them, on the basis of the patterns of usage of the words in the original text. Importantly, these meanings and relationships are not explicitly encoded by humans, but are learnt in an unsupervised way from the analysed text.

The researchers found that the obtained word embeddings for materials-science terms produced word associations that reflect rules of chemistry, even though the algorithm did not use any specific labels to identify or interpret chemical concepts. When combined using various mathematical operations, the embeddings identified word associations that corresponded to concepts such as 'chemical elements', 'oxides', 'crystal structures', and so on. The embeddings also identified clusters of known materials (Fig. 1) corresponding to categorizations that could be used to classify new materials made in the future.

But Tshitoyan *et al*. went further than just establishing relationships between words — they also demonstrated how their approach could be used for prospective materials discovery. They began by training a machine-learning model to predict the likelihood that a material's name will co-occur with the word 'thermoelectric' in the text (thermoelectric materials are those in which a temperature difference generates a voltage, or vice versa). They then searched the text to find materials that had not been reported to have thermoelectric properties, but whose names have a high semantic relationship with the word 'thermoelectric' — and that might therefore actually be thermoelectric.

The authors validated this approach by training a model using literature published before a particular cutoff year, and then checking to see whether it identified materials that were reported to be thermoelectric in subsequent years. The top 50 materials picked using this method were 8 times as likely to have been studied as a thermoelectric in the 5 years after they had been reported than were randomly chosen materials. Tshitoyan and colleagues' approach therefore demonstrates yet another successful application of text mining, which has now been used in fields ranging from materials science to protein identification[3] and cancer biology[4].

The combination of unsupervised machine learning and text mining for scientific discovery is intriguing, given the burgeoning growth of both supervised and unsupervised methods for natural-language processing in the past few years, and the increasing availability of digitized scientific literature that encompasses more than 100 years of publications. Of course, many challenges remain. Chief among them is the fact that unsupervised methods are typically less accurate than models obtained from supervised learning. Moreover, although word embedding looks promising as a way of identifying materials that have particular properties, it cannot be used to identify materials not described in the literature, whose names are not part of the existing vocabulary. However, such methods could be used to find previously unrecognized properties of existing materials, which could then be repurposed.

The field of materials informatics is emerging in parallel with the growth of materials databases, in much the same way as chemoinformatics arose 20 years ago with the establishment of chemistry databases[5]. Progress is fast, because methods based on data and literature mining are established tools for data scientists working in the chemical and materials sciences[6]. Future studies that use natural-language processing and unsupervised learning in ways similar to those used by Tshitoyan *et al*., or that use both unsupervised and supervised learning, can be expected to increase the impact of data science on materials design and discovery. So, will the next big discovery in superconductors, for example, be made through conventional human intuition or by machine? In all likelihood, it will be a smart combination of both human and machine intelligence. ■

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NEUROSCIENCE

Star-like cells drive hyperactivity

A molecular dialogue between neurons and star-shaped cells called astrocytes in the striatum of the mouse brain leads to behavioural hyperactivity and inattentiveness that are reminiscent of attention-deficit hyperactivity disorder.

ZHIHUA GAO & HAILAN HU

Astrocytes are star-shaped cells that account for about 40% of cells in the mammalian brain. Initially considered to be the 'glue' that sticks neurons together, astrocytes actually have crucial roles in brain homeostasis and in regulating the formation, maturation, function and elimination of synapses, the connections through which neurons communicate with each other[1–4]. Although much progress has been made in elucidating the roles of astrocytes[1–4], our understanding of how they regulate neural circuits and affect behaviours that are associated with neurological and psychiatric disorders is just emerging[5–9]. Writing in *Cell*, Nagai *et al.*[10] present evidence in mice that selective activation of astrocytes in the striatum, a brain region that integrates signals from many parts of the brain to coordinate voluntary movement[11], drives behavioural changes that resemble the symptoms of attention-deficit hyperactivity disorder (ADHD) in humans through a dialogue with striatal neurons.

ADHD is a prevalent psychiatric and neurodevelopmental disorder that affects approximately 5% of children worldwide, and its major symptoms include excessive activity (or restlessness) and difficulty in sustaining attention[12]. Although dysfunction in the striatum has been implicated in ADHD[13], the underlying mechanisms of how the striatum — and, in particular, striatal astrocytes — might contribute to the disorder, remain elusive. The striatum largely consists of a special type of medium-sized neuron that is inhibitory (that is, it suppresses the activity of connected neurons) and that features many tiny protrusions called spines that receive synaptic inputs from other neurons. When activated, these medium spiny neurons (MSNs) release the inhibitory neurotransmitter molecule GABA (γ-aminobutyric acid) to reduce the activity of other neurons, and together the MSNs control behavioural movement[14].

Because MSNs are intermingled with astrocytes and form close contacts with them[15], Nagai *et al.* set out to examine whether MSN activation might affect the activity of surrounding astrocytes. The authors monitored astrocyte activity by making these cells express a genetically encoded calcium indicator — a protein that fluoresces in response to increases in the concentration of calcium ions (which are involved in cell signalling). They found that, when they stimulated MSNs using an electric current, the calcium-ion signalling in nearby astrocytes increased. This increase depended on the release of GABA from the MSNs, and on the activation of type B GABA receptors ($GABA_B$ receptors),

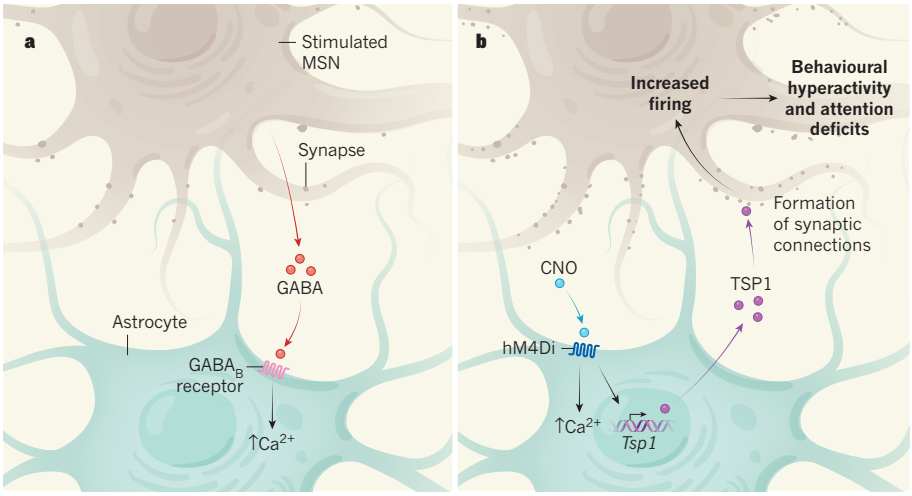

Figure 1 | An astrocyte–neuron dialogue that leads to behavioural hyperactivity in mice. **a**, Stimulation of cells called medium spiny neurons (MSNs) in the striatum region of the brain releases the neurotransmitter molecule GABA (γ-aminobutyric acid), which activates $GABA_B$ receptors (an example of a group of membrane proteins called inhibitory G_i protein-coupled receptors; G_iPCRs) on striatal cells known as astrocytes. This results in an increase in levels of calcium ions (Ca^{2+}) in the astrocytes. **b**, Nagai *et al.*[10] used the drug clozapine *N*-oxide (CNO) to activate an engineered, CNO-activated G_iPCR (called hM4Di) that was expressed by astrocytes in the mouse striatum to mimic the activation of $GABA_B$ receptors specifically in astrocytes. CNO treatment increased the calcium-ion levels in astrocytes and upregulated the cells' expression of the protein thrombospondin 1 (TSP1). TSP1 is known to promote the formation and growth of synaptic connections between neurons. Nagai *et al.* showed that, in CNO-treated mice, TSP1 enhances the responses of MSNs to synaptic inputs from upstream neurons and increases the firing of MSNs, leading to behavioural hyperactivity and attention deficits.

which are located in the cell membrane and, when bound to GABA, inhibit activity in the rest of the cell. These receptors are examples of a type of membrane protein known as an inhibitory G protein-coupled receptor (G_iPCR), which suppresses cell activity by releasing an inhibitory G protein (G_i) inside the cell.

$GABA_B$ receptors are expressed by both neurons and astrocytes. The authors set out to dissociate the effects of astrocytic and neuronal $GABA_B$ receptors in the striatum, but were unable to deplete these receptors specifically from striatal astrocytes. So, instead, they turned to a tool that mimics the activation of these receptors in astrocytes. They expressed hM4Di, an engineered version of another G_iPCR (the human M4 muscarinic receptor), selectively in striatal astrocytes of mice. The hM4Di receptor is selectively activated by a drug called clozapine *N*-oxide (CNO). Thus, treating these mice with CNO robustly increased calcium-ion levels in hM4Di-expressing astrocytes. The authors observed that CNO treatment of the mice also induced inattentiveness and behavioural hyperactivity — assessed by measuring the animals' movements and the time spent investigating novel objects, among other behaviours — reminiscent of human ADHD.

Next, Nagai *et al.* asked how the activation of astrocytic G_iPCRs drives behavioural hyperactivity. By examining the firing patterns of MSNs adjacent to astrocytes that expressed hM4Di, they found that CNO treatment boosted the electrical impulses of MSNs and enhanced MSN responses to inputs from neurons in the brain's cerebral cortex. To unravel the molecular mechanisms that underlie these astrocyte-driven changes in MSN activity, Nagai *et al.* analysed the levels of RNA transcript molecules in striatal astrocytes, and found that the expression of a molecule called thrombospondin 1 was substantially upregulated in G_iPCR-activated astrocytes.

Thrombospondin 1 promotes the formation of new synapses during brain development[16]. Nagai *et al.* found that, in the striatum of adult mice, astrocytes can hijack the same molecular mechanism to promote the growth of MSN synapses and thus increase MSN firing. Crucially, blocking thrombospondin 1 signalling — using a molecular inhibitor of the neuronal thrombospondin 1 receptor — prevented CNO-induced increases in MSN synaptic growth and MSN firing as well as CNO-induced behavioural hyperactivity. Collectively, these results suggest that overactivation of striatal astrocytes in adult mice can reactivate a developmental mechanism whereby thrombospondin 1 promotes synaptic growth, resulting in abnormal striatal activity and behavioural hyperactivity.

Nagai and colleagues demonstrate how the acute, specific activation of astrocytes in a particular brain region can lead to ADHD-like behaviour. They illuminate a bidirectional interaction between neurons and astrocytes, through which the two cell types augment each other's activity (Fig. 1). The fact that this seems to be a positive-feedback-like mechanism might explain why activation of astrocytic G_iPCRs can induce behavioural abnormalities so quickly (within 2 hours). The work adds nicely to the growing body of research that demonstrates the importance of astrocytes in brain function and psychiatric disorders[5–7].

The study also raises many questions. For example, given that astrocytes are diversified in different brain regions[15], is the same G_iPCR-induced activation mechanism shared by astrocytes throughout the brain? In addition, the G_s protein-coupled group of receptors, which stimulate cell activity, also boost calcium levels in striatal astrocytes[15]; are there differences in the spatial and temporal dynamics of the astrocytic calcium signals that are activated by these two seemingly opposite pathways[17]? If so, do these pathways engage different downstream signalling events and drive different functions?

The striatum contains two subtypes of MSN — one that expresses the dopamine 1 receptor (D1 MSNs) and one that expresses the dopamine 2 receptor (D2 MSNs) — and these subtypes act in opposing pathways to coordinate voluntary movement[13]. Although Nagai *et al.* showed that both D1 and D2 MSNs signal to astrocytic $GABA_B$ receptors, does thrombospondin 1 from activated astrocytes selectively act on one of these two MSN subtypes to drive movement? These questions await future investigation.

With the advent of modern genetic tools, such as those that enable precise measurement of gene expression in single cells or that allow specific manipulation of different cell populations, future studies will continue to uncover diverse and exciting functions of these star-like cells. Such functions might provide the basis for strategies to treat ADHD and other psychiatric disorders. ■

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