Apolipoprotein E (apoE) is the lipoprotein expressed in the central nervous system (CNS). ApoE is also the best validated genetic risk factor for Alzheimer’s Disease (AD) and outcome following a wide a variety of acute neurological insults. The cholesterol transporter ABCA1 moves lipids onto apoE as the rate-limiting step in brain HDL biosynthesis. In AD mice, ABCA1 deficiency exacerbates amyloidogenesis, whereas selective overexpression of ABCA1 ameliorates amyloid burden. Liver X Receptor (LXR) agonists such as GW3965, which stimulate ABCA1 and apoE expression, reduce Aβ levels and rescue cognitive deficits in AD mice. We show that ABCA1-mediated lipidation of apoE is a crucial mechanism underlying the beneficial effects of LXR agonists on cognition and Aβ metabolism and highlights ABCA1 and apoE as a potential therapeutic targets for AD. We also show that the ability of GW3965 to promote motor and cognitive recovery after mild concussive brain injury is reduced in apoE-deficient mice. Together, these observations support a central role for apoE function in mediating the beneficial effects of LXR agonists for both chronic and acute CNS damage.