

HDL-bound S1P affects the subventricular niche and early neuropathological features of Alzheimer's disease



Hee Kyung Jin¹, Byung Jo Choi², Kyung Yeol Kim², Jung Woo Hur², Sang Bo Kim², and Jae-sung Bae^{2*}

¹College of Veterinary Medicine, Kyungpook National University, Daegu, Korea

²Department of Physiology, School of Medicine, Kyungpook National University, Daegu, Korea

Background

Circulating blood factors are critical for homeostasis of the adult ventricular-subventricular (V-SVZ) and subgranular zones, which contain neural stem cells (NSCs) crucial for sustained neurogenesis. Circulating sphingosine-1-phosphate (S1P) bound to apolipoprotein M (ApoM), a principal component of high-density lipoproteins, is involved in various biological processes, but its role in neurogenic niches is poorly understood.

Methods

To investigate the function of the circulating ApoM-S1P complex in AD, we employed multiple genetic models, including ApoM-deficient (*ApoM*^{-/-}), ApoM-transgenic (*ApoM*^{TG}), and APP/PS1 mice, as well as conditional S1PR1-knockout mice. We further conducted in vivo administration of ApoM⁺HDL complexes and serum transfer experiments to evaluate the specific effects and mechanisms of ApoM-S1P signaling in AD-related pathology.

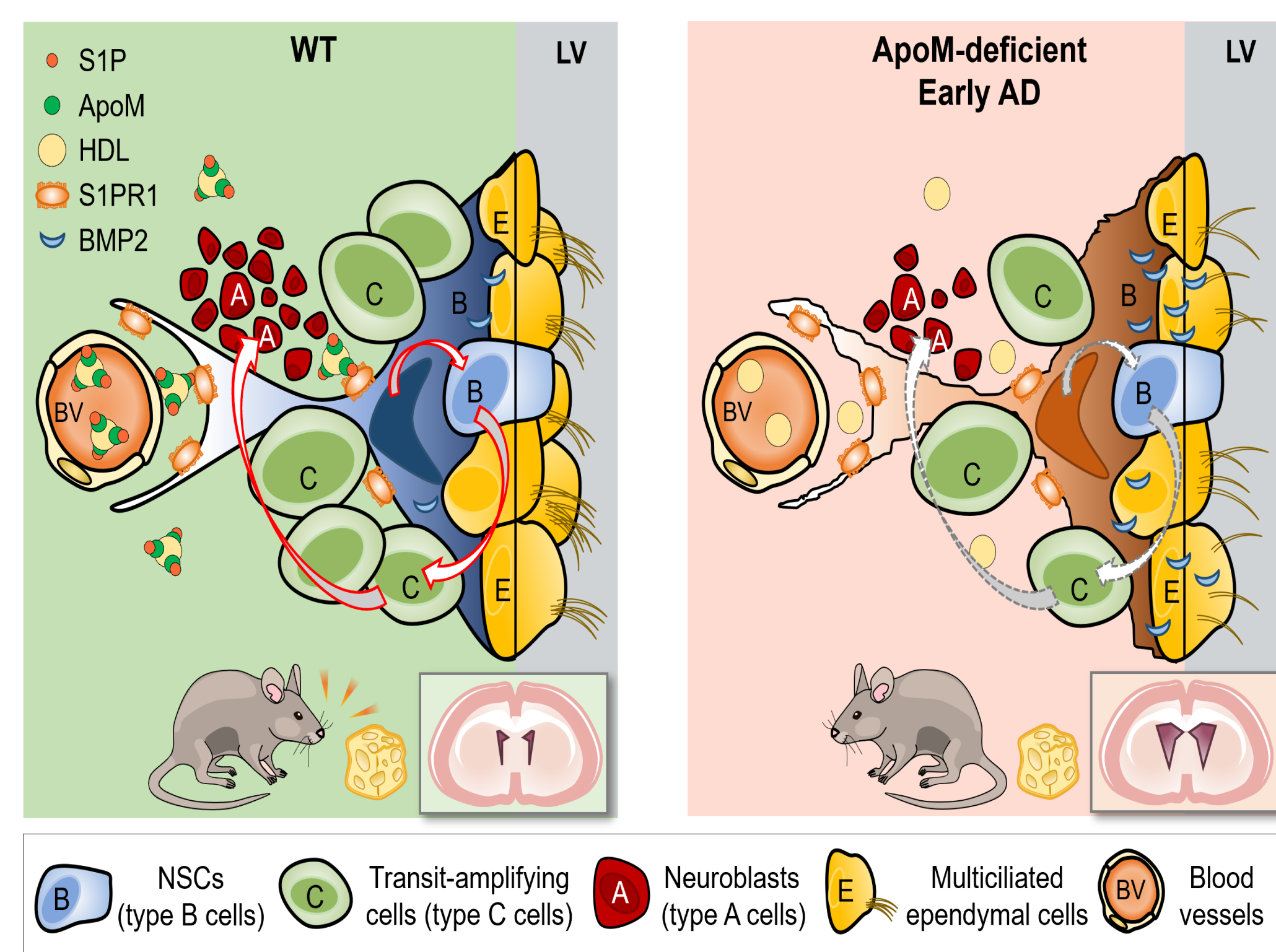
Results

Herein, using *ApoM*^{-/-} mice, we show that blood ApoM-S1P deficiency impairs the SVZ-NSC pool, neurogenesis, ependymal cell polarity, and cerebrospinal fluid flow, leading to olfactory dysfunction and ventricular enlargement, early neuropathological features of Alzheimer's disease (AD). Enhancing the complex significantly rescues these defects by activating S1P1 receptor signaling in SVZ-NSCs. Consistently, blood ApoM-S1P levels are reduced in early AD patients and correlate with olfactory deficits and ventricular enlargement. Similar abnormalities are recapitulated in young APP/PS1 mice and reversed by restoring blood ApoM-S1P levels.

Discussion

We expect that our findings will serve as a basis for the future development of prophylactic agents for early AD, and stimulate further studies assessing the synergistic therapeutic effects of the blood ApoM-S1P complex or S1PR1 agonists with current therapeutic agents for improvement of neuropathological features in early and late-stage AD.

Keywords : Apolipoprotein M; Sphingosine-1-phosphate; Subventricular zone; Olfaction; Lateral



Impact of blood ApoM-S1P complex on regulation of V-SVZ neurogenic niche.

Figure 1. Depletion of blood ApoM-S1P complex causes abnormality of the NSC pool in the SVZ.

Figure 2. Depletion of blood ApoM-S1P complex impairs SVZ neurogenesis and olfaction.

Figure 3. Depletion of blood ApoM-S1P complex induces loss of polarity in ependymal cells, leading to LV enlargement.

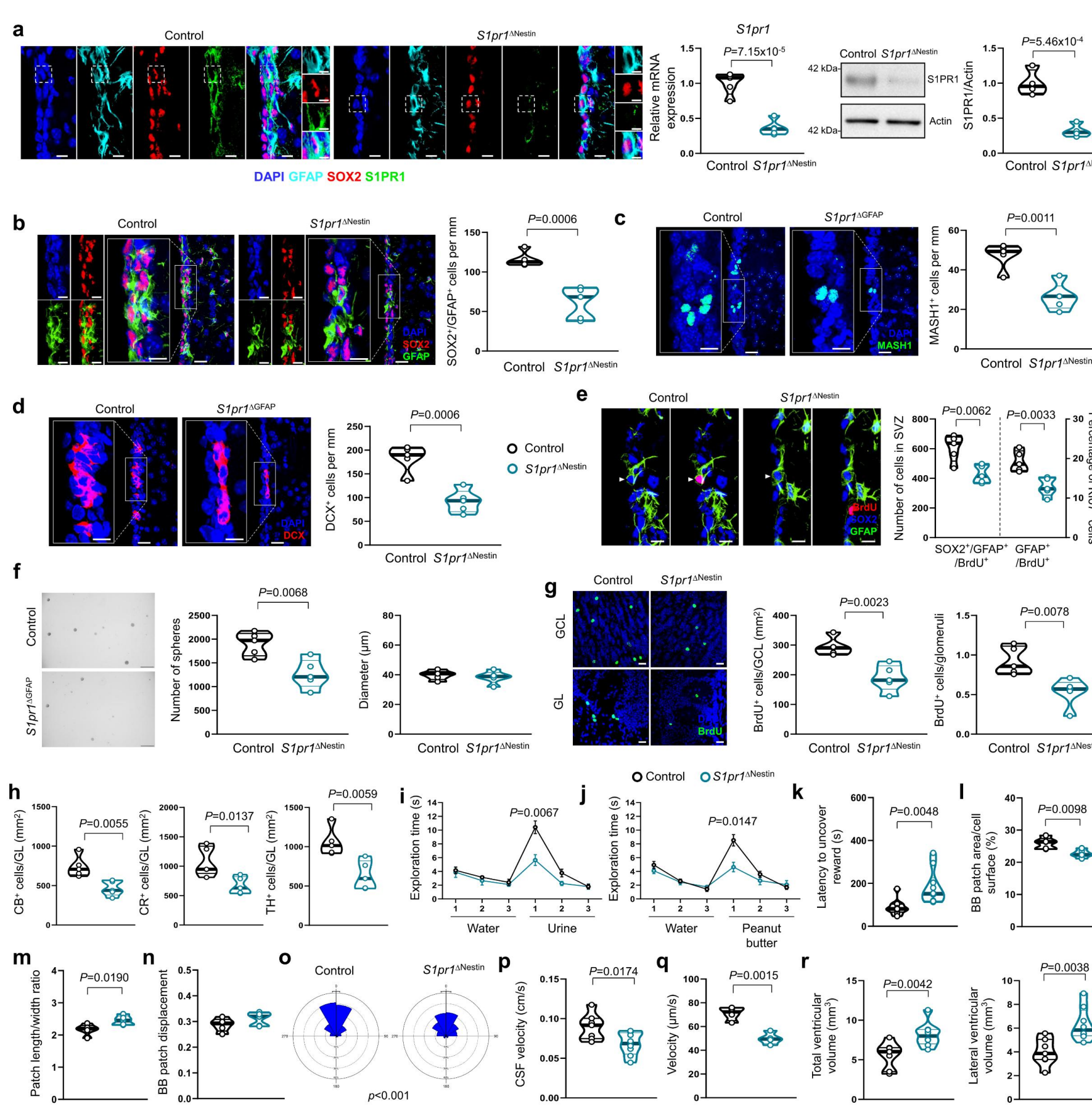


Figure 4. S1PR1 in the SVZ-NSCs is essential for maintaining neurogenesis and ependymal planar polarity.

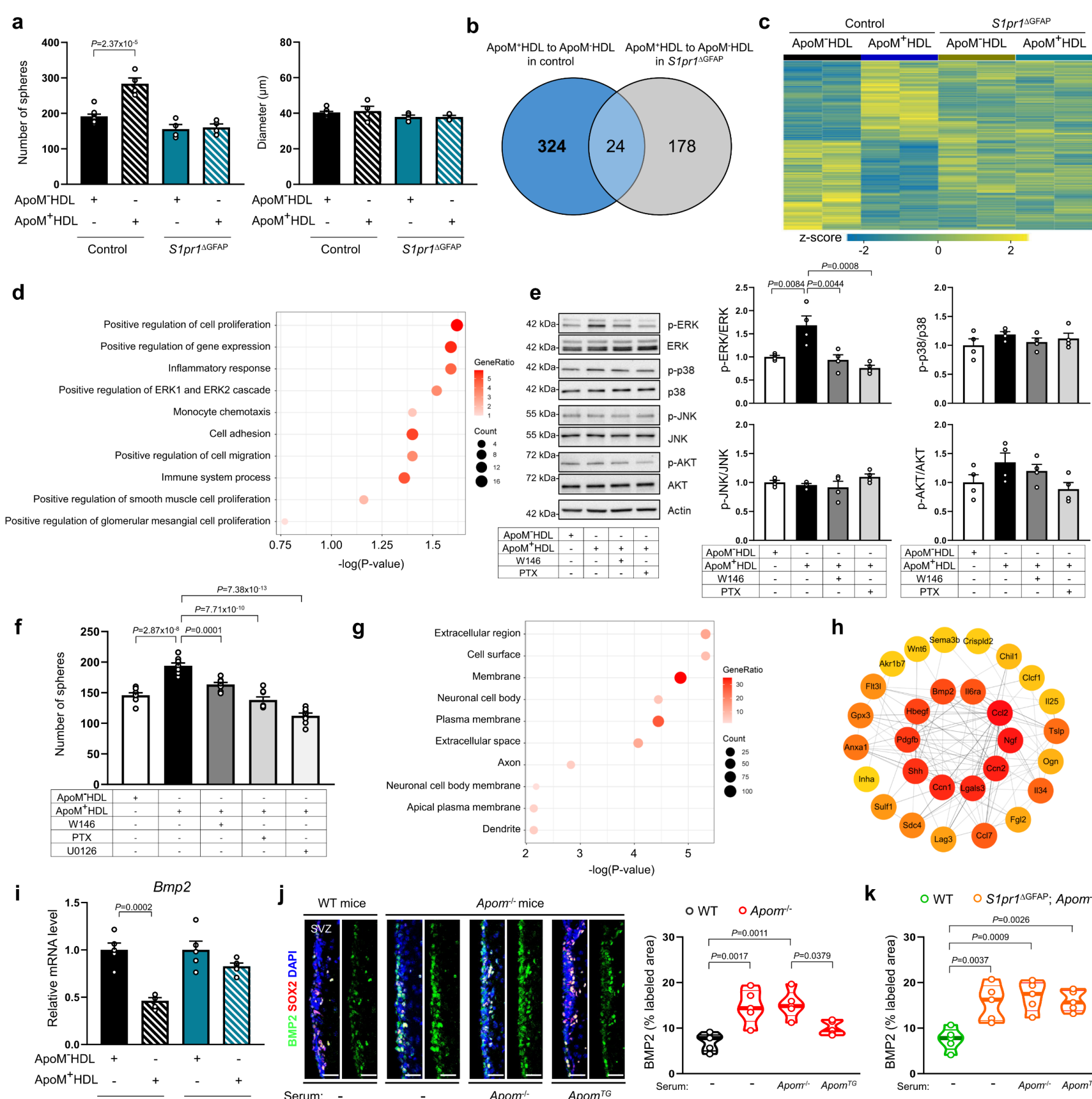


Figure 5. ApoM-S1P-S1PR1 signaling promotes SVZ-NSCs self-renewal via ERK pathway and inhibits BMP2 expression.

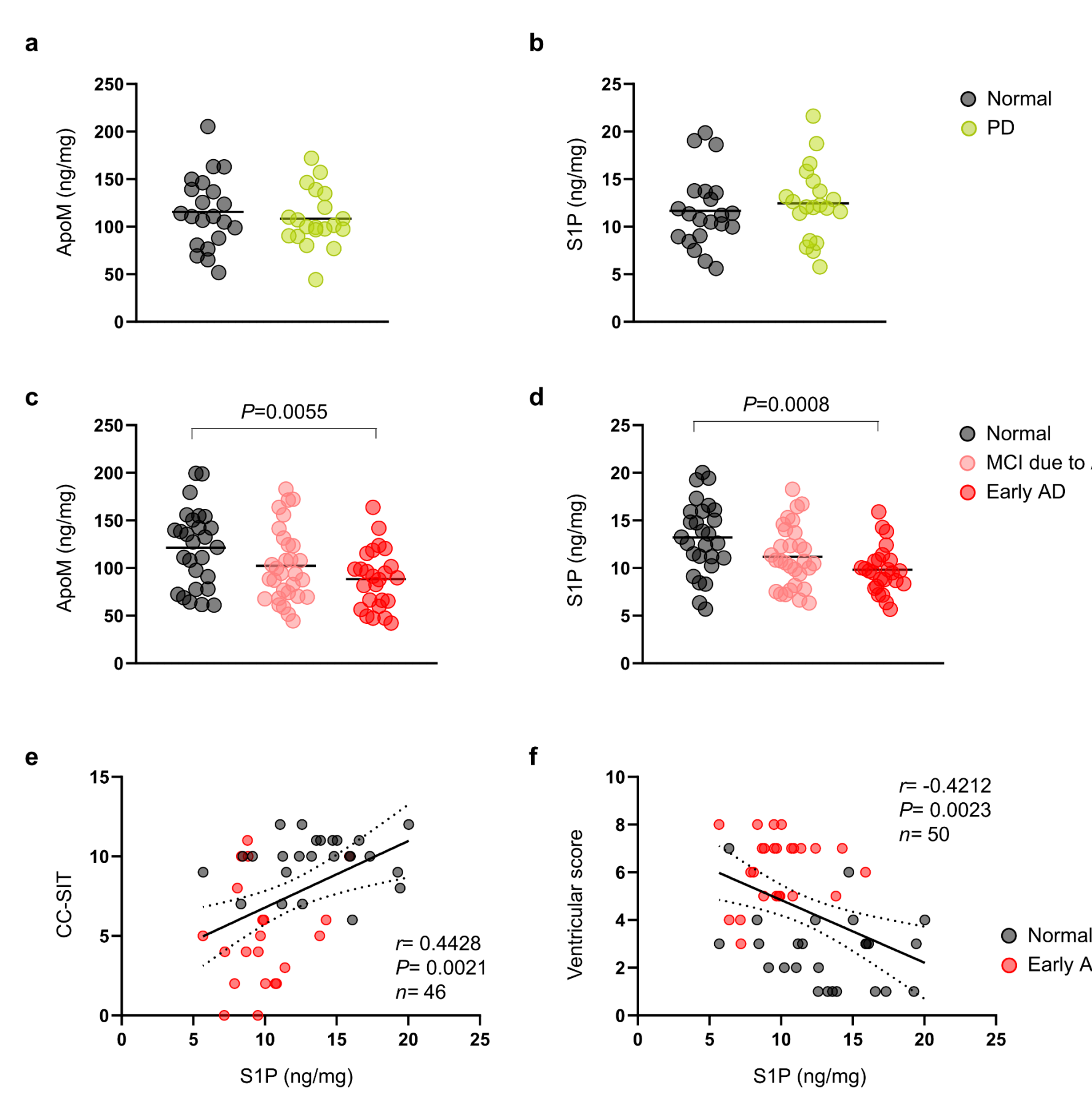


Figure 6. Decrease of blood ApoM-S1P complex correlates with olfactory dysfunction and LV enlargement in early AD patients.

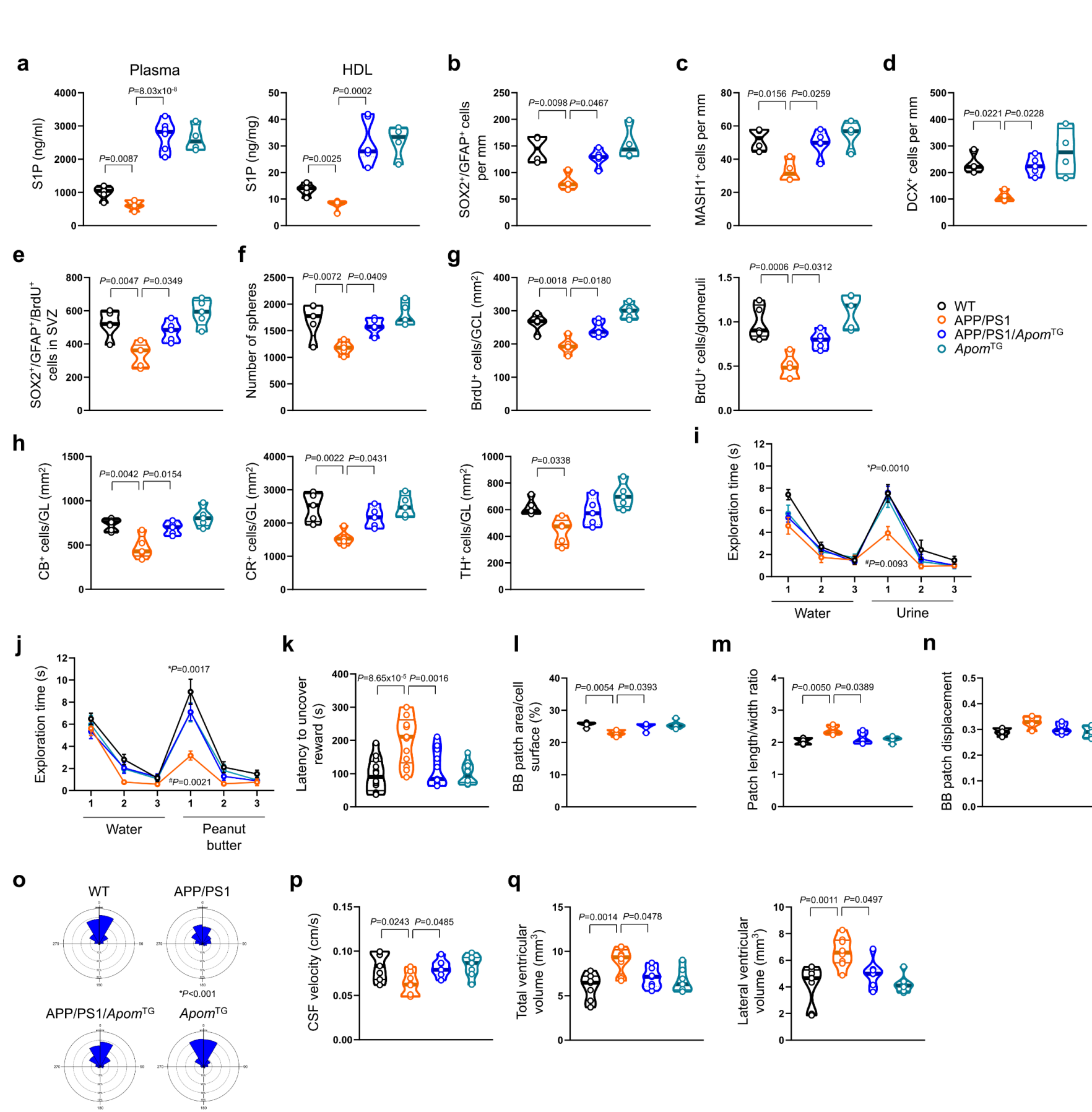


Figure 7. Enhancement of blood ApoM-S1P complex ameliorates early events in APP/PS1 mice.