Abstract

Cognitive flexibility is the ability to adjust thinking and behavior based on changing conditions. Cognitive rigidity has been described in a variety of psychiatric and neurodevelopmental disorders and has been suggested to contribute to symptom maintenance. Therefore, we aimed to study cognitive flexibility and other behavioral characteristics in several rodent models relevant to schizophrenia, obsessive-compulsive disorder, and autism spectrum disorder. In a two-hit mice model relevant to schizophrenia, we found the between-group difference in set-shifting and decreased number of parvalbumin interneurons in the hippocampus of stressed female mice. Interestingly, we found no impairment in any other behavioral task. In two pharmacological rat models relevant to OCD, we showed that sensitization to D2/D3 receptor agonist quinpirole and serotonin 1A/7 agonist 8-OH-DPAT produced severe spatial learning and memory impairment in the Active Allothetic Place Avoidance task. The impairment was so severe that the reversal couldn't be tested. Surprisingly, drugs decreasing glutamatergic neurotransmission, memantine and riluzole, further impaired the performance in both models, although no such effect was observed when they were applied alone. Lastly, we showed that the knockout of a collapsin response mediator protein 2 (CRMP2) produced behavioral and neurobiological impairments relevant to autism spectrum disorder. CRMP2 knockout mice had defects in axonal guidance, pruning, and dendritic spine remodeling, decreased social interaction in the postnatal period and adulthood, increased perseveration in the Y-maze and decreased anxiety in the Elevated Plus Maze. Surprisingly, they had normal spatial memory and reversal learning in the Active Allothetic Place Avoidance task.

Keywords: Cognitive flexibility, animal models, schizophrenia, obsessive-compulsive disorder, autism spectrum disorder