1. SUMMARY:

In this thesis we reported astrocytic atrophy characterized by a reduction in the surface area and volume of GFAP-positive glial cells in the prefrontal cortex of 3xTg-AD mice – an important morphological alteration starting far before any well known histopathological hallmark of AD. This change is present in parallel with homeostatic failure suggested by the decreased expression of GS. Those alterations can have drastic effects on brain connectivity and the biochemistry of the main neurotransmitters within the brain, such as glutamate and GABA. GFAP is implicated in a variety of processes, such as cell migration and proliferation, neurite outgrowth, astrocytic glutamate transporter expression (GLAST and GLT-1) and synaptic plasticity, so that every change can shift the astrocytes' role from physiology to pathology. In the case of affected GFAP-IR astrocytes, the withdrawal of processes from neurons and synapses can lead to a severe transmission crush, due to the uncontrolled spillover of the neurotransmitter from the synaptic cleft, inadequate metabolic support and the lack of a physiological barrier between the affected synapse and other synapses in its close vicinity. This will directly disturb the reciprocal connections between the affected brain regions, inluding the important structures for memory and emotions, such as the entorhinal cortex, the hippocampus and the PFC. Through the glutamate transporters (GLT-1, GLAST) and specific enzymes (GS), astrocytes are able to successfully protect the brain from excess of glutamate. After cytoskeletal astrocytic atrophy (independent of Aβ accumulation), the observed GS deficiency can result in a shortage of glutamine for neurons due to the distorted glutamate-glutamine cycle and subsequently in an insufficient synaptic effect. The mechanisms and regulations of the aging brain are complicated and still not fully understood. Different markers can show opposite changes depending on brain region, as was proven by studying GFAP, GS and S100β expression in senescent astrocytes. Further study of astroglial aging in needed to reach the next step in helping the brain to remain less affected in the face of advancing age. The common agreement underlines the fundamental importance of maintaining harmony between the elimination and compensatory remodeling of neuronal nets. This reshaping is highly dependent on homeostatic stability, support and defence.

The basis for proper brain function lies in well functioning networks, in which neurons and glia are evenly involved. The results of studies presented in this thesis underline the crucial role of astrocytes in maintaining metabolic stability within the synaptic and neuronal environment, which makes them a promising therapeutic target in the prevention as well as the treatment of AD.