ABSTRACT 30

FOXP2 FUNCTIONS IN MOTOR-SKILL LEARNING

Catherine A. French[1], Mariana Correia[1], Simon E. Fisher[2,3], Rui M. Costa[1]

[1] Champalimaud Neuroscience Programme, Champalimaud Centre for the Unknown, Lisbon, Portugal
[2] Language and Genetics Dpt, Max Planck Institute for Psycholinguistics, Nijmegen, The Netherlands
[3] Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands

A significant number of children fail to acquire normal speech and language skills, despite adequate intelligence and opportunity. Foxp2 was the first gene directly implicated in these difficulties, and offers a unique entry point into the underlying neural mechanisms. Disruptions of Foxp2 cause a rare speech and language disorder, a core feature of which is problems in sequencing orofacial movements. The gene encodes a transcription factor which is expressed in cortico-striatal/ -cerebellar circuits required for sensorimotor integration and motor-skill learning, and imaging studies have identified structural abnormalities in these same regions in affected individuals. Foxp2 is also highly conserved in several other vertebrate species, where expression is seen both during development and in adulthood. Mice carrying an aetiological Foxp2 mutation have motor-skill learning deficits and lack striatal long-term depression. They also show abnormally high striatal activity in vivo which is aberrantly modulated during acquisition of a motor task. In zebra finches, Foxp2 knockdown in the striatal song nucleus Area X disrupts developmental and social modulation of song variability.

We generated a conditional mouse to disrupt Foxp2 in specific brain regions (cortex, striatum or cerebellar Purkinje cells), or at a defined time point (adulthood). This genetic approach was combined with an operant task where a sequence of 8 lever presses must be completed to obtain a reward. After 12 days a time constraint was added and the sequence had to be performed at increasingly high speeds. We found that Foxp2 in discrete circuits contributes differentially to motor-sequencing speed and stereotypy. Cerebellar mutants executed press sequences of all speeds more slowly than controls, whereas impairments in striatal and cortical mutants were typically seen when the task became more difficult. Interestingly, striatal mutants also executed some press sequences more variably. Global Foxp2 disruption in adulthood was achieved using a tamoxifen-inducible Cre. Tamoxifen was administered at 10 weeks of age and around one third of Foxp2 knockdown animals died in the following weeks. Surviving animals were healthy and showed normal motor-sequence learning, despite appearing to be less motivated. This indicates that developmental Foxp2 expression is critical for the learning of motor-skills in adult animals.