Universität Basel

Research Project

Assembly and function of motor circuits

Third-party funded project

Project title Assembly and function of motor circuits
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An important goal in neuroscience is to understand how the assembly of neuronal circuits contributes to the emergence of function controlling dedicated animal behaviors. Motor behavior represents the ultimate output of nearly all nervous system activity. An intricate network of neuronal circuits within the spinal cord communicating bi-directionally with higher centers in the brainstem and brain, as well as integrating sensory feedback from the periphery ensures the accuracy of motor output. Despite its seeming complexity, the final motor output system displays an exquisite degree of organization, and is experimentally accessible at a high degree of specificity, using genetic, molecular, anatomical and physiological analysis linked to a direct behavioral output. The overall goal of our studies will be to extract information on how – at the neuronal circuit level – specificity of connections in the motor system can explain behaviors as complex as motor behavior. Our major focus over the next several years will be to contribute to our understanding of how motor circuits influence and regulate the activity of functionally defined groups of motor neurons in the spinal cord. All experimental approaches described here have the common goal to study how establishment and connectivity of circuits relates to and controls the emergence of motor function. The projects described in the detailed research plan will represent a major effort in my laboratory over the next several years. They are presented in four main sections, but technologies and concepts overarch the entire proposal. (1) Regulation of connectivity and transcription by retrograde NT3 signaling: These studies aim at providing us with an understanding of the mechanisms regulating connectivity and transcription controlled by retrograde NT3 signaling. We will (a) study the distribution of premotor interneuron subpopulations in mice with genetically altered NT3 levels, (b) determine genome-wide transcription profiles of isolated proprioceptive afferents derived from mice with altered NT3 levels, and (c) establish a strategy based on next generation sequencing approaches to identify subpopulation gene expression based on profiles of individual neurons and computational analysis. (2) The role of proprioceptive feedback circuits in assembly and function of motor circuits: The main aim of this project is to reveal the role of the proprioceptive feedback system in motor circuit assembly and function in the spinal cord. We will (a) identify the nature of the signal required for extensor-specific premotor connectivity, (b) establish systems for conditional ablation or alternation of activity patterns in proprioceptors, and (c) determine consequences of proprioceptor ablation at different developmental time points for circuit connectivity and motor behavior. (3) Timing of neurogenesis in motor circuit connectivity and function: This part of the project aims at elucidating the importance and rules of timing of neurogenesis for the establishment of motor circuits. We will (a) address whether individual spinal progenitor cell clones give rise to spinal premotor interneurons with distinct function and elucidate how timing of neurogenesis intersects with the acquisition of transcriptional profiles, and (b) establish whether causality between neuronal birthdating and motor circuit function exists. Together, these experiments will reveal the contribution of neurogenesis timing to the establishment and function of motor circuits. (4) Premotor network analysis of motor neurons of different evolutionary emergence: This project will address the question of whether premotor networks controlling the activation of motor neurons with different evolutionarily standing exhibit distinct or similar spinal distribution patterns. We will categorize which neuronal types of the premotor network are shared or split between ancestrally distinct motor neuron populations. These will include motor neurons innervating axial muscles, body wall muscles, as well as proximal and distal limb muscles, comparing hind- and forelimb patterns; providing insight into different circuit modules and strategies of motor control.

Keywords Motor control, Developmental biology, Neural circuit assembly, Spinal cord, Transcription factors, Mouse genetics, Neuronal specification

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Published results

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