Current lifestyle places individuals under increasingly greater loads of psychological and physical stress. Although the mechanisms that are triggered by stress are primarily adaptive facilitating homeostasis, chronic stress can become maladaptive. Specifically, stress and its primary manifestation, glucocorticoid (GC) secretion is strongly associated with memory deficits, impaired cognitive performance as well as mood and affective disorders such as depression. A causal role of chronic stress in the etiopathology of Alzheimer’s disease (AD) has been also suggested. Although cumulative evidence suggests a continuum between depression and AD, and stress is suggested to play a detrimental role in both diseases, considerably less attention has been given to the suggested role of stress as a connecting factor. We have been investigating the inter-relationship between these various pathogenic elements in transgenic and non-transgenic mice, with particular focus on mechanism(s) through which stress precipitates brain pathology. Our studies show that stress and GC trigger APP misprocessing towards amyloid-β production and abnormal tau hyperphosphorylation/aggregation resulting in associated impairments of cognitive and emotional status. Furthermore, we show that the presence of tau predisposes animals to stress/GC detrimental effects highlighting dendritic and synaptic tau and its malfunction as a key protein regulating neuronal dysfunction and synaptic degeneration. Conclusively, these studies suggest that tau plays a crucial role in the mechanism through which stress and GC exert their neuro-remodelling and neurodegenerative effects upon the substrates of cognition and emotion.