

ABSTRACT

Schizophrenia is a severe neuropsychiatric disorder characterized by positive, negative and cognitive symptoms with poor functional outcomes, placing an enormous burden on the individual, caregivers and society. Although deficits in cognition are an integral part of the disease and the best predictor of functional outcomes, there is as yet no established treatment addressing them. Avoidance of a hidden place on a continuously rotating arena (Carousel) requires cognitive control and is a rodent model of cognitive coordination of information from dissociated spatial frames, which is impaired in acute pharmacological and neurodevelopmental model of schizophrenia. Cognitive training on the Carousel during adolescence alleviates adult cognitive deficit in a neurodevelopmental model of schizophrenia and improves neural coordination (oscillations in the beta and gamma band), which is thought to be necessary for cognition.

We examined if cognitive training during adolescence eliminates the deficit in neuronal coordination observed in adult rats after acute systemic NMDA receptor antagonist MK-801 (0.15 mg/kg). During adolescence, rats were either trained in spatial avoidance on Carousel or merely handled. As adults, rats received two 5-min exploration sessions in the same (A/A) or in two distinct environments (A/B) to induce immediate-early gene (IEG) expression in hippocampal CA1 neurons. We analysed the brains using expression of IEGs *Arc* and *Homer 1a* (catFISH) to map neuronal populations (ensembles) activated during two exploratory sessions.

Consistent with previous research, exploration of a novel environment significantly increased and MK-801 decreased expression of IEGs *Arc* and *Homer 1a*. We also replicated the finding that in saline-treated animals, CA1 ensembles activated by exploring same environment twice (A/A) are more similar than ensembles activated by A/B. The difference in A/A to A/B similarity we observed was significant, but not as stark as reported by other authors, a difference that we ascribe to the suboptimal housing conditions of rats and noise during IEG-induction phase of the experiment. As to our main hypothesis, that similarity of A/B acitvated ensembles in MK-801-treated rats would be lower in trained animals, similarity was decreased more than two-fold in trained animals compared to non-trained controls. The difference, however, did not reach significance, which we ascribe to small number of subjects we used combined with suboptimal conditions during IEG-induction phase of the experiment. Overall, our results are suggestive of protective effect of adolescent cognitive training on neuronal coordination in acute systemic MK-801 rat model of schizophrenia.

Key words: cognitive control, cognitive coordination, neural coordination, spatial navigation, rotating arena, Carousel, animal model, schizophrenia, non-competitive NMDA antagonists, dizocilpine (MK-801), immediate-early genes (IEG), *Arc*, *Homer 1a*, catFISH