

Cholinergic modulation of cerebellar dependent motor learning

Supervisory team:

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Project description:

The improvement of motor skills with practice occurs through motor learning in the cerebellum and is required for everyday life. Acetylcholine (ACh) is required for learning and memory and regulation of sleep/wake cycles. An extensive network of cholinergic fibres courses throughout the cerebellum but little is known about the significance of ACh projections to the cerebellum. This project will test the hypothesis that cholinergic projections from the pedunculopontine nucleus (PPN) to the cerebellum regulate synaptic and neuronal function to bring about encoding, consolidation and maintenance of motor learning during different phases of sleep and wake. The student will join an interdisciplinary team of 7 postdocs and 8 PhD students supervised by Profs Bashir and Apps.

The hypothesis will be tested directly using *in vitro* and *in vivo* electrophysiological methods, optogenetic manipulation of cholinergic inputs to cerebellum, behavioural investigation of motor learning and computational modelling. The *in vitro* methods allow the study of cellular mechanisms in ways not possible in behaving animals, whereas the awake *in vivo* animal experiments allow study of neural circuits and their functional and behavioural significance. The brain slice and whole animal work will be mutually reinforcing. *In vivo* work: forelimb motor learning paradigms will be used in freely moving animals.

Rats will be chronically implanted with tetrodes in the PPN, cerebellar cortex and/or cerebellar nuclei to monitor single unit and LFP activity during motor learning. Pharmacological antagonists and/or optogenetic manipulation of cholinergic inputs will determine the role of different ACh receptor subtypes and the timing of ACh inputs during learning.

In vitro Work: whole cell patch clamp recordings from cerebellar slices combined with optogenetic stimulation of ACh inputs will investigate how ACh controls: i) intrinsic properties; ii) synaptic inputs; and iii) the plasticity of these synaptic inputs in Purkinje cells and CN output neurons to provide an essential foundation for understanding molecular, cellular and synaptic mechanisms by which ACh controls cerebellar function. The *in vitro* and *in vivo* data will be implemented within a biophysical model to test hypotheses of ACh modulation of cerebellar neuronal networks.

Together results from this project will forge new understanding of how ACh controls cerebellar function to bring about motor skills that are essential for everyday life.