Long-term potentiation (LTP) and long-term depression (LTD) are two forms of synaptic plasticity, which comprise cellular processes that enable learning and memory. Learning and memory demonstrate a high variability in acquisition and stability among behavioural states, aging, and health conditions. Neuromodulatory systems, such as the serotonergic, noradrenergic or dopaminergic system, are involved in mediating this variability. In this thesis, the influence of specific receptor sub-types of these neuromodulatory systems on hippocampal synaptic plasticity was investigated in freely behaving rats. Moreover, those receptors were tested for their potential to rescue amyloid-beta (Aβ)-induced deficits in LTP expression in an animal model of Alzheimer’s disease.

Focus was especially made on the role of the serotonergic 5-HT$_4$ receptor, the β-adrenergic and the D1-like dopamine receptors in regulating very persistent (> 24 h) forms of hippocampal synaptic plasticity. The serotonergic 5-HT$_4$ receptor influences cognitive performance in learning tasks and on a cellular level, the 5-HT$_4$ receptor exercises a unique veto function in Schaffer-collateral CA1 synapses: pharmacological agonism or antagonism of this receptor lowers the threshold to induce LTP or LTD, respectively (Kemp and Manahan-Vaughan, 2005). Here, the effect of 5-HT$_4$ receptor manipulation on different forms of synaptic plasticity in the dentate gyrus was investigated. Pharmacological agonism prevented LTD and weakly curtailed robust LTP in young adult rats (2-4 month old). This finding contrasts with findings in the CA1 region, suggesting that the 5-HT$_4$ receptor regulates hippocampal synaptic plasticity in a sub-region specific manner in young healthy rats. Moreover, information encoded by LTP is prioritised over LTD-related encoding if the 5-HT$_4$ receptor is pharmacologically activated.

The β-adrenergic and the D1-like dopamine receptors are involved in behaviour-driven modulation of cognitive performance and hippocampal synaptic plasticity. Activation of both receptors lower the threshold for LTP induction in young healthy rodents. Middle-aged rats were tested for this facilitation of LTP when sub-threshold high-frequency stimulation (subHFS) was applied in the presence of the agonist. Pharmacological activation of either the
β-adrenergic or the D1-like dopamine receptor failed to prolong or enhance weak potentiation in middle-aged rats (8-14 month old), although LTP (> 24 h) could nonetheless be induced by specific patterns of afferent stimulation. This indicates that relatively early in aging, a reduction in β-adrenergic and D1-like dopamine receptor regulation of LTP develops. This may comprise one of the neurobiological changes in neural homeostasis that accompanies and contributes to the gradual accumulation of deficits in hippocampal learning that occur in aging.

The abovementioned findings prompted the question as to whether changes in neuromodulatory control is a contributor to the deficits in hippocampal synaptic plasticity that develop in animal models of Alzheimer’s disease. Neuromodulatory nuclei are affected early in Alzheimer’s disease in humans and manipulation of β-adrenergic or the D1-like dopamine receptors has been shown to interact with Aβ-induced deficits in cognition or synaptic plasticity in transgenic AD models. Here, middle-aged rats were treated with amyloid-beta (Aβ) oligomers, which resulted in a permanent deficit in the ability of the animals to express hippocampal LTP. Interestingly, coincidental, but not separate activation, of both β-adrenergic and D1-like dopamine receptors rescued LTP expression in these Aβ-injected animals. Though, the timing and relative amount of receptor activation is highly relevant for successful LTP expression in Aβ-treated animals.

Taken together these data demonstrate a highly specific role of serotonin, noradrenaline and dopamine receptor sub-types in modulation of the encoding of neuronal information by hippocampal synaptic plasticity and indicate an involvement of β-adrenergic and D1-like dopamine receptors in Aβ-induced changes in synaptic plasticity in hippocampal function.