

Healthy mice exhibit Alzheimer's disease pathology after the exposure of extracellular vesicles from prodromal-AD patients

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INTRODUCTION

Extracellular vesicles (EVs) have been described to be involved in the pathogenesis of Alzheimer's disease (AD)^{1,2}. However, the exact mechanism and effects remain uncertain³. This study aims to elucidate their role through the exposure of isolated EVs from the cerebrospinal fluid (CSF) of patients with AD and Mild Cognitive Impairment (MCI Aβ-/Aβ+) to C57BL/6 healthy mice (**Fig 1**).

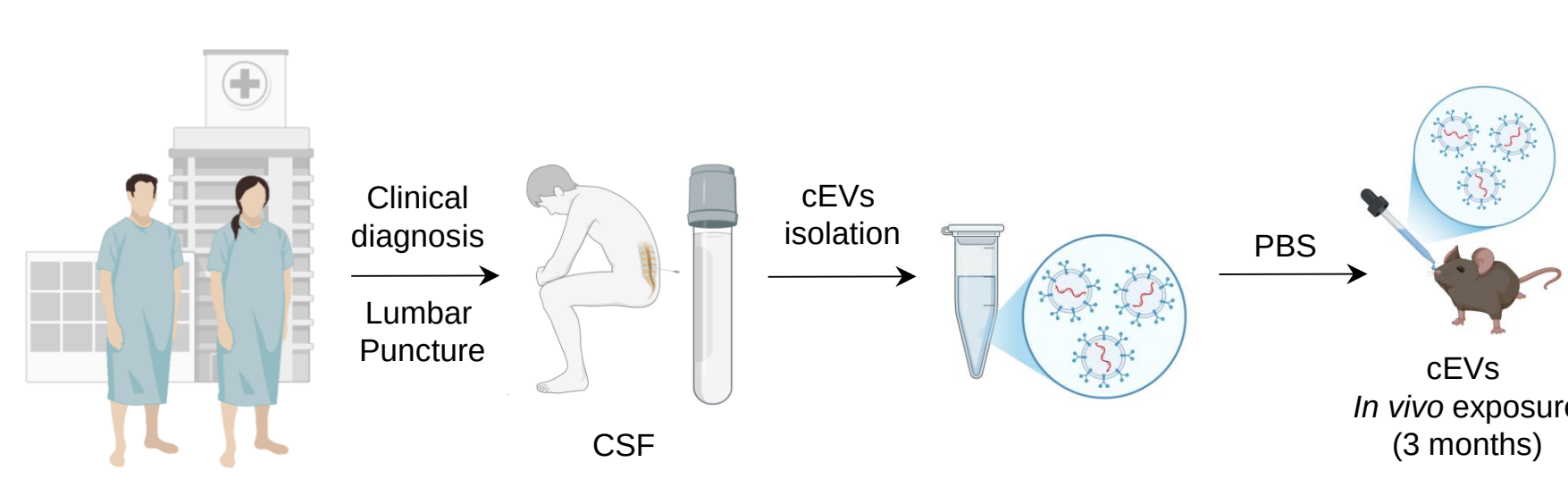


Fig 1. Scheme of the study design

MATERIALS & METHODS

Morris water maze (MWM) and Novel object recognition (NOR) tests were used to evaluate the memory deficits. Brain neuroinflammation, synapses and neuronal integrity were evaluated with GFAP, Iba1, synapsin, Sox2, Tubβ3, and NeuN immunohistochemistry's. Proteomic profiles of mice plasma were analyzed by using NULISaseq™ Mouse Panel 120 (Alamar BioSciences)⁴. (**Fig 2**.)

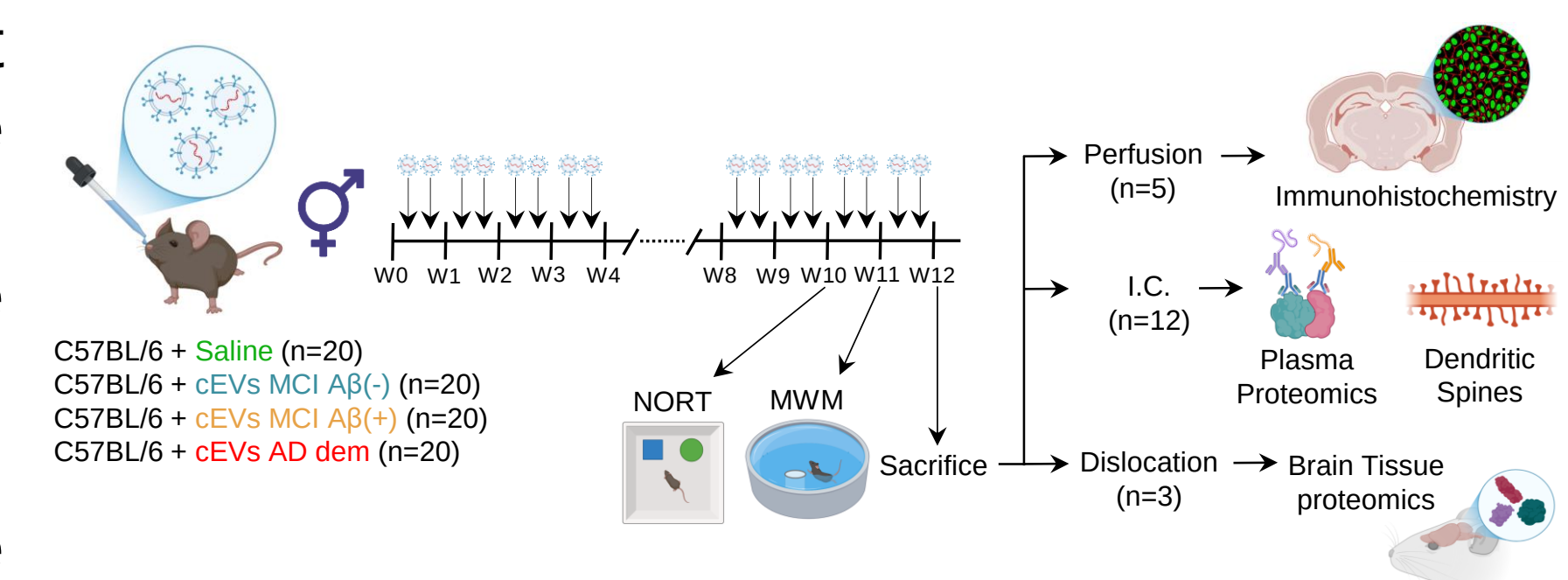


Fig 2. In vivo cEVs exposures and experimental assays

RESULTS & DISCUSSION

Behavioral tests

Mice exposed to MCI Aβ+ and AD CSF-EVs showed significant memory deficits in both MWM and NOR tests compared to their MCI Aβ- and saline littermates (**Fig. 3**).

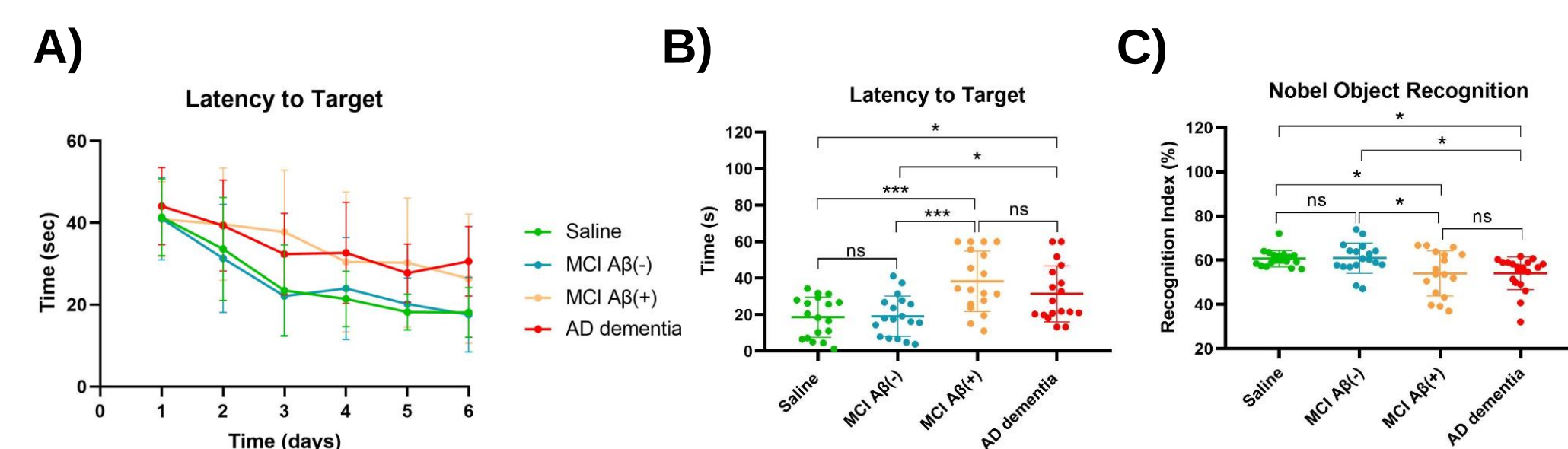


Fig 3. Behavioral tests' results **A)** MWM training phase. **B)** MWM test day. **C)** NOR.

Dendritic Spines

Mice exposed to MCI Aβ+ and AD CSF-EVs showed reduced levels in the number of dendritic spines, specifically in the hippocampus area, compared to their saline littermates (**Fig. 4**).

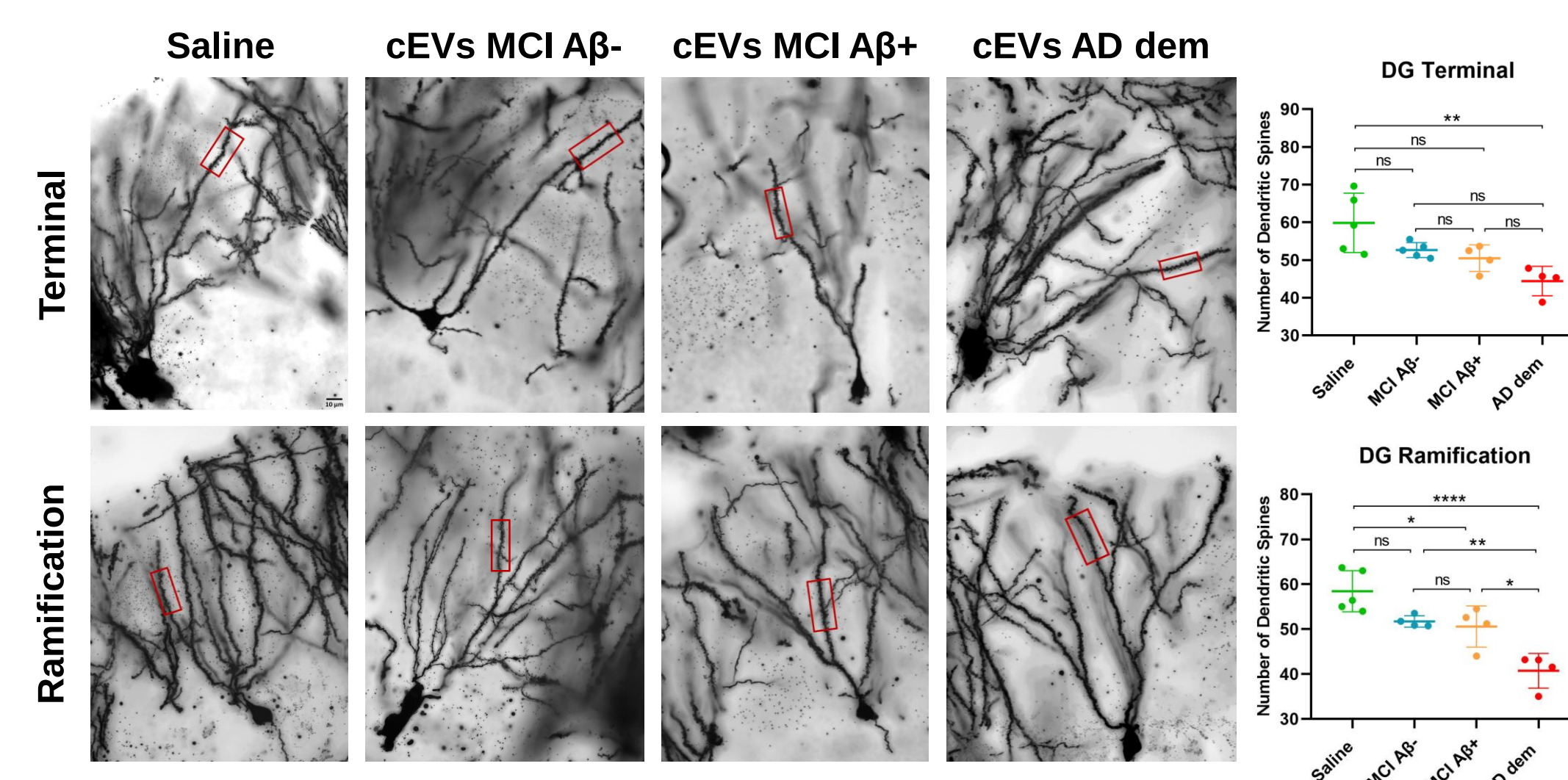


Fig 4. Dendritic Spines' analysis results in the hippocampus *dentate gyrus* of the study groups.

Immunohistochemistry

Immunohistochemistry's results showed differences in several brain cell morphology of the MCI Aβ+ and AD groups compared to the MCI Aβ- and saline groups. Specifically, microglia and astrocytes exhibited an activated morphology (cell body expansion and increased ramifications), and neurons appeared with abnormally accumulations of Tubβ3 in the soma and reduced axonal extensions (shortened and thinner), typical patterns of AD-pathology. (**Fig. 5**).

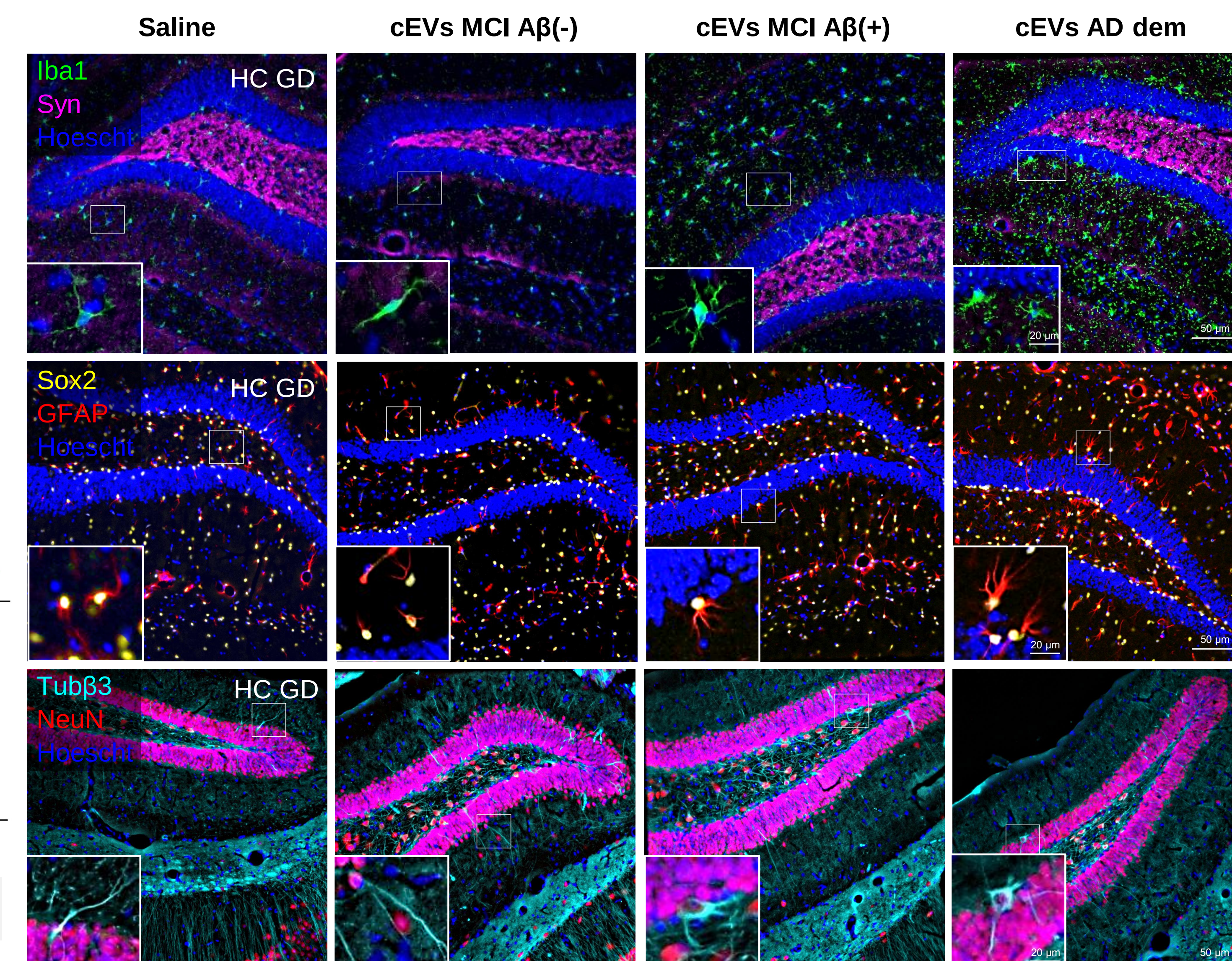


Fig. 5 Immunohistochemistry's visualization of cell morphology and expression of the hippocampus *dentate gyrus* against **A)** Iba1 (green) and synapsin (magenta) **B)** GFAP (red), Sox2 (yellow), and **C)** Tubβ3 (cyan), NeuN (red) and Hoechst (blue)

Plasma mice proteomics

Several AD-related proteins resulted altered in the mice plasma of both MCI Aβ+ and AD CSF-EVs' exposed groups compared to their saline littermates (**Fig. 6**).

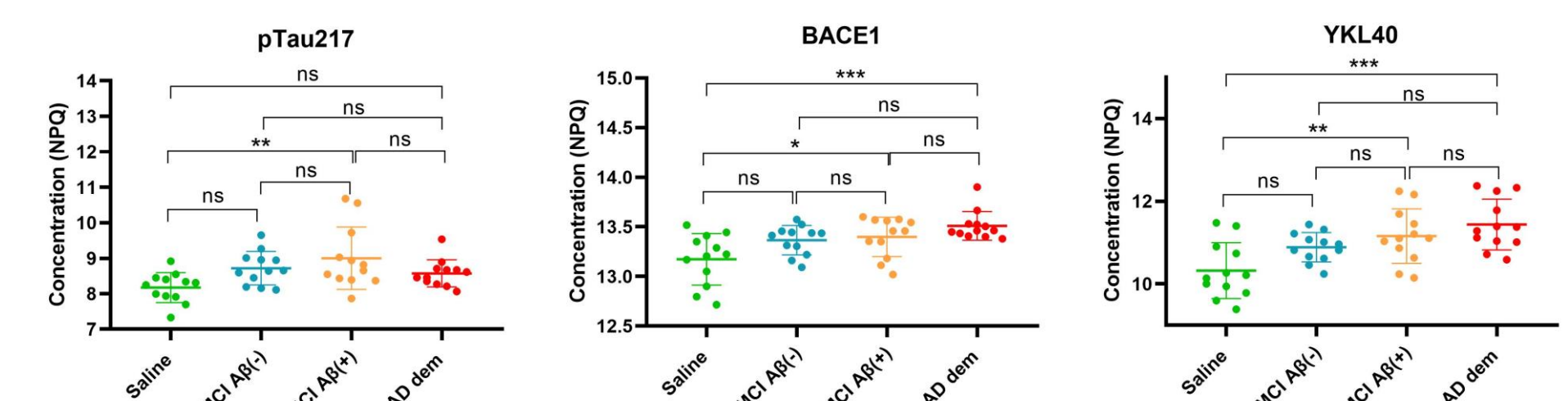


Fig 6. Examples of some significant proteins of the proteomics analysis of plasma mice with the NULISaseq™ Mouse Panel 120

CONCLUSION

Long-exposure of prodromal and AD CSF-EVs altered the memory function and promoted neuroinflammation and neuronal damage in healthy mice. Further experiments are still needed for a better understanding of the EVs role in AD development.

ACKNOWLEDGMENTS

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