be widely adopted by other fields of study. Thus, exciting possibilities exist for uLIPSTIC to become a standard tool to advance the study of cell–cell communication in the immune system and beyond.

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Neuroscience

Non-neuronal brain cells modulate behaviour

Anna Kruyer

A single gene in astrocytes can constrain repetitive behaviours, indicating that these cells are regulators of behavioural disruption in conditions such as Huntington's disease and obsessive–compulsive disorder. **See p.358**

Neurons have long been considered the brain cells chiefly responsible for behaviour, but this longstanding perspective overlooks an important cell type — the astrocyte. On page 358, Ollivier *et al.*[1] report that a subpopulation of brain astrocytes can control repetitive behaviors. The authors' findings make a compelling argument for considering astrocytes as a crucial regulator of behavioural disruption in various cognitive and psychiatric disorders.

Astrocytes are a diverse type of glial cell, whose name refers to its inferred function as 'glue' that holds neurons and other brain cells in place. Consistent with this moniker, astrocytes and other glia are mostly considered supporting cells for neurons, which are given exclusive credit for encoding the brain's fundamental functions: thinking and controlling behaviour. Emerging research contends with this assumption by showing that astrocytes play an important part in modulating signalling between neurons at junctions called synapses. Thus, astrocytes are elevated from neuronal glue to puppeteers of neuronal function, and key drivers of behaviour.

Ollivier *et al.* describe a subpopulation of astrocytes, notable for their expression of the gene *Crym*, in a portion of the brain called the striatum that encodes motivation and habit. Although the protein that *Crym* encodes, μ-crystallin, was discovered in 1957 (ref. 2), its role in the brain has remained mostly unexplored until now.

Interest in the function of μ-crystallin in the brain was spurred by genetic studies that demonstrated a relationship between the *Crym* gene and seemingly disparate brain disorders. In obsessive–compulsive disorder (OCD) and Huntington's disease (HD), for example, *Crym* expression is inversely correlated with disease severity[3,4]. Ollivier and colleagues' careful examination of μ-crystallin localization revealed that its dense expression in the striatum is targeted not to neurons, but to a population of astrocytes. They used animal models to explore the behavioural consequences of *Crym* downregulation in striatal astrocytes, as observed in people with OCD and HD.

Using a series of behavioural tests, the authors report that an artificially reduced expression (knockdown) of *Crym* has no effect on motor control or anxiety, but produces a striking increase in 'perseveration', or repetitive behavioural patterns that serve no apparent purpose. In rodents, perseveration reveals itself through an increase in

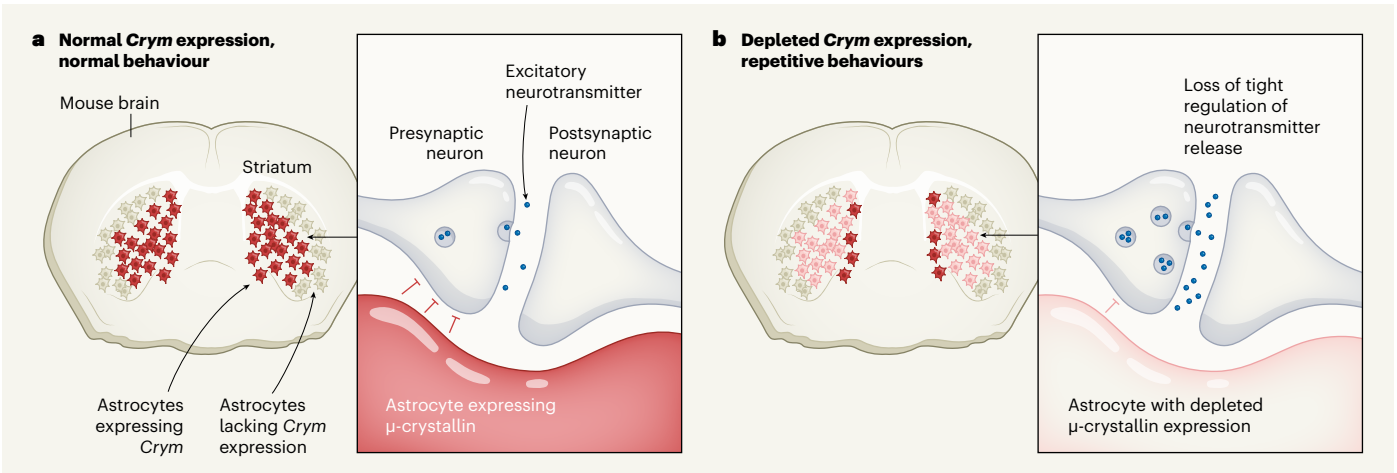

Figure 1 | Signalling between brain astrocytes and neurons permits flexible, rather than repetitive, behaviours. **a**, In a part of the mouse brain that controls motivation and habit (the striatum), Ollivier *et al.*[1] discovered a subpopulation of non-neuronal cells, known as astrocytes, that is distinctive for its dense expression of the gene *Crym*, which codes for the protein μ-crystallin. They found that *Crym*-expressing astrocytes (red) contribute to the tight control of the release of excitatory neurotransmitter molecules at synapses (junctions between neurons), and hence to normal behaviour in mice. **b**, When the authors artificially depleted *Crym* expression in striatal astrocytes (pink), they observed a disinhibition of excitatory neurons and an increased release of excitatory neurotransmitter molecules, leading to neuronal hyperactivity. *Crym* depletion resulted in a lack of behavioural flexibility in mice, leading them to engage in repetitive behavioural patterns such as excessive self-grooming.

time spent on behaviours such as burying marbles, self-grooming, licking their enclosure's waterspout and exploring familiar objects. Perseveration is a component of many psychiatric and cognitive disorders that are characterized by difficulties in switching between different thoughts and behaviours — an ability known as cognitive and behavioural flexibility. Such disorders include both OCD and HD, as well as stroke and other forms of brain injury, some dementias, autism spectrum disorder, psychosis and attention deficit hyperactivity disorder[5]. Previously, it was not understood that perseveration could be isolated as an independent feature of behaviour, or that it was mediated by non-neuronal cells.

To determine how μ-crystallin reduction contributes to perseveration, the authors next explored the physiology of neurons signalling to the striatum in mice that lacked *Crym* expression in astrocytes. They found a shift in the overall balance of excitatory and inhibitory signals produced by neurons (Fig. 1). This balance is normally maintained by astrocytes that tightly regulate the release of neurotransmitter molecules and their removal from synapses[6]. Knowing this, the authors applied a technology to silence overactive excitatory neurons in mice lacking *Crym* expression in astrocytes, and observed a reduction in behavioural perseveration. This indicated that restoring normal astrocyte–neuron signalling in this pathway is a potential therapeutic strategy to alleviate perseveration.

Work remains to be done to understand the finer details of the signalling that occurs between astrocytes and neurons to regulate behavioural flexibility, and exactly how reductions in μ-crystallin interrupt this signalling. The authors indicate that a decrease in the release of inhibitory molecules through an astrocyte protein called GAT-3 might be responsible for the imbalance between excitatory and inhibitory signals that is triggered by *Crym* knockdown — an exciting topic that is ripe for future investigation. μ-crystallin is known to alter gene expression in response to thyroid hormones, and to possess enzymatic activity[7]. But how these functions contribute to the observed changes in the regulation of neuron activity by astrocytes remains to be seen.

"Astrocytes are elevated from neuronal glue to puppeteers of neuronal function."

Despite remaining questions, the experiments conducted beautifully by Ollivier *et al.* make a clear and compelling case for a broader exploration of glial cells in brain diseases. These findings also point directly to disrupted signalling between astrocytes and neurons as a fundamental factor influencing a cardinal symptom of several brain disorders, and reveal new therapeutic avenues for its management.

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