

## ABSTRACT

Spinocerebellar ataxias (SCAs) constitute a heterogeneous group of diseases characterized by the dysfunction of the cerebellum and disturbed coordination of movements. Aside from these, many SCA patients suffer also from cognitive impairments and diverse mental issues, including apathy, depression and anxiety. Although often overlooked, growing evidence suggests their profound contribution to the reduced life quality and poor health outcomes. However, their nature remains largely unclear. This thesis aims to address this by studying the mouse models of hereditary ataxia.

To achieve this, psychiatric-relevant behavioural abnormalities and their underlying neuropathology were studied in mice with cerebellar-specific degeneration (lurcher) and the knock-in mouse model of spinocerebellar ataxia 1 (SCA1 mice). The methodology included complex behavioural testing, histological techniques, biochemical analyses, immunofluorescence imaging, and measuring the mitochondrial oxidative metabolism. Obtained data were then analysed using modern statistical approaches accompanied by computer-intensive methods such as bootstrapping simulations.

Experiments confirmed cognitive deficits in both lurcher and SCA1 mice. Interestingly, behavioural characterization identified numerous psychiatric-relevant behavioural impairments in SCA1 mice that have not been identified in any SCA animal model so far, including reduced prepulse inhibition, diminished cognitive flexibility, and increased anxiety- and depressive-like behaviour. This phenotype partially contrasts with the behaviour of cerebellar-specific lurcher mice, which showed a lack of depressive-like behaviour. In SCA1 mice, some psychiatric-relevant impairments preceded the onset of substantial ataxia. SCA1 mice also exhibited hippocampal atrophy with decreased neuroplasticity indicators, reduced mitochondrial bioenergetics and hugely impaired neurogenesis. Interestingly, the hippocampal atrophy commenced earlier than cerebellar degeneration and directly reflects some behavioural deficits, namely depressive-like behaviour and cognitive inflexibility. These results suggest that mental issues in SCA1 have biological roots partially independent of the cerebellum and suggest new avenues in the search for novel SCA1 therapies.

