decoding of declarative memory. In this model, replaying activity in the hippocampus did not allow memories to become established in the neocortex independently of the medial temporal lobe, but it did allow the system to maintain access to episodic memories that were stored in the hippocampus, by keeping them 'in register' with changing cortical representations.

Models such as this are valuable for testing hypotheses and for formulating new ones, but their greatest value comes when they are used in conjunction with empirical studies. This modelling study makes a number of predictions that can now be tested. For example, in the absence of hippocampal replay of activity patterns, episodic recall should degrade because of continuing cortical plasticity. This could be tested by measuring how quickly memories are forgotten after hippocampal lesions.

Rachel Jones

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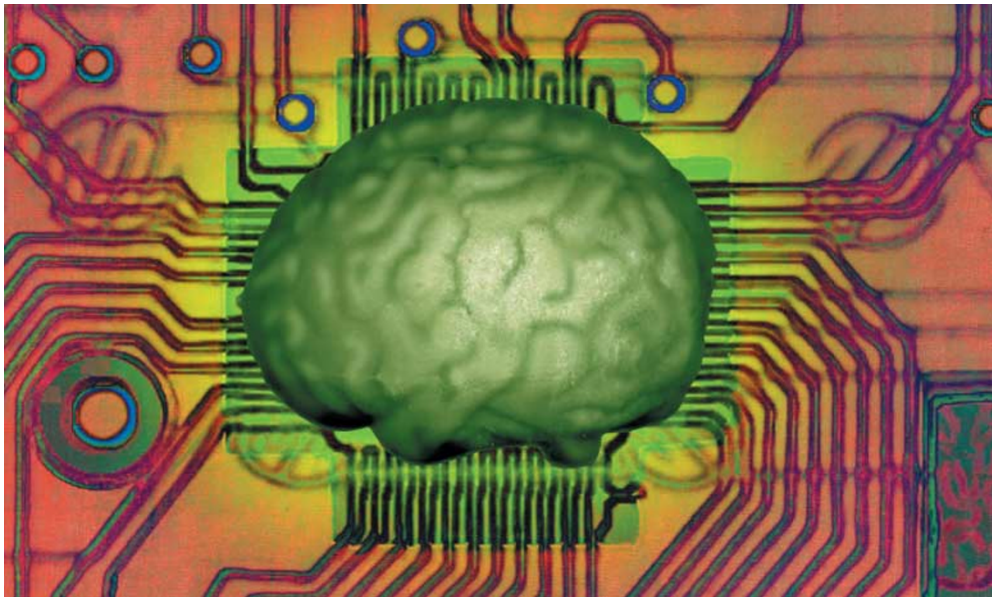

NEUROLOGICAL DISORDERS

Hyperexcitability induces ataxia

Degeneration-related reduction of inhibitory output from Purkinje neurons is a feature of cerebellar ataxia, a lethal disease that is characterized by postural and gait abnormalities and impairment of speech. Loss of this inhibitory output causes hyperexcitability of the deep cerebellar nuclei (DCN) to which these Purkinje neurons project. As DCN are thought to modulate motor coordination, George Chandy and colleagues investigated the link between ataxia and hyperexcitability of DCN neurons.

The team used a transgenic approach to generate a mouse model of cerebellar ataxia in which hyperexcitability of DCN neurons develops in the absence of neurodegeneration. Based on the rationale that small-conductance calcium-activated potassium (SK) channels regulate the firing rate of DCN neurons, mice were transformed with a green fluorescent protein-tagged dominant-negative SK3 alternate transcript under the control of a neuron-specific promoter that is particularly active in the DCN.

This strategy suppressed the expression of SK proteins in DCN neurons of transgenic mice, resulting in a more than tenfold decrease in the amplitude of the after-hyperpolarization current of DCN neurons and enhanced frequency of spontaneous firing. Pharmacological inhibition of SK channel activity with apamin had a similar effect. Importantly, these changes occurred in the absence of cerebellar neurodegeneration.

Transgenic mice developed many characteristics of cerebellar ataxia, including activity-dependent tremor and incoordinated movement without postural abnormalities or muscle wasting. In addition, their performance on tests of balance, motor learning, grip strength and gait was significantly impaired relative to their non-transgenic littermates. Symptom severity was correlated with the level of transgene expression in the DCN. There was also a temporal correlation between the onset of ataxia (at postnatal day 11) and first detection of transgene expression in DCN neurons (at postnatal day 10).

Besides DCN, the transgene was expressed in the red nucleus, the pontine nucleus and the motor cortex. However, expression levels in these areas were poorly correlated with disease severity. This observation, in combination with strong transgene expression in the red nucleus of a non-ataxic mouse line, led the authors to assert that the contribution of transgene expression in non-DCN brain regions to the ataxic phenotype is minimal.

So, it is likely that some forms of cerebellar ataxia are due not to neurodegeneration *per se*, but to the resulting hyperexcitability of DCN neurons. Controlling hyperexcitability with SK openers such as the neuroprotectant riluzole might therefore be of benefit to sufferers of this devastating disorder.

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