Exploring the triad of behaviour, genes and neuronal networks: Heritability of instrumental conditioning and the Arc/Arg3.1 gene in hippocampal coding
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Chapter 7. Summary

In this thesis, we set out to study the genetic background of neuronal function that enables adaptive behaviours that are essential for survival, such as understanding the relations between actions and outcomes and forming accurate representations of the environment. In the experimental protocols we used, exploratory and cue-response behaviour were motivated by sweet rewards, mimicking real-life situations in which we form memories of environments and action-outcome series associated with rewards. Finally, we dissected the off-line processes that underlie consolidating such memories by recording neuronal activity during sleep.

In Chapter 2, we showed results that validate the usefulness of a novel, appetitively motivated instrumental learning protocol that allows fast and efficient screening of inbred mouse lines and assessing the genetic background of instrumental learning. Using this multi-step protocol, we were able to distinguish multiple stages of chained operant learning (nose poke–lever press task). Furthermore, we demonstrated that these stages are dissociable, heritable and regulated by different chromosomal areas. We went on to characterize the operant performance in common laboratory mouse strains that are often used as genetic background in transgenic studies and identified mouse lines that could be used for studying specific deficits in incentive learning processes that require chaining cues and actions together.

In Chapter 3, we extended the protocol prescribed in Chapter 2 to cover extinction learning. Inhibiting previously acquired responses is a complex process, and impaired response suppression is closely attributed to various neuropsychiatric disorders. In line with previous behavioural and neuroanatomical findings — mostly from fear learning studies — which have shown that acquisition and extinction are dependent on different brain areas, we demonstrate that these traits are dissociable also on a behavioural level; performance in the acquisition stage does not predict performance in the extinction stage. Furthermore, we showed that also extinction performance was heritable. We characterized the performance of common laboratory mouse strains and suggested recombinant-inbred mouse lines that could serve as models for studying perseverant disorders.
Previous studies have shown that Arc/Arg3.1 protein is important for contextual and spatial learning. In Chapter 4, we dissected the role of Arc/Arg3.1 in neuronal processes that take place during active exploration of an environment. We recorded cellular and network activity in the hippocampal CA1 and found that while the basic firing properties and place fields of pyramidal cells in Arc/Arg3.1 knockout (KO) mice were intact, the hippocampal oscillatory activity in the high frequency range was attenuated and synchronized firing, as measured by locking of neuronal spikes to oscillations in the hippocampus, was impaired. Furthermore, we observed less sharp wave–ripple activity in KO mice during the intermittent rest periods taking place between active bouts of exploration, which thought to represent replay of recently experienced events. These alterations in the CA1 neuronal network activity may contribute to the previously reported spatial learning deficit in Arc/Arg3.1 KO mice.

In Chapter 5, we assessed the neuronal activity of Arc/Arg3.1 KO mice during sleep. In line with the earlier evidence that has demonstrated Arc/Arg3.1 to have a crucial role in synaptic plasticity and long-term memory, we showed that Arc/Arg3.1 KO mice had decreased hippocampal sharp wave–ripple activity and that e correlated firing activity during sleep was impaired. These processes have been previously connected with off-line memory consolidation, and may explain why Arc/Arg3.1 mice are impaired in various long-term memory tasks.

Together, these findings paint an intriguing picture of the genetic background and neuronal processes involved in complex behaviours that are crucial for survival. In order to further understand and unravel this intricate linkage, we will need to continue to study the triad of genes, neuronal networks and behaviour from all its corners.