Introduction: ApoE4 is the most prevalent genetic risk factor for Alzheimer’s disease (AD). Brain synaptic aberrations are a pivotal pathology in AD.

Aim: To examine whether the synaptic dysfunction induced by ApoE4 in target replacement (TR) mice starts at a young age and to investigate the specific pre-synaptic constituents which are damaged by ApoE4.

Methods: Hippocampi of young (4 months old) ApoE3 and ApoE4 TR mice were subjected to western blot (WB) analysis and immunohistochemistry (IHC). The levels and localization of specific synaptic markers were measured.

Results: The hippocampal levels of Synaptophysin, a general marker of synaptic vesicles were similar in ApoE3 and ApoE4 mice as determined by WB (100±6.7 vs. 98±5.4 respectively; P=0.81). In contrast, the levels of Vglut, a pre-synaptic vesicle transporter of excitatory glutamatergic synapses were reduced in ApoE4 mice (100±6.2 vs. 64±3.5; P< 0.001). Immunohistochemical investigation of Vglut localization demonstrated that the effect is specific to the CA1 sub-field of the hippocampus. The levels of the inhibitory GABAergic marker GAD67, as measured by WB, were also reduced in ApoE4 mice but to a lesser extent (100±6.3 vs. 82±4.9; P< 0.05). In addition, the levels of the cholinergic pre-synaptic vesicular transporter, Vacht were also reduced in ApoE4 mice (100±8.9 vs. 77±4.9; P=0.05).

Conclusions: Young ApoE4 TR mice exhibit synaptic deficits. The observed ApoE4 induced decrease in vesicular transporters and not on the general vesicular marker, Synaptophysin, suggests a specific intra-synaptic mechanism. This will be addressed in the near future.