Axonal conduction velocity in CA1 area of hippocampus is reduced in mouse models of Alzheimer's disease

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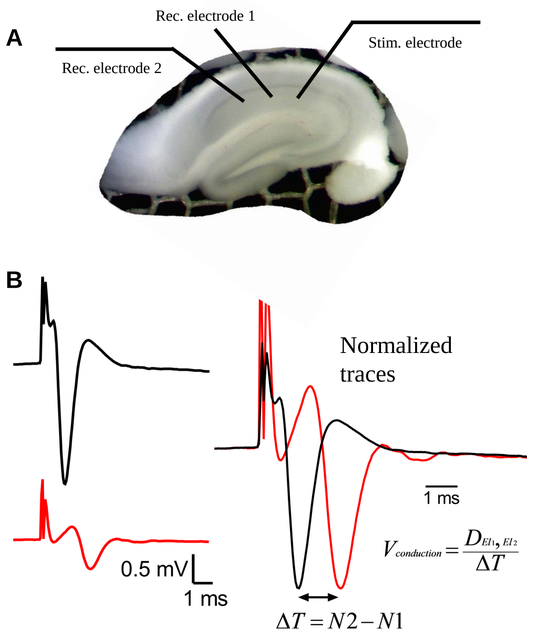
Background

The timing of action potentials arrival at synaptic terminals partially determines the integration window of synaptic inputs and is important for information processing in the CNS. Therefore, axonal conduction velocity (V_c) is a salient parameter, influencing the timing of synaptic inputs. Even small changes in V_c may disrupt information coding in networks where accurate timing is crucial, adversely affecting such brain functions as cognition and memory. We asked whether changes in V_c might be present in genetic models of Alzheimer's disease (AD), where cognitive function is disrupted.

Methods

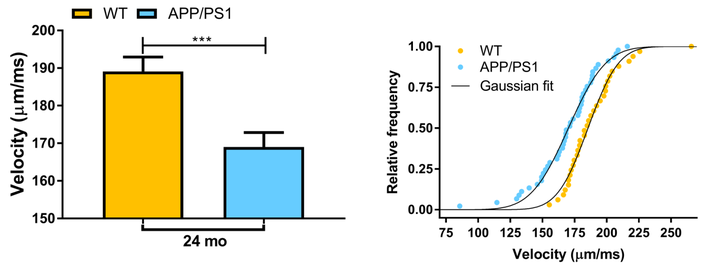
We measured V_c in axons of Schaffer collaterals in CA1 area of hippocampus in two transgenic mouse models of AD that over-express β-amyloid, line 41 (6mo) and APP/PS1 (24mo). We used a transverse hippocampal slice preparation with two extracellular recording electrodes to capture propagation of compound action potentials (CAPs) elicited by a stimulating electrode in the presence of synaptic transmission blockers (CNQX, APV, and picrotoxin). V_c (in µm/ms) was calculated as *d/t*, where *d* is the linear distance between recording electrodes (200µm-600µm) and *t* is the time of CAP propagation. **Statistics**: Data are presented as mean±SEM. T-test or 2-way ANOVA).



A. *An image of a hippocampal slice showing placement of stimulating and recording electrodes in the stratum radiatum layer of CA1.* ***B***. *Representative recordings from electrode 1 and 2.*

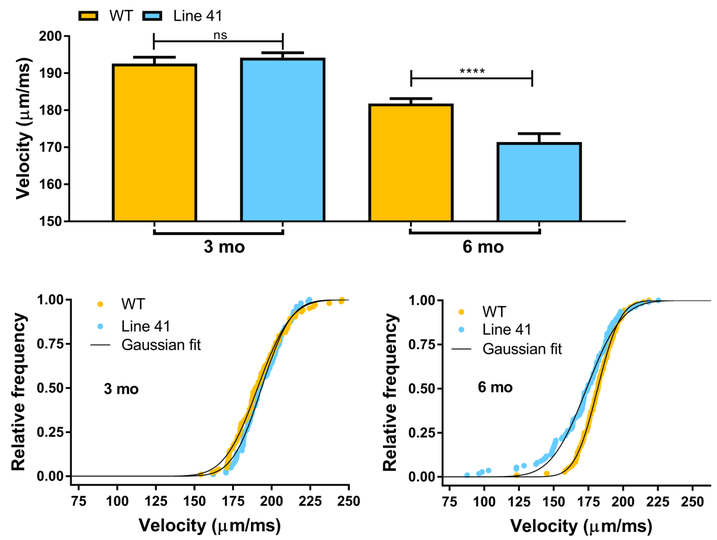
Results

Axonal conduction velocity is reduced in APP/PS1



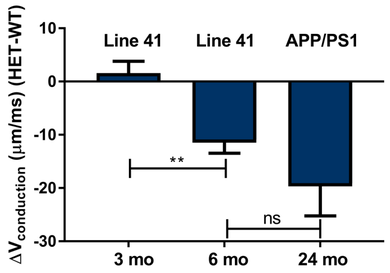
Left panel. *Schaffer collateral conduction velocity is lower in 24 mo old APP/PS1 compared to WT controls (WT n= 3 mice, 33 slices; APP/PS1 n= 4 mice, 45 slices; t-test, p = 0.0005).* ***Right panel***. *Cumulative frequency distribution of conduction velocities is shifted to the smaller values in APP/PS1 (cumulative Gaussian fits are statistically different, p < 0.0001).*

Reduction in axonal conduction velocity is age-dependent in Line 41



Top panel. *Only 6 mo and not 3 mo old Line 41 mice show a reduction in conduction velocity compared to age-matched controls (3 mo WT n= 5 mice, 103 slices; Line 41 n= 5 mice, 103 slices; 6 mo WT = 5 mice, 108 slices; Line 41 = 5 mice, 111 slices. One-way ANOVA, F(3,421) = 37.27, p < 0.0001; Bonferroni's multiple comparisons test, p < 0.0001).* ***Lower panel.*** *Cumulative frequency distribution of conduction velocities for 6 mo and not 3 mo old Line 41 is shifted to the lower values (cumulative Gaussian fits are statistically different, p < 0.0001).*

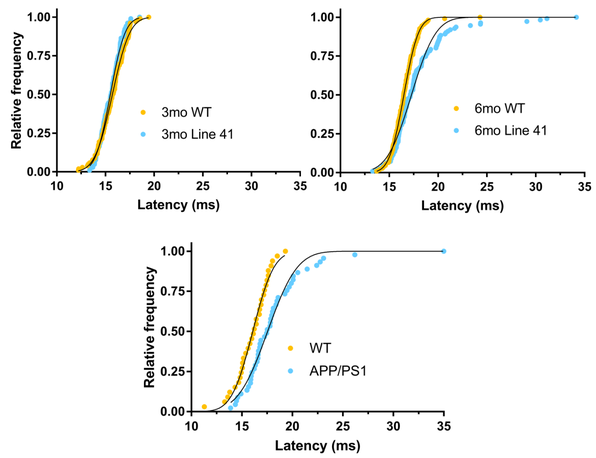
Functional significance of axonal conduction velocity reduction



Difference in conduction velocity between HET and WT for 3 and 6 mo old Line 41 and 24 mo old APP/PS1. One-way ANOVA, F(2,241) = 10.05, p < 0.0001; Bonferoni's multiple comparisons test, p < 0.0021).

Schaffer collaterals

- Schaffer collaterals run in transverse and oblique directions. Their extent may be as far as 3000 µm (Anderson et al., 1971).
- **For 6 mo old Line 41 the average difference of the action potential arrival delay could be ~ 1 ms. Considering only the slowest fibers (WT: 123.4 µm/ms and Line 41: 87.8 µm/ms, this delay could be as large as ~10 ms.**
- **For 24 mo old APP/PS1 the average difference of the action potential arrival delay could be ~ 2 ms. Considering only the slowest fibers (WT: 155.3 µm/ms and APP/PS1: 85.7 µm/ms, this delay could be as large as ~15 ms.**



Distribution of latencies assuming linear distance of 3000 µm.

Associational and commissural fibers

- CA3 pyramidal cells give rise to associational and commisural pathways in addition to Schaffer collaterals (Paxinos, 1995)
- CA3 and CA2 pyramidal cells project to all portions of the hippocampus (Ishizuka et al., 1990; Amaral and Witter, Ch. 21 in Rat Nervous System, Ed. Paxinos G.)
- Axonal arborizations of single CA3 and CA2 cells project to as much as 75% of the septo-temporal extent of the ipsi- and contra-lateral CA1 fields (Tamamaki et al., 1984, 1988)
- **If one speculates that both associational and commissural fibers in AD models also exhibit slowing of AP propagation, the distances that these fibers span are even greater, which could result in even larger time delays in AD mouse models.**

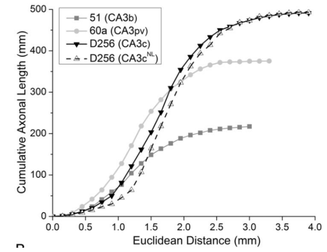


Figure 3 from Ropirredy et al 2011 showing cumulative axon length vs. Euclidean distance

Summary

- We find that conduction velocity in two similar AD mouse models is reduced compared with age-matched WT controls
- Reduction in conduction velocity may result in temporal dysregulation of hippocampal networks, affecting memory and cognition

References

Anderson et al., 1971. Expl Brain Res. 13, 222-238.
Paxinos, G. 1995. The Rat Nervous System. Ed. G. Paxinos.
Ishizuka et al., 1990. J Comp Neurol. 295(4): 580-623.
Amaral and Witter. 1995. Ch. 21 in Rat Nervous System, Ed. Paxinos G.
Tamamaki et al. 1984. Brain Res, 307(1-2): 336-340
Tamamaki et al. 1988. Brain Res, 452(1-2): 255-272
Ropirredy et al., 2011. Brain Struct Funct, 216(1): 1-15