Effects of conditional Foxp2 deletion on motor-sequence learning

ABSTRACT:

Disruptions of *FOXP2* cause a speech and language disorder, a core deficit of which are problems in sequencing orofacial movements. The gene encodes a transcription factor that is expressed in cortico-striatal/ -cerebellar circuits which are required for sensorimotor integration and motor-skill learning, and imaging studies of affected individuals have identified structural abnormalities in these regions. FOXP2 is also highly conserved in several other vertebrate species including mice, where expression is seen in comparable brain areas during development and in adulthood. The aims of this study were to 1) establish the contributions of Foxp2 in specific brain regions to motor-sequence learning 2) examine Foxp2 functions in adulthood. We generated conditional mice with selective Foxp2 disruptions in the cortex, striatum or cerebellar Purkinje cells, and assessed effects on motor-sequence learning using an operant lever-pressing task. Foxp2 in each of the circuits contributed differentially to the speed and variability of lever-press sequences. Pronounced deficits were seen in cerebellar Purkinje cell mutants and, in collaboration with Prof. Chris De Zeeuw, we showed that Purkinje cells lacking Foxp2 have increased excitability and are atypically modulated *in vivo* during locomotion. We also used an inducible Cre to disrupt Foxp2 globally in adulthood. This resulted in the deaths of around one third of mutant mice, although surviving animals appeared healthy and executed lever-press sequences normally. In sum, we found that early Foxp2 expression is critical for motor-sequence learning and model-based decision making, but continued expression in mature animals is important for other behaviours such as sociability.

Keywords
Motor-sequence learning, Foxp2, Speech and language, Conditional gene disruption, *in vivo* electrophysiology

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