

Re-expression of Developmental Na_v1.3 Promotes Early Hippocampal CA3 Hyperexcitability in 5xFAD mouse model



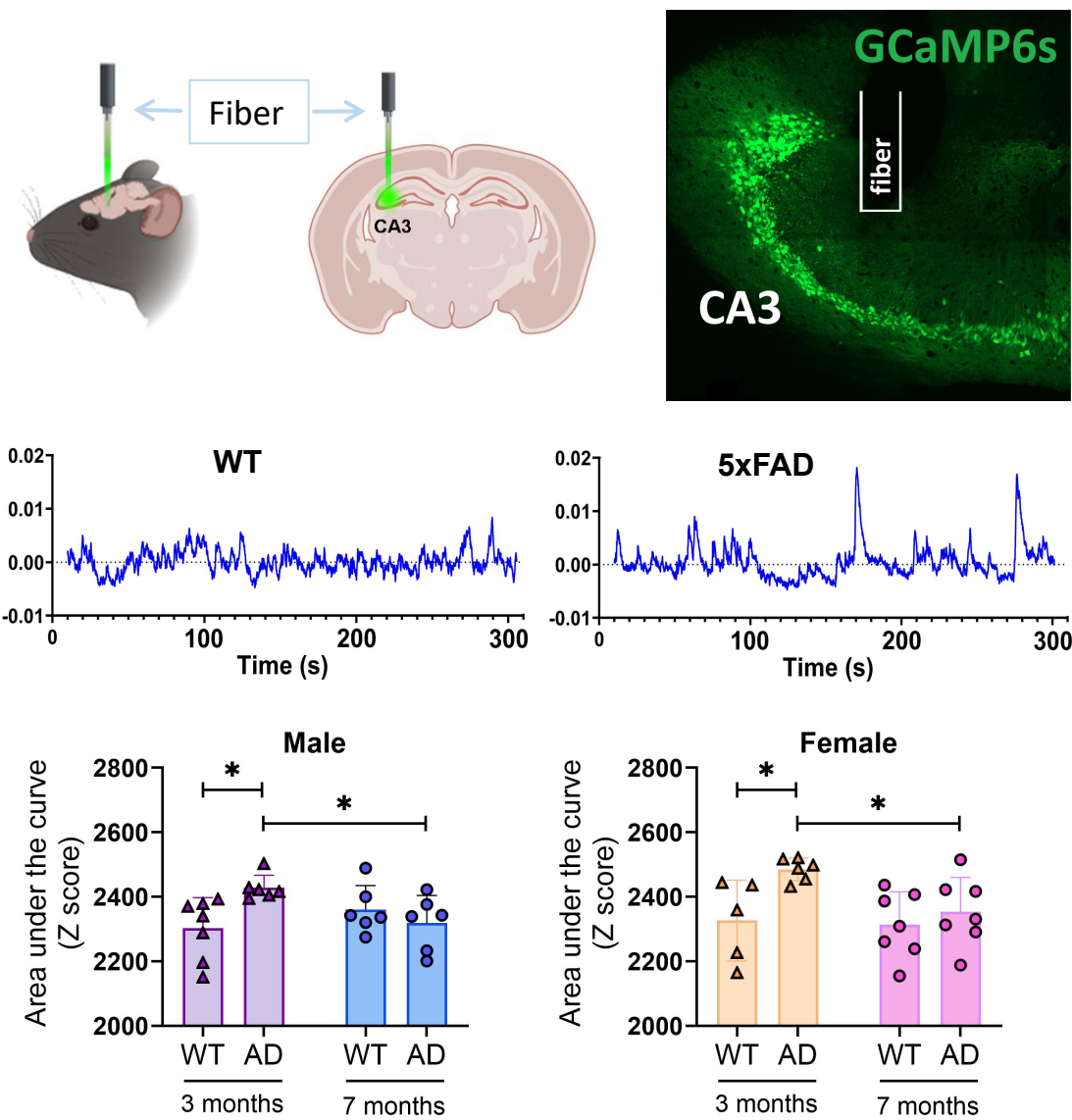
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Medicine

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Hippocampal CA3 hyperexcitability is exhibited with upregulated Na_v1.3 and rescued by Na_v1.3 knockdown.

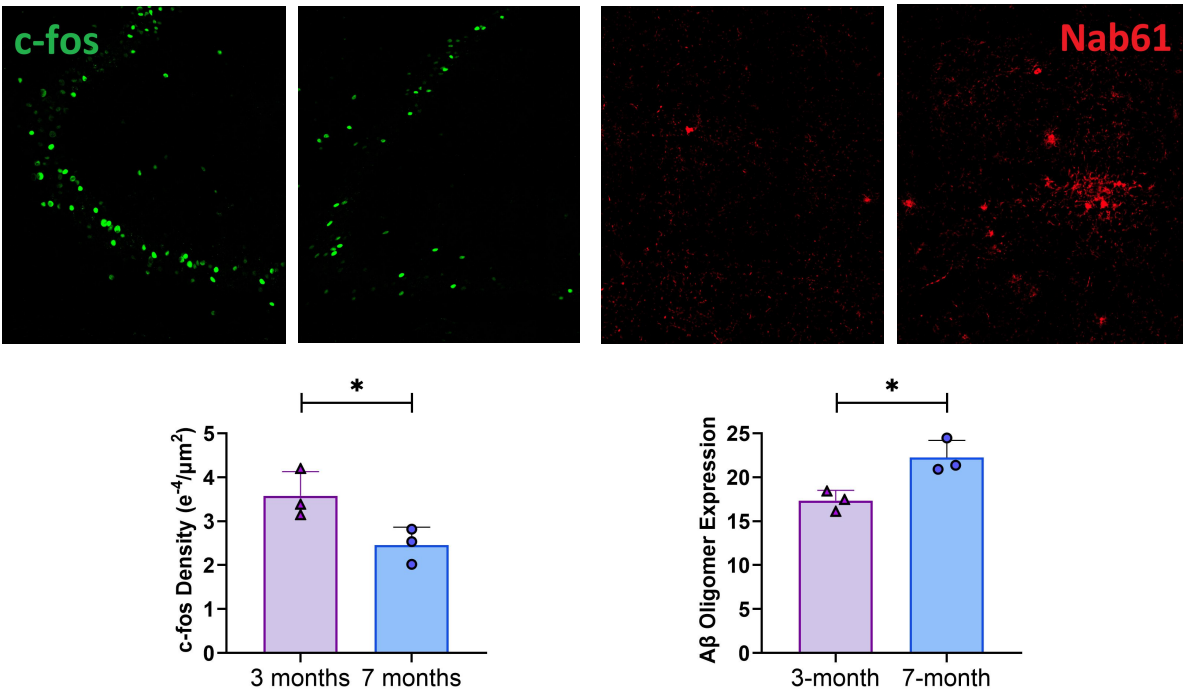
Introduction:
Neuronal hyperexcitability is a prevalent feature in early stages of Alzheimer's Disease (AD), hastening cognitive decline and neurodegeneration [1]. Variable expression of voltage-gated sodium channel (Na_v) subtypes in specific neuronal populations influence sensitivity of network excitability with differential presynaptic and postsynaptic localization [2]. Interestingly, mature excitatory neurons, following injury or disease, augment their high-frequency firing by reverting to an Na_v profile indicative of an earlier developmental window [3], but have yet to be explored in AD hyperexcitability. Here, we test the hypothesis that circuit-specific re-expression of developmentally dominant Na_v1.3 potentiates hippocampal CA3 hyperexcitability in early stage of disease of 5xFAD mice, compared to both later-stage disease and non-AD controls.

Hippocampal CA3 neuronal activity is increased in early AD mice

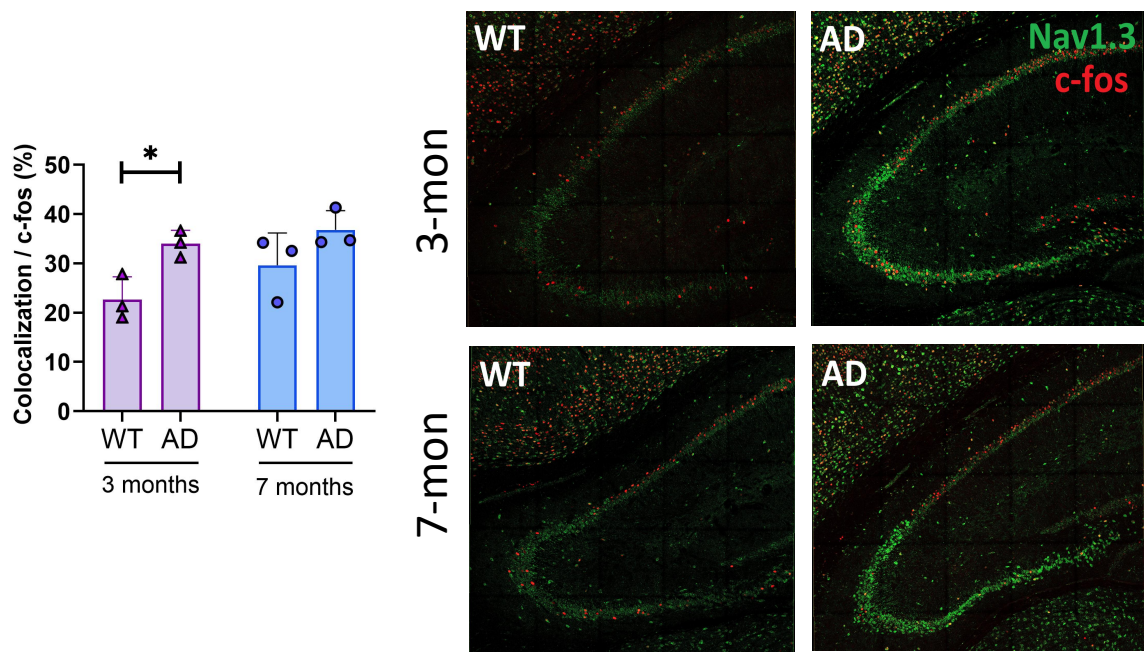


References: 1. Palop J J, Mucke L. Network abnormalities and interneuron dysfunction in Alzheimer disease. Nature Reviews Neuroscience, 2016, 17(12): 777-792.
2. Johnson K W, Herold K F, Milner T A, et al. Sodium channel subtypes are differentially localized to pre- and post-synaptic sites in rat hippocampus. Journal of Comparative Neurology, 2017, 525(16): 3563-3578.
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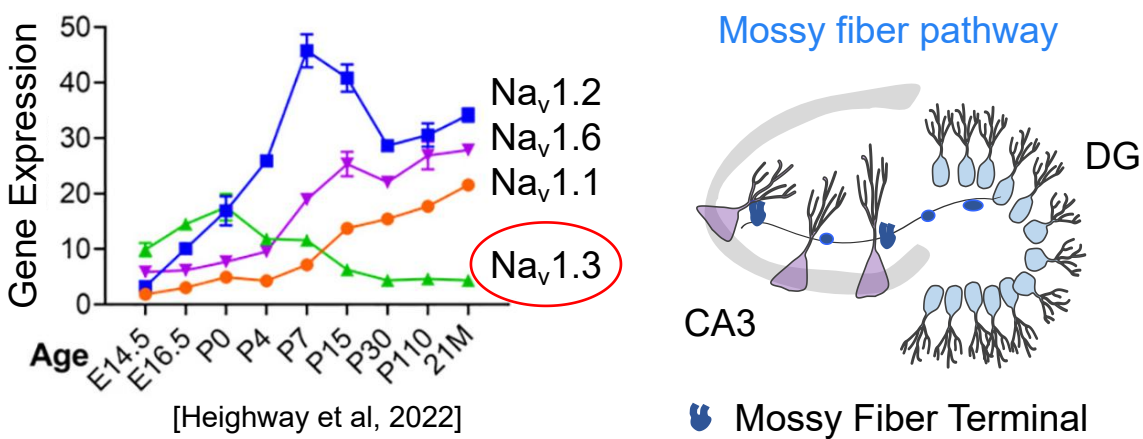
Increased CA3 activity corresponds with low Aβ oligomers in AD mice



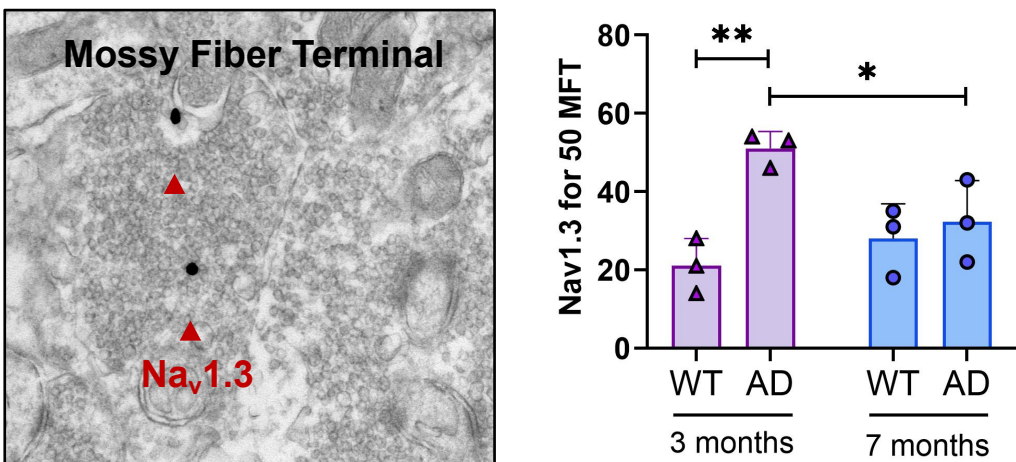
Na_v1.3 expression is enriched in c-fos⁺ neurons in early AD mice



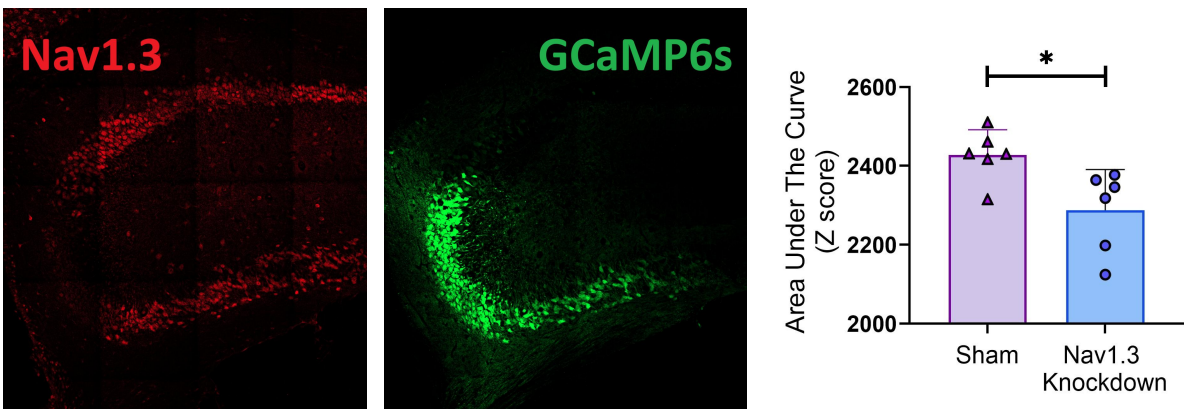
Methods:
Fiber Photometry: To measure neuronal activity in the CA3, male and female wildtype and 5xFAD mice (3-mo, early stage; 7-mo, late stage) were injected with AAV1-Syn-GCaMP6s-WPRE-SV40 virus and implanted with an optical fiber at the same site (ML: 1.9mm, AP: -1.9 mm, DV: -2.2 mm). Nav1.3α shRNA lentiviral particles (Santa Cruz, sc-42647-V) was used for Na_v1.3 knockdown. Real-time measurements of neuronal activity was carried out three weeks later in free behaving animals (n=6-7).
Immunofluorescence: Hippocampal tissue from male and female wildtype and 5xFAD mice (3-mo, early stage; 7-mo, late stage; n=3/group) were labeled for c-fos (226017, 1:500) and Na_v1.3 (ASC-004, 1:200).
Electron Microscopy: Immunogold-silver labeling of Nav1.3 (ASC-004, 1:200) was performed using post-embedding from hippocampal tissue of male and female wildtype and 5xFAD mice (n=3/group; 150 MFT/group).



Na_v1.3 is re-expressed on mossy fiber terminals in early AD mice



Na_v1.3 knockdown rescues CA3 hyperactivity in early AD mice



Results:
- Early stage 5xFAD mice exhibit *increased* CA3 neuronal activity compared to older, late-stage 5xFAD or wildtype mice.
- Early stage 5xFAD mice have *higher expression* of Na_v1.3 in mossy fiber terminals compared to older, late-stage 5xFAD or wildtype mice.
- *Decreased* CA3 neuronal activity was observed after Na_v1.3 knockdown in early stage 5xFAD mice.