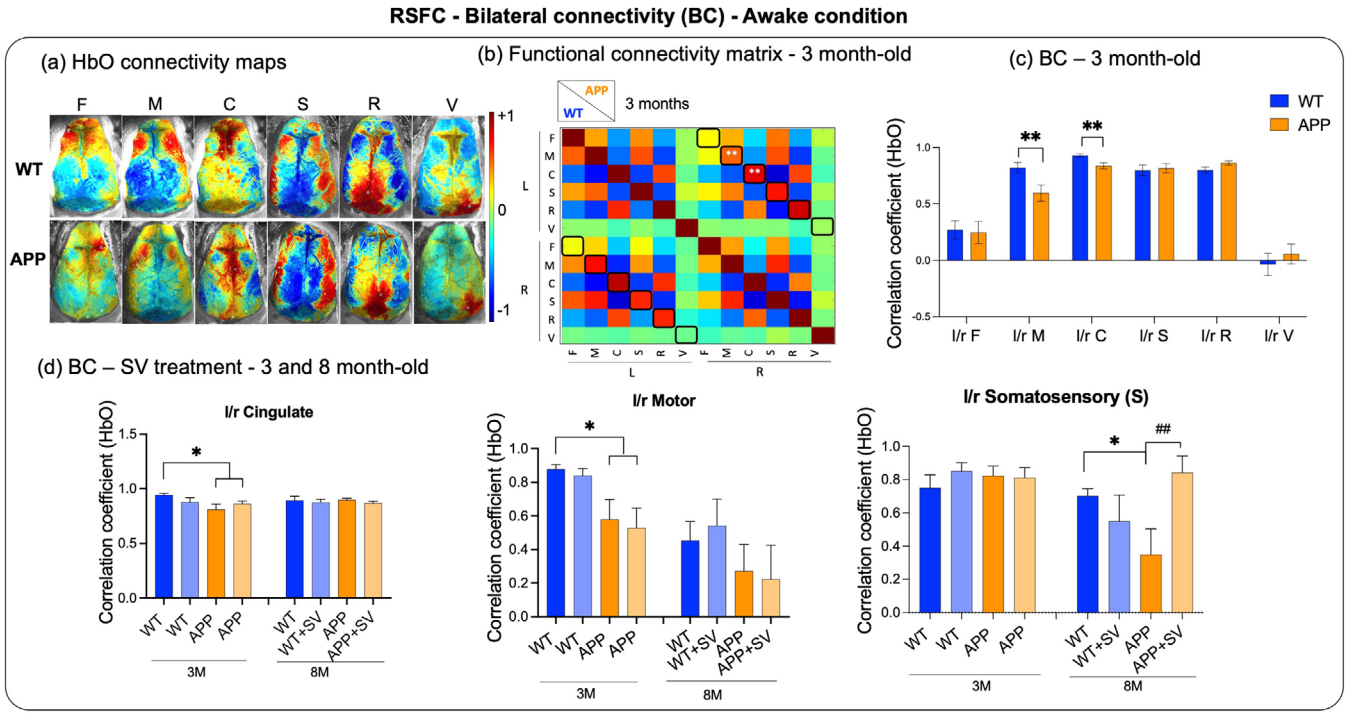

Figure 2: Resting-state functional connectivity (RSFC) in awake WT and APP mice. HbO connectivity maps (a) and functional connectivity matrixes at 3 months-old mice (b), using regions of interest (seeds) corresponding to the left and right frontal (F), cingulate (C), motor (M), somatosensory (S), retrosplenial (R) and visual (V) cortices. Bilateral functional connectivity (BC) measured at 3 months-old WT and APP mice (c), and longitudinally at 3 and 8 months-old (d), in animals treated or not with Simvastatin (SV). Student's t-test was used to determine significance between WT and APP mice at 3 months, and two-way ANOVA (genotype and treatment as factors) with repeated measures was performed to compare multiple groups followed by a Fisher's LSD post-hoc multiple comparison test. *p<0.05, **p<0.01, ***p<0.001.

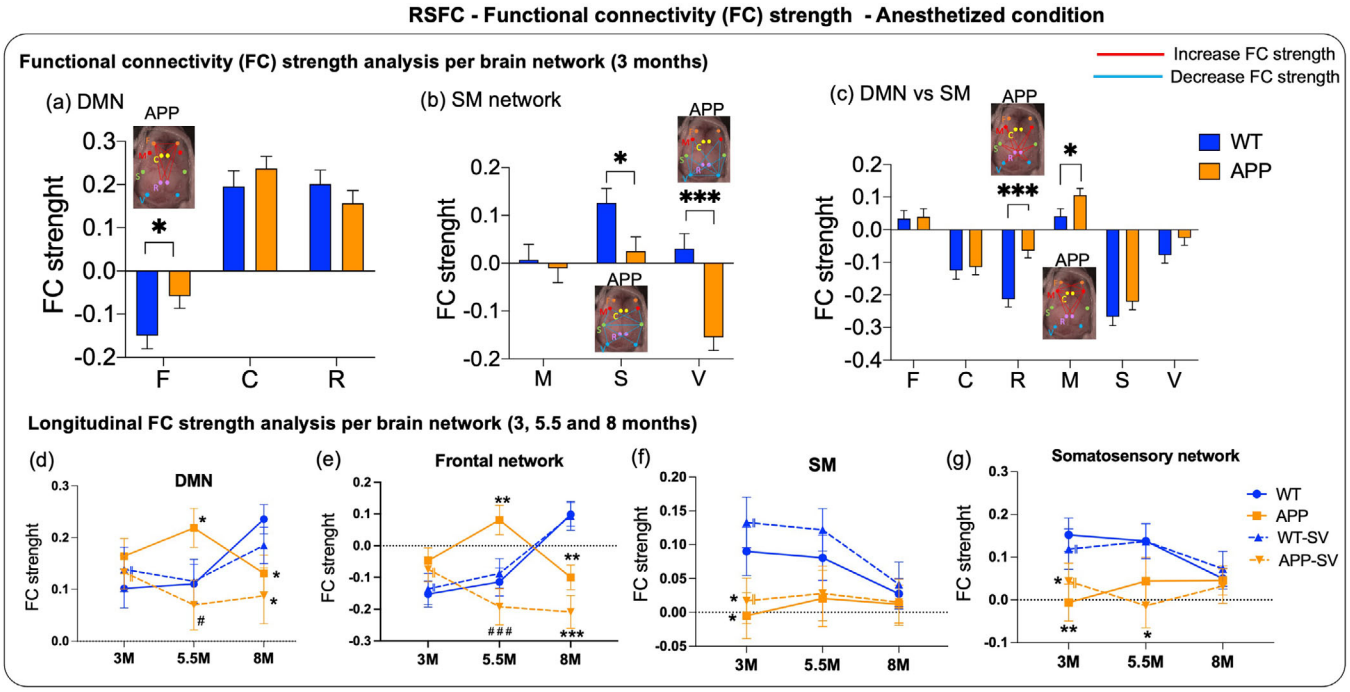

Figure 3: Functional connectivity (FC) strength analysis performed for WT and APP mice within the default-mode network (DMN) (a), the sensory-motor (SM) network (b), and between DMN and SM networks (c) in anesthetized condition. FC strength in 3 months-old APP mice revealed an increase in the FC strength within the Frontal (F) cortex (a), a strong hypoconnectivity within the somatosensory (S) and visual (V) cortices (b), and a increase in FC between the retrosplenial (R) and SM network, and motor (M) cortex and the DMN (c). Longitudinally, anesthetized APP mice showed a significant increase in the FC strength within the DMN at 5.5 months (d), followed by a significant decrease at 8 months compared to WT controls. These changes were mainly driven the F cortex (e), and counteract by SV. A significant decline in FC strength within the SM network was observed in young (3-months-old) APP mice (f), which was driven by decreased connectivity in the S (g) cortex. Student's t-test was used for two groups comparison (WT and APP at 3 months), and two-way ANOVA (genotype and treatment as factors) with repeated measures for multiple groups followed by a Fisher's LSD post-hoc multiple comparison test. *p<0.05, **p<0.01, ***p<0.001.

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