OIST SEMINAR

Hosted by Brain Mechanisms for Behaviouir Unit

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DATE: Thursday, December 18th, 2014

TIME: 15:00 – 16:00

VENUE: Meeting Room D015, Level D, Lab 1

Correcting abnormal motor thalamus activity in parkinsonian rats improves movements

Abstract:

Motor thalamus (Mthal) is a key node in the cortico-basal ganglia (BG) loop that controls complex, cognitive aspects of movement. In Parkinson's disease (PD), profound changes in neuronal activity occur in BG nuclei and cortex and because Mthal is located between these two structures, altered Mthal activity has been assumed to underlie PD motor deficits. We investigated if changes in Mthal activity underlie impaired movements in PD-model rats and then examined if normalising Mthal activity restores movements. We recorded Mthal neuronal firing rate and pattern in control and 6-hydroxydopamine lesioned rats during reach-to-grasp movements. Mthal firing rate in control rats was modulated in a temporally precise pattern during reaching, with a peak at the time of reach-end and troughs just before and after it. Low threshold calcium spike (LTS) events were rare, but also decreased in incidence just after reach-end. The inhibitory modulations in firing rate and LTS events were abolished in PD-model rats. To determine if movements can be restored by normalising Mthal neural activity in PD-model rats, and to assess a potential therapy, we stimulated the Mthal using a physiological pattern previously recorded in the Mthal of a control rat during reaching. For this, glutamatergic Mthal neurons were selectively transduced with channelrhodopsin-2 by injecting a lentiviral vector (CaMKII-ChR2(H134R)-mCherry) and activated using blue light. Rats performed the reaching task in acute parkinsonian (0.03-0.07 mg/kg haloperidol, s.c.) or control (vehicle injection) conditions and reaching performance was recorded before, during and after optogenetic stimulation. Control rats executed >30 reaches/min, which was unaffected by any of the stimulation patterns. PD-model rats displayed marked akinesia (<4 reaches/min), which was significantly improved by optogenetically stimulating with the physiological reaching pattern, whereas tonic patterns (130 Hz and 6.2 Hz, a rate control for the reach pattern) failed to improve reaching performance. These data confirm that nigrostriatal dopamine depletion is accompanied by specific deficits in movement-related Mthal activity, which is likely to impair motor programme development in the motor cortex in PD. In addition, correcting this pathophysiology significantly improves movements, confirming that the Mthal may be an effective site to treat non-tremor motor symptoms, but the pattern of stimulation is critical.

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