



Impact Of Multiple Biological Alzheimer's Disease Risk Factors On Structural And Functional Integrity In The Anterior Olfactory Nucleus

#0386

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P2-06



KEY TAKE HOME:

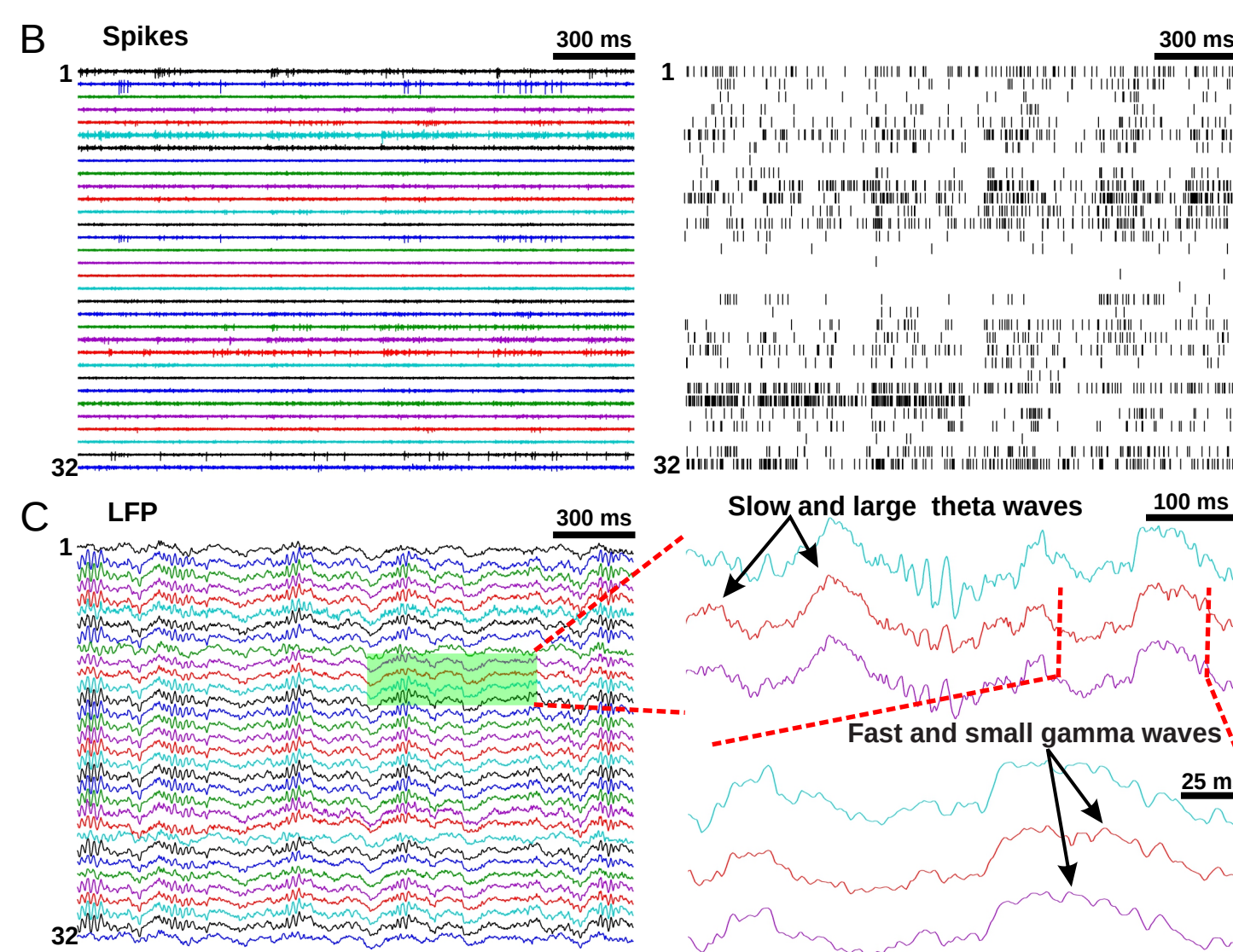
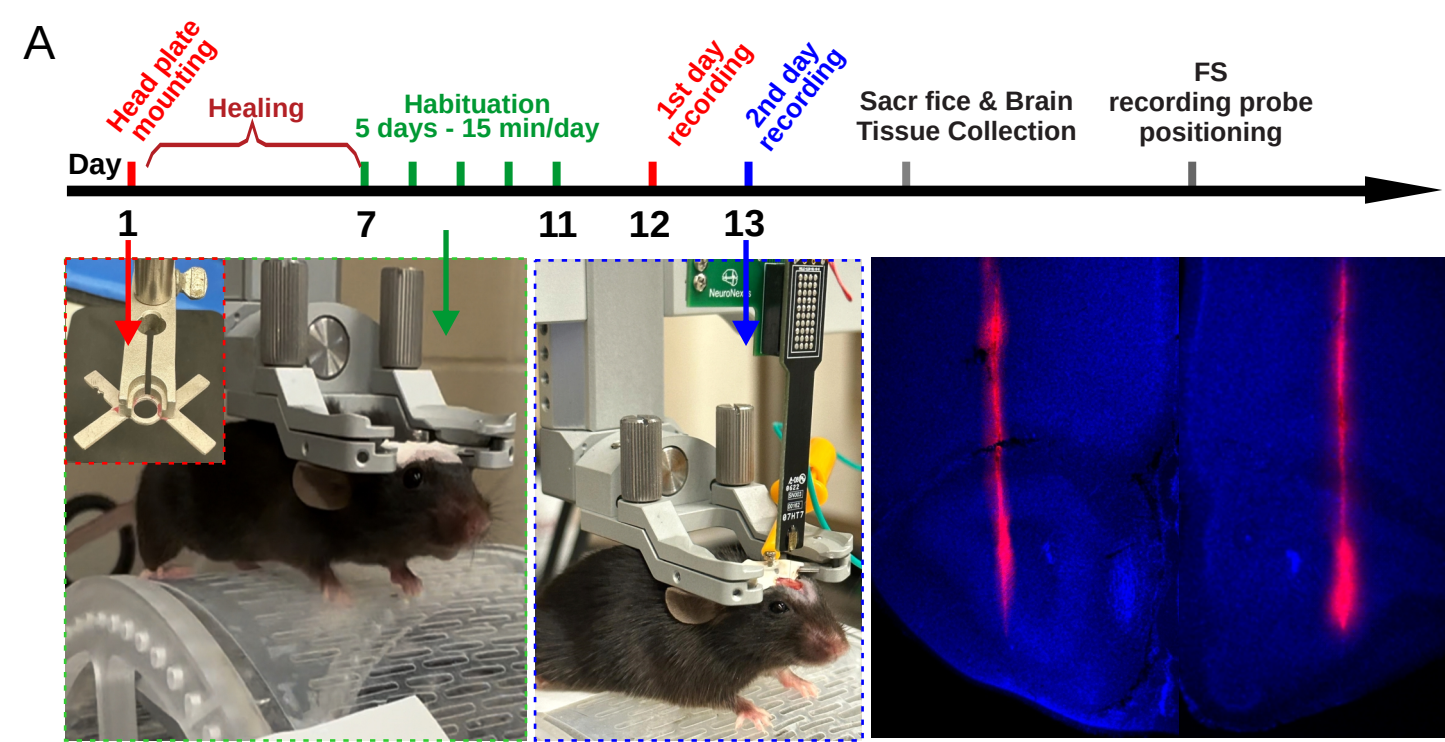
APOE4 progressively disrupts the structural and functional integrity of AON pyramidal neurons through age- and sex-dependent alterations in dendritic morphology, intrinsic excitability, and synaptic excitation-inhibition balance. The convergence of these deficits in aged females provides a potential cellular basis for the increased susceptibility of female APOE4 carriers to Alzheimer's disease.

INTRODUCTION

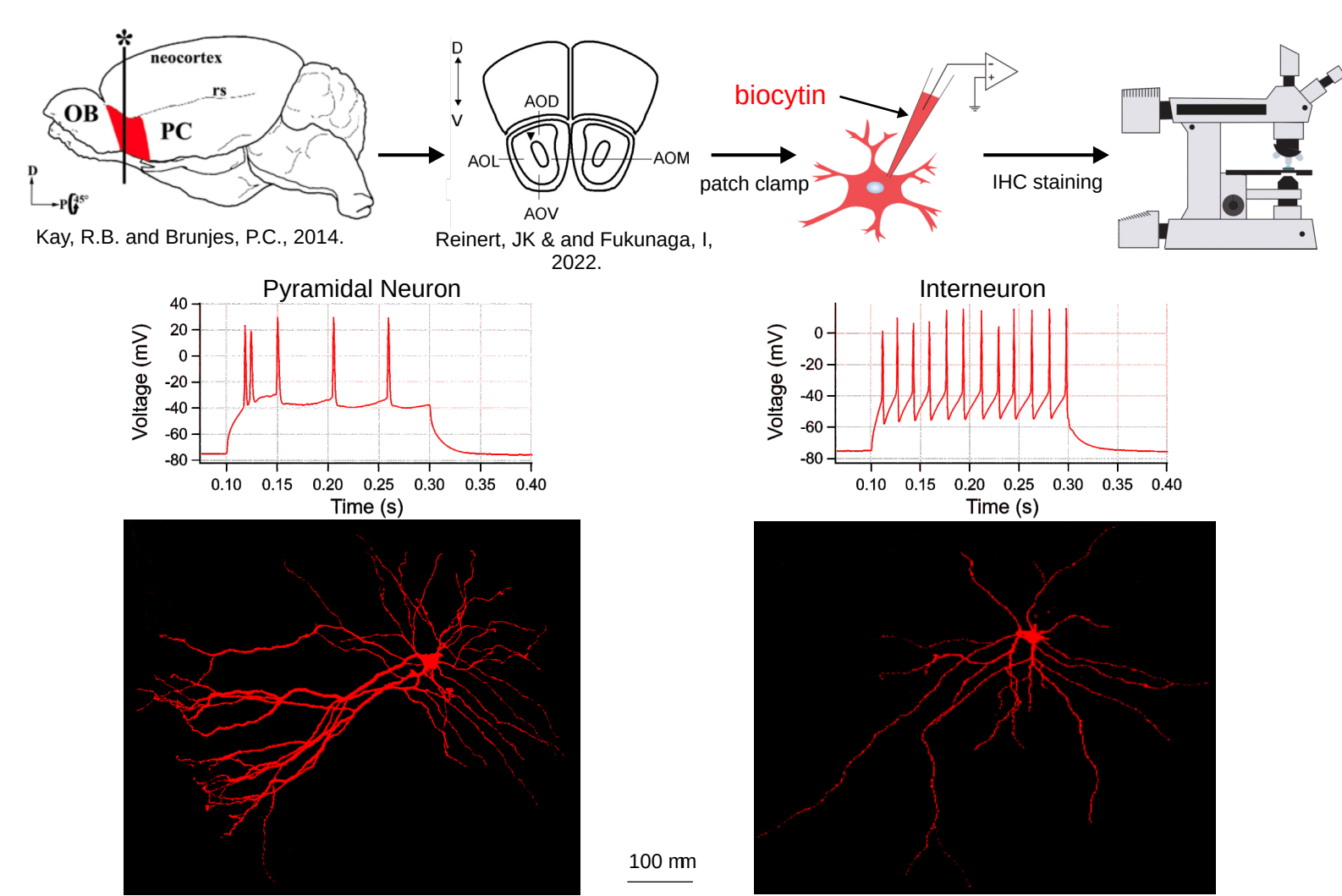
Olfactory deficits precede cognitive symptoms in Alzheimer's disease (AD) by years to decades and may serve as prodromal biomarkers. While multiple olfactory structures may contribute to olfactory dysfunction in AD, the anterior olfactory nucleus (AON) is uniquely positioned within the olfactory network and exhibits early AD pathology. However, AON pathophysiology remains largely unexplored. Our recent publication reported that: apolipoprotein E (APOE) $\epsilon 4$, the strongest genetic risk factor for sporadic Alzheimer's disease (AD), reduces excitability in the AON; adult females show higher excitability than males, a difference that is lost with age. Excitability and network activity vary by genotype and sex, while aging consistently increases network oscillation power, underscoring their complex interplay in an AD-vulnerable circuit. However, how APOE $\epsilon 4$ interacts with age and sex to affect the structural and functional organizations at the cellular and synaptic levels remains elusive. We addressed this question by focusing on pyramidal neurons with whole cell patch clamp in brain slices combined with post hoc reconstruction of the recorded cells to assess potential morphological alterations caused by these AD risk factors. Analysis of interneurons is ongoing.

METHODS

In Vivo



Ex Vivo



RESULTS

Prior In Vivo Findings

TABLE 1 The summary of spiking frequency data.

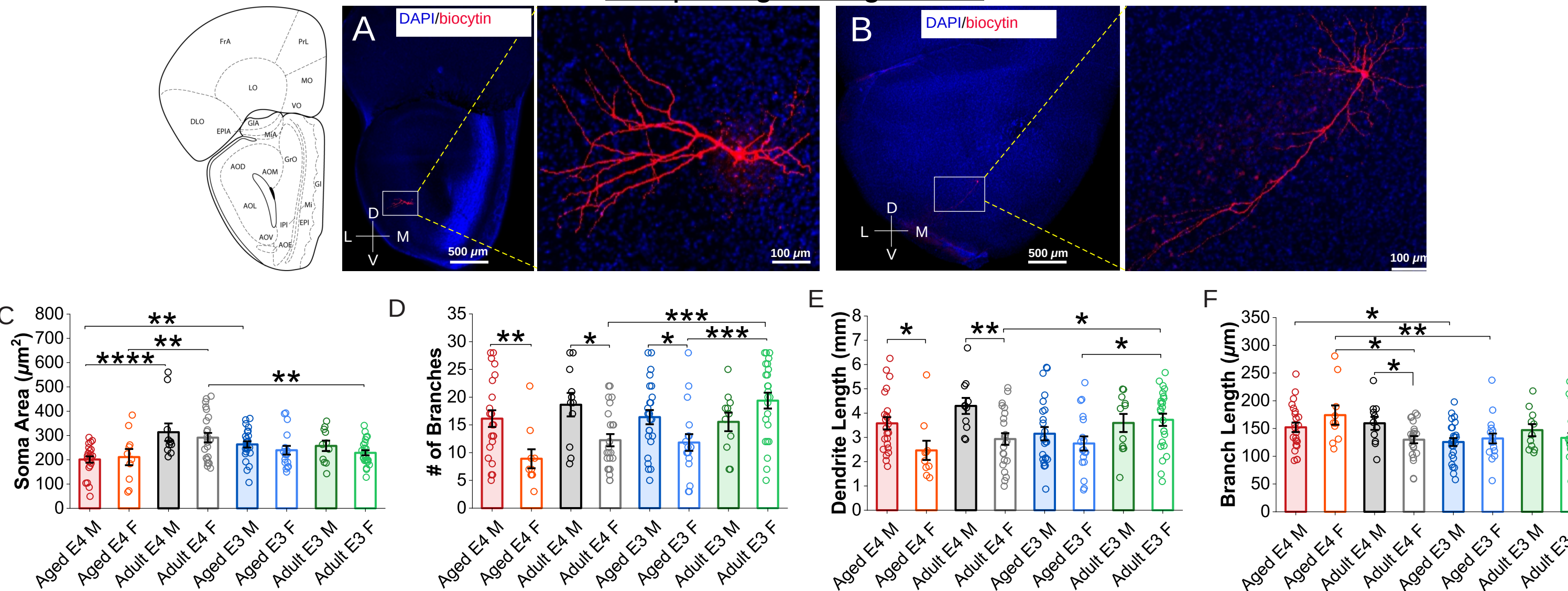
Group comparison	Alterations
Strain dependent	
M Adult $\epsilon 4$ versus adult $\epsilon 3$	↓
Aged $\epsilon 4$ versus aged $\epsilon 3$	↔
F Adult $\epsilon 4$ versus adult $\epsilon 3$	↓↓
Aged $\epsilon 4$ versus aged $\epsilon 3$	↔
Sex dependent	
$\epsilon 3$ Adult F versus adult M	↑↑
Aged M versus aged F	↔
$\epsilon 4$ Adult F versus adult M	↑
Aged F versus aged M	↔
Age dependent	
$\epsilon 3$ Aged M versus adult M	↑
Aged F versus adult F	↔
$\epsilon 4$ Aged M versus adult M	↑↑↑
Aged F versus adult F	↑

TABLE 2 Summary of power spectrum density of oscillatory activities.

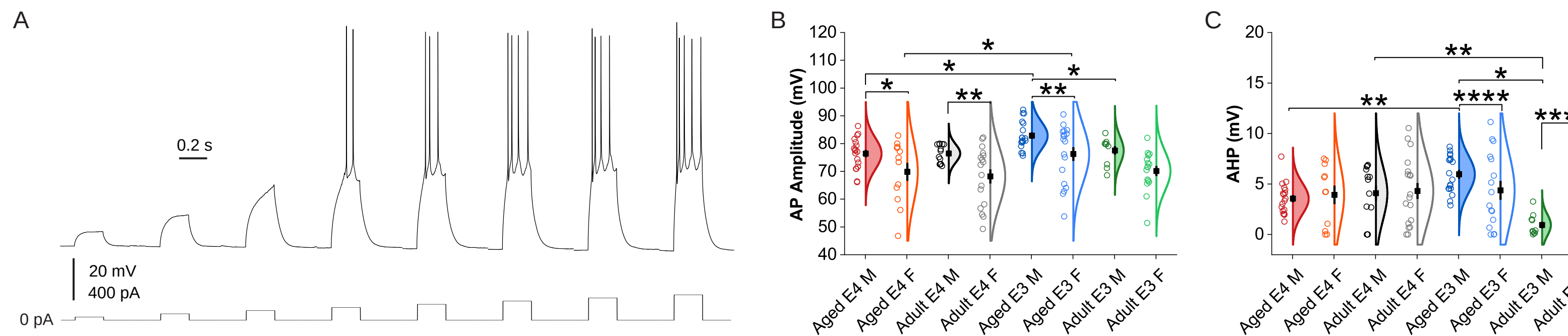
Group comparison	Alterations in power spectrum density	β : 12–30 Hz	Low γ : 30–60 Hz	High γ : 60–100 Hz
Strain dependent				
M Adult $\epsilon 4$ versus adult $\epsilon 3$	↔	20–30↑	30–46↑	↔
Aged $\epsilon 4$ versus aged $\epsilon 3$	↔	26–30↑	30–35↑	↔
F Adult $\epsilon 4$ versus adult $\epsilon 3$	↔	↔	↔	62–100↑
Aged $\epsilon 4$ versus aged $\epsilon 3$	↔	13–30↑	30–60↑	60–100↑
Sex dependent				
$\epsilon 3$ Adult F versus adult M	↔	12–30↑	30–60↑	60–100↑
Aged M versus aged F	↔	9–17↑	49–60↑	60–7285–100↑
$\epsilon 4$ Adult F versus adult M	↔	6–12↑	12–30↑	30–60↑
Aged F versus aged M	↔	↔	39–46↑	↔
Age dependent				
$\epsilon 3$ Aged M versus adult M	↔	↔	↔	82–100↑
Aged F versus adult F	↔	↔	18–30↑	30–48↑
$\epsilon 4$ Aged M versus adult M	↔	↔	↔	85–100↑
Aged F versus adult F	↔	3–12↑	12–30↑	60–100↑

(Uzun, C. et al, Alzheimers Dement. 2025)

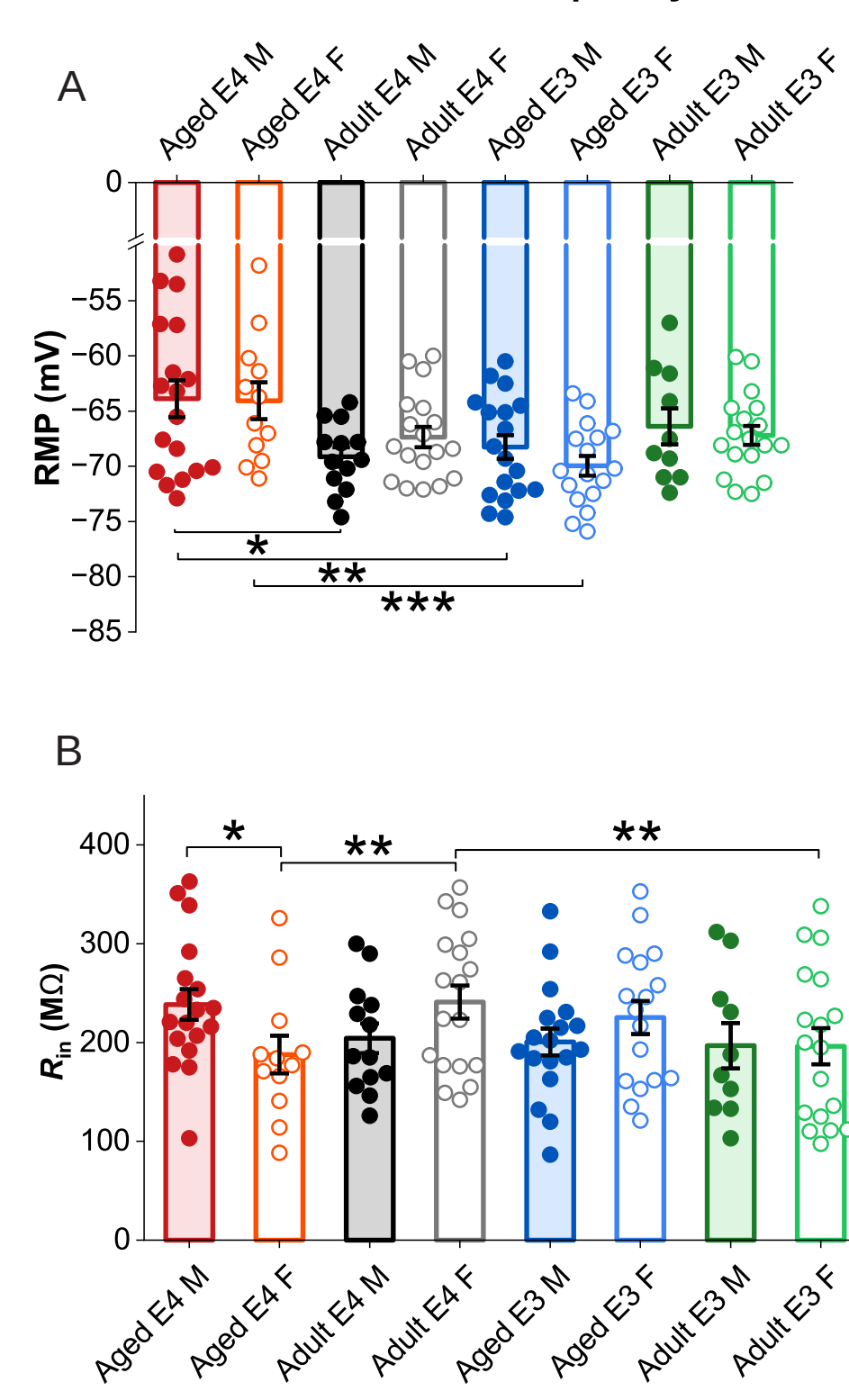
Morphological Signatures



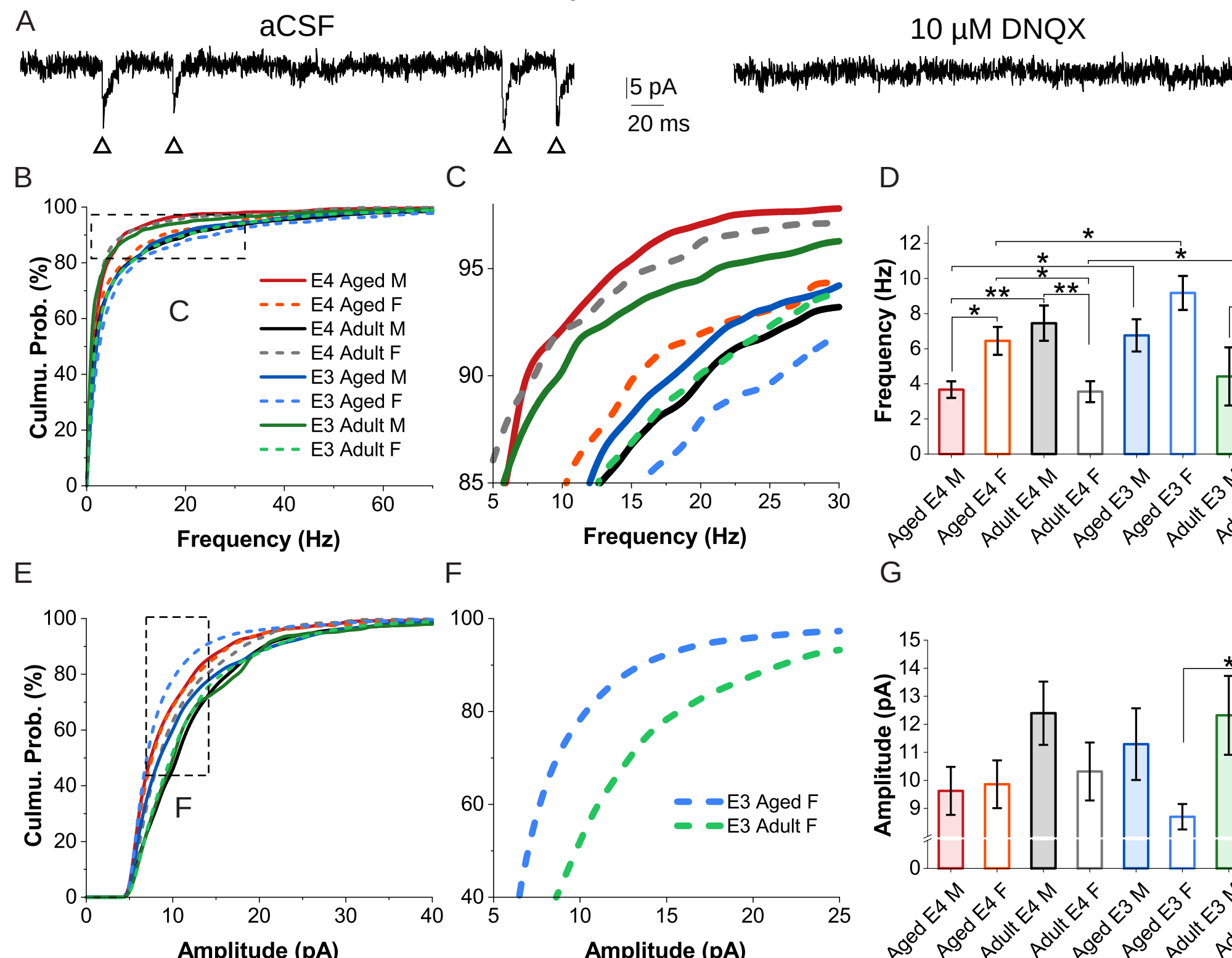
Characterization of Evoked Action Potentials



Intrinsic Property

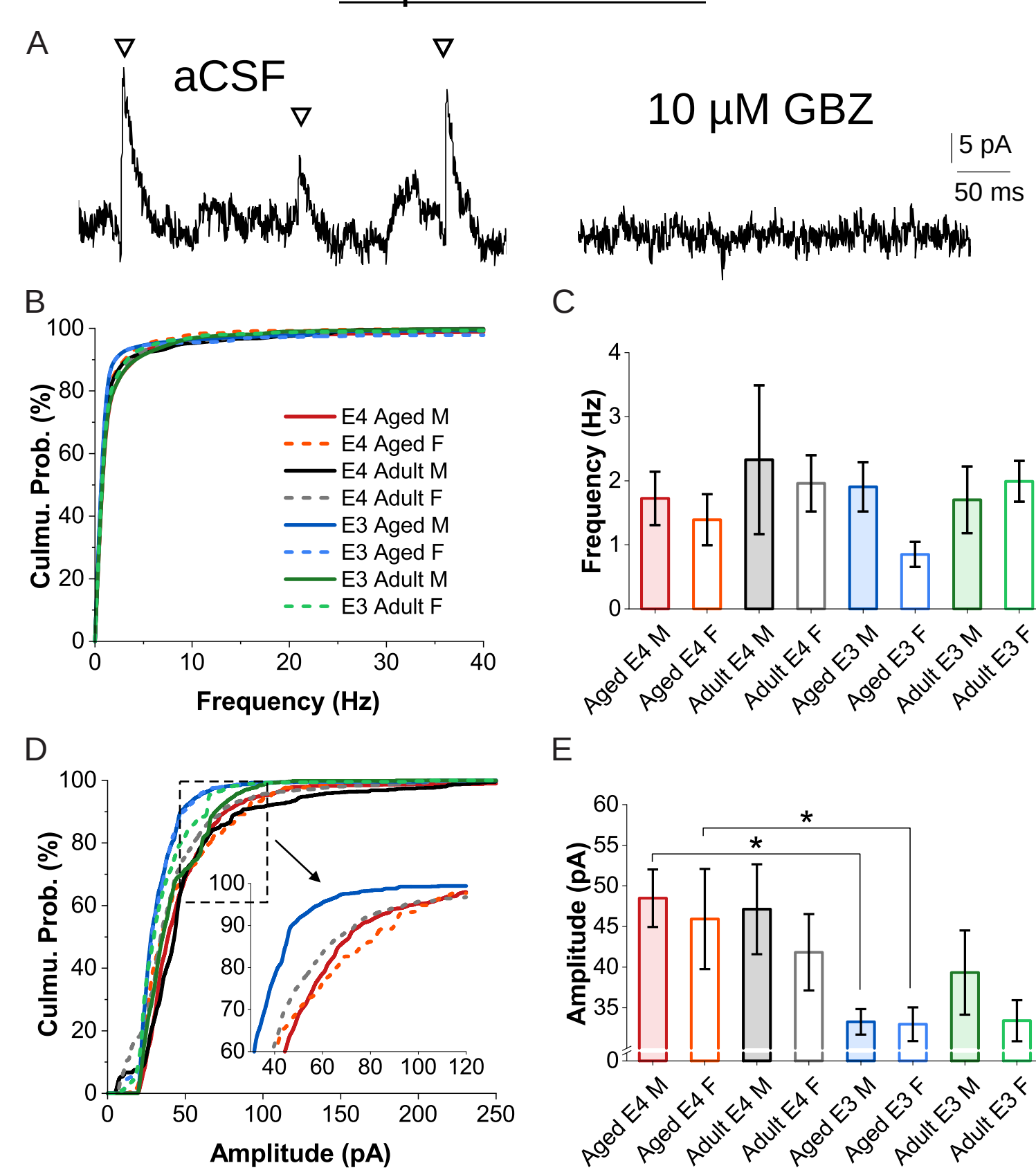


Impact on sEPSCs



RESULTS (cont'd)

Impact on sIPSCs



CONCLUSIONS

- Morphometric analyses revealed APOE4-dependent dendritic simplification and age/sex-dependent somatic remodeling, including paradoxical hypertrophy in adult and subsequent atrophy in aged females, indicating progressive structural impairment;
- APOE4 altered membrane intrinsic properties and action potential (AP) characterization, such as depolarized resting membrane potential, reduced input resistance, diminished AP amplitude, and age-dependent bidirectional changes in afterhyperpolarization. These results collectively suggest destabilized intrinsic excitability;
- APOE4 shifted synaptic excitation-inhibition balance toward inhibitory dominance by reducing frequency but not amplitude of sEPSCs while enhancing amplitude but not frequency of sIPSCs. These results also suggest that the sites of APOE4 actions on synaptic activities depend on the synaptic types: presynaptic for glutamergic and postsynaptic for GABAergic types.
- (4) Aging and sex interactively sculpted these effects as aged APOE4 females exhibited the most severe convergence of structural regression, enhanced synaptic inhibition, and diminished spike output, consistent with the disproportionately elevated AD risk in females.

REFERENCES

- Murphy C. Olfactory and other sensory impairments in Alzheimer disease. Nat Rev Neurol. 2019; 15:11–24.
- Brunert D, Medinaceli Quintela R, Rothermel M. The anterior olfactory nucleus revisited - An emerging role for neuropathological conditions? Prog Neurobiol. 2023; 228:102486.
- Belloy ME, Andrews SJ, Le Guen Y, et al. APOE genotype and Alzheimer disease risk across age, sex, and population ancestry. JAMA Neurol. 2023; 80:1284–1294.
- Fortea J, Pegueroles J, Alcolea D, et al. APOE $\epsilon 4$ homozygosity represents a distinct genetic form of Alzheimer's disease. Nat Med. 2024; 30:1284–1291.
- Uzun C, Li Y, Liu S (2025) APOE4 disrupts neuronal and network-level function in the anterior olfactory nucleus: influence of age and sex. Alzheimer's & Dementia. e70865.

ACKNOWLEDGEMENTS & CONTACT

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