MULTIFACETED SCHIZOPHRENIA

Marchisella, E.

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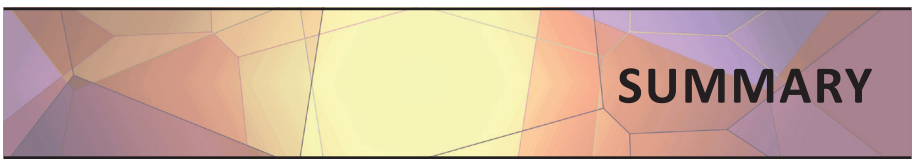
SUMMARY

Systematic behavioral phenotyping of genetically modified mice is a reliable method that can be used to detect the molecular factors involved in animals' behavior, with translational relevance for neuropsychiatric disorders. In this thesis, we performed an in-depth behavioral analysis of four putative animal models of schizophrenia. We studied three genetic models (*DISC1*, *ErbB4* KO & CNVs microdeletion models) that mimic disease-associated gene mutations and one biological model that mimics a dysfunction in the GABAergic system, thought to be associated with schizophrenia pathophysiology.

Chapter 2 presents a study on the constitutive loss and acute pharmacological manipulation of the ErbB4 signaling [602]. So far, little is known on the role of *ErbB4* in attention and inhibitory control, two aspects of executive functions that are impaired in schizophrenia. In this chapter, we investigated the effects of constitutive loss of *ErbB4* in the central nervous system of mice on performance in a 5-choice serial reaction time task (5-CSRTT). Transgenic mice did not show deficits in various parameters of attention and premature responses. Nonetheless, *ErbB4*$^{-/-}$ mice recapitulated a specific set of behavioral phenotypes associated with schizophrenia, including a deficit in spatial learning and memory in the Barnes Maze and contextual fear learning, as well as a trend for a deficit in sensorimotor gating.

Furthermore, we investigated the effect of acute pharmacological inhibition of ErbB tyrosine kinase receptor using the pan-ErbB kinase inhibitor JNJ-28871063 (JNJ). JNJ did not affect attention and inhibitory control in an automated version of the 5-CSRTT. In conclusion, this study suggested no direct involvement of a classical Nrg-ErbB4 pathway in attention and inhibitory control in mice, while it confirms the involvement of this pathway in other domains relevant to schizophrenia.

Chapter 3 focuses on the behavioral analysis of three mouse models of Copy Number Variations (CNVs), namely the 1q21, 15q13.3, and 22q11.2 microdeletions. It has been shown that microdeletions of 1q21, 15q13.3, and 22q11.2 loci have a strong statistical association with the occurrence of schizophrenia and other psychiatric disorders [32–34]. In this chapter, we described how we systematically compared the behavioral phenotypes of mice carrying a single allele microdeletion of the syntenic portion of the 1q21, 15q13.3, and 22q11.2. Our results showed that the *Df(h22q11.2)/+* mice exhibited a significantly decreased pre-pulse inhibition at 100 ms compared with their wild-type controls and a radial arm maze deficit. Alterations in anxiety and sociability were found for the *Df(h15q13)/+* mice on the elevated plus maze test and the social interaction test. The *Df(h1q21)/+* line did not show impairments in the cognitive and social domains tested. Collectively, these data demonstrated that *Df(h22q11.2)/+* and *Df(h15q13)/+* microdeletions in mice result in behavioral phenotypes that partly mimic symptoms associated with these deletions in humans.

Chapter 4 describes the behavioral signature of the *DISC1* gene in two transgenic mouse models. Specifically, in the first model, the transgenic mice overexpress the full-length of *DISC1* transgene (tg*DISC1*) mimicking the rats model from Trossbach et al., 2016 [368]. In the second model (*Der1*), heterozygous and homozygous mice carry a segment of the human chromosome 11 in a part of the murine genome, where half of the *DISC1* has been removed and as such resembles the genetic

translocation seen in humans [154]. We systematically compared the behavior of the tg*DISC1* and *Der1* mice in our schizophrenia test battery. Overall, our results showed no significant differences between the transgenic mice of the two lines and their respective controls in any of the tested domains. However, the tg*DISC1* mice exhibited impaired social behavior in the 3-chambers test.

Chapter 5 outlines a study on the attentional performance of mice presenting a DREADDs-induced PV^+ dysfunction. Deficits in attentional processing are a core symptom of schizophrenia, and until now, only a few studies have functionally investigated PV^+ interneurons in attention tasks in rodents. In this chapter, we studied the role of these cells in attention and inhibitory control by regulating their activity with chemogenetic receptors (DREADDs) exclusively activated by specific ligands (CNO or SALB). The results showed no direct involvement of the prefrontal PV^+ interneurons in attentional performance of mice in an automated version of the 5-CSRTT; thus, we concluded that the PV^+ interneuron population in the mPFC might play only a secondary role in high cognitive functions, such as attention.

Chapter 6 summarizes and compares the results presented in this thesis, as well as discusses their implications. Moreover, recommendations for future research experiments are given.