Summary

This thesis aimed to examine various aspects of the interaction between emotion and cognition. In Chapter 1, the background and aims of each study were briefly introduced. A few recent studies were detailed to illustrate that emotion and cognition often interact together in a dynamic manner rather than the strict modular fashion previously assumed. For instance, a certain component of emotion (motivation) can modulate an important aspect of cognition (attention) in a top down manner and thereby influence the behavioral outcome.

In Chapter 2, the facilitating effect of increased motivation on spatial memory performance by comparing was demonstrated 6J and DBA mice. The two strains were tested in a modified Barnes maze test which allowed the impact of motivation by keeping spatial configuration and motoric requirement constant while the nature of reinforcers varied. While the results from the version of the test where an aversive reinforcer was used replicated the previous findings which showed inferior performance in DBA, the use of appetitive reinforcer improved the performance in DBA to the level of 6J mice. Importantly, DBA mice increased the use of spatial strategy significantly as well indicating the genuine presence of spatial learning. The results cautions against drawing conclusion on spatial memory in rodent based on single test especially when there is a clear possibility that noncognitive factors, such as motivation or motoric skills, differ between experimental groups.

Chapter 3 focused on the validation of the novel spatial memory test used in the previous chapter. The performance in the modified design was compared with the one in the classical design with all other experiment condition constant. As indicated by the increased number of errors and poorer performance in the long term memory test, mBM test seems to pose significantly more cognitive challenges for mice. The pseudorandom patterning of the holes in mBM in contrast to the circular hole arrangement in the classical design considerably decreased the usage of serial strategy which has been one of main confounding factors in the Barnes maze test and

which often occurs in animals with higher level of anxiety. The increased task complexity together with the dominant use of spatial strategy indicates that mBM is an effective spatial memory test.

Chapter 4 presents the results of a substrain comparison study in the context of PTSD. Despite their close genetic proximity, our results show a few distinctive differences between C57BL/6J and C57BL/6N, which reflects the increased susceptibility to stressors in the 6N strain. First, 6N showed marked fear extinction impairment in the Passive avoidance test. Second, the anxiety-level increased significantly more in 6N after an aversive procedure (forced swim test). Third, as in the case of PTSD patients, there was a subtle cognitive impairment in 6N which was manifested with increasing task load. Moreover, 6N persisted in ineffectual explorative pattern throughout the training, which is reminiscent of certain perseverative behavior patterns in PTSD patients. Finally, real-time quantitative PCR analysis identified 5 candidate genes by comparing gene expression levels in the hippocampus which might underlie the marked vulnerability to traumatic events in 6N mice. Taken together, 6N mice exhibit many facets of human PTSD symptoms, identifying this strain as a valuable PTSD animal model.

In Chapter 5, the role of 5-HT_{1A} receptors in fear memory was investigated. In particular, the memory-facilitating effect of the partial 5-HT_{1A} agonist S15535 which has been reported to show procognitive effects in several tests. Our results indicate that S15535 behaves in a similar manner to the full agonist 8-OH-DPAT by impairing the fear conditioning performance in a dose-dependent manner albeit with a smaller effect size. NAD-199, a 5-HT_{1A} antagonist facilitated fear conditioning performance indicating that the blockade of postsynaptic 5-HT_{1A} receptors leads to a mild memory enhancement. Taken together, our data show that stimulation of 5-HT_{1A} receptors lead to memory impairment and blockade of them to memory facilitation in fear conditioning. The discrepancy from the previous findings regarding the procognitive effect of S15535 might be due to the differences in the tests used since the action of

partial agonists depends strongly on the endogenous level of the ligand and can differ between the tests.

While there are inconsistencies regarding the effect of 5-HT_{1A} receptors on cognition, there is a general agreement that 5-HT_{1A} receptors play an important role in the anxiolytic action. A considerable number of studies also indicated the attenuation of stress-induced tachycardia by 5-HT_{1A} agonists, which was regarded as beneficial. However, our data in mice show that 8-OH-DPAT induces a pronounced bradycardia with preserved heart rate increase upon the presentation of a conditioned stimulus (tone). Importantly, this change in HR by 8-OH-DPAT was accompanied by several pathological aspects including prolonged QT elongation and arrhythmic episodes. Considering that more studies are reporting the aversive effects associated with SSRI use on heart rate variability, and that the anxiolytic effect of SSRIs is predominantly mediated by 5-HT_{1A} receptors, the current results might bear important clinical implications.