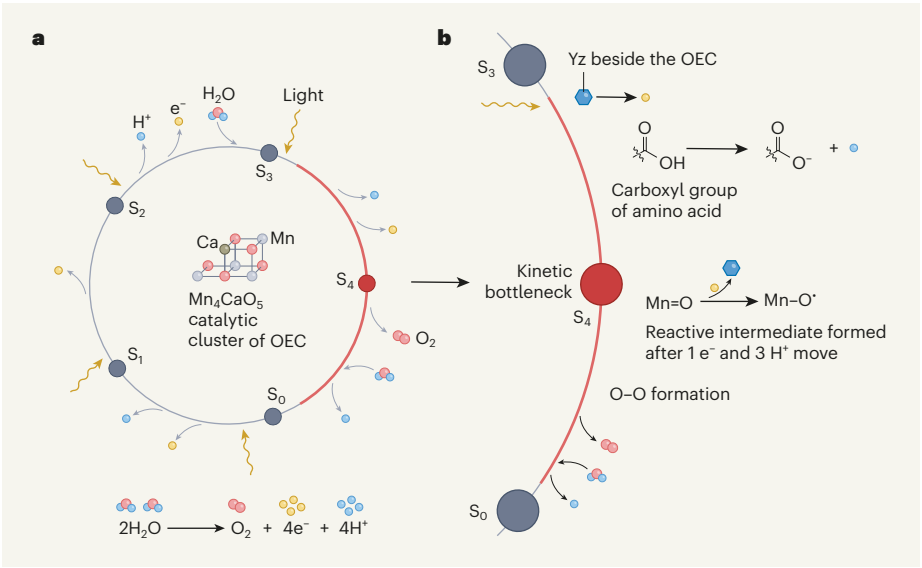

Figure 1 | Key steps in photosynthesis. a, A light-dependent reaction splits water into oxygen (O_2), hydrogen ions (H^+) and electrons (e^-). This occurs in a region of the enzyme photosystem II called the oxygen-evolving complex (OEC), which is a catalytic cluster of manganese (Mn), calcium (Ca) and oxygen ions. The OEC cycles between states termed S-states. **b**, Bhowmick *et al.*[1] and Greife *et al.*[2] reveal the sequence and timing of individual steps during the $S_3 \rightarrow S_4 \rightarrow S_0$ transition. These events include electron and H^+ movements (exits or transfers) in and around the OEC that involve Y_Z and other amino-acid residues. At the S_4 stage, a crucial reactive group (Mn–O•) is generated, and this step is rate-limiting (a kinetic bottleneck) for the entire reaction. The wiggly line across the bond attached to the carboxyl group indicates that the group is attached to an amino-acid residue.

infrared spectroscopy (FTIR) to study the kinetics of the $S_3 \rightarrow S_4 \rightarrow S_0$ transition. Building on a remarkable experimental set-up that enabled detection of time-resolved vibrational spectra of the OEC over thousands of catalytic cycles, the authors identified distinct processes that occur during the transition. The results suggest that formation of the Y_Z radical after the S_3 state is followed by a deprotonation event at 340 µs, for which the spectral features can be associated with an amino-acid residue. The authors' quantum-chemical calculations attribute this to either Asp61 or a pair of residues (Glu65 and Glu312), in remarkable agreement with Bhowmick and colleagues' conclusion.

Formation of a reactive manganese-bound oxygen radical (Mn–O•, the S_4 transient reactive intermediate) involves an extraordinary simultaneous transfer of one electron and three protons, and is identified as the rate-limiting step (kinetic bottleneck) of the whole reaction. The subsequent O–O bond formation and O_2 release are faster, by comparison. This shows that preparing for O–O bond formation is harder than actually performing this step, which makes sense if, in this way, the enzyme avoids the accumulation of highly reactive intermediate products.

Both studies provide crucial insights into, and new constraints on, the mechanism of biological water oxidation. The studies complement each other as well as previous work[3,4] on the timing of the early deprotonation event, the proton-exit pathway and the stability of the S_4 state. The mechanistic interpretations are broadly in line with expectations from previous computational studies[5] but offer a much-needed experimental framing.

This does not mean that the mechanism is fully solved. The XFEL snapshots of Bhowmick and colleagues cannot be viewed as 'freeze-frames' of a movie depicting a reaction pathway, because the proposed chemical events and intermediates are mostly inferred, rather than observed. Furthermore, a large part of the mechanism derived from the quantum-chemical approach presented by Greife *et al.*, although consistent with the experimental data, is not the only possible explanation. Lack of direct information about where the electrons are in the catalyst during the $S_3 \rightarrow S_4 \rightarrow S_0$ transition means that no mechanistic scenarios can be safely excluded at this point. In view of the central role of Y_Z and the necessity of understanding proton movement, these are obvious targets for future investigation using complementary experimental approaches[6,7] and by theoretical methods. The hardest questions in biological water-splitting seem much closer to a final answer than ever before.

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Cancer neuroscience

How thought itself can drive tumour growth

George M. Ibrahim & Michael D. Taylor

Tumour cells can form connections with neurons in the brain. Examination of a variety of types of evidence concerning human brain cancer sheds light on how these tumour–neuron interactions affect cognition and survival times. **See p.599**

Few effective treatments are available for a common and universally fatal type of adult brain tumour called a malignant glioma. Although these tumours exist exclusively in the central nervous system, the interactions between malignant glioma cells and the 86 billion neurons in the human brain are poorly understood. This is particularly relevant because most people with the disease develop progressive cognitive decline that robs them of quality of life during their final months[1]. Krishna *et al.*[2] show on page 599 that malignant gliomas can grow by modifying brain circuitry, thus taking cognitive function away from their host and ultimately leading to death. These insights might lead to fundamentally new approaches to glioma treatment and provide a means of limiting cognitive decline in affected individuals.

The human brain is a complex system that involves highly coordinated interactions between large-scale specialized groups of

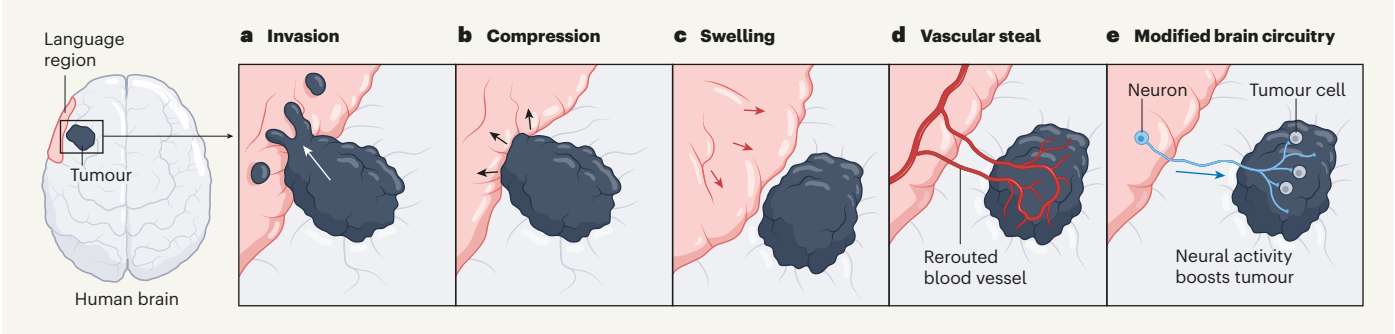

Figure 1 | Models for cognitive problems associated with brain tumours. The human brain contains regions that are important for language processing, such as an area on the left side of the brain. **a**–**d**, Various models have been proposed to explain neurological deficits in people with brain tumours. The tumour might invade or compress tissues, cause swelling in adjacent tissues or reroute blood supply to the tumour. **e**, Krishna *et al.*[2] provide evidence for a model in which brain tumours cause cognitive decline by modifying the neuronal circuitry of the brain. Tumours can form connections called synapses with neurons, and these connections can boost tumour growth when the neurons are actively signalling[5]. The authors report that activity in regions of the brain involved in a language task also drove activity in tumour-associated regions that do not normally function in language processing. High functional connectivity associated with neuronal signalling in tumours predicts aggressive tumour behaviour, cognitive decline and poor survival.

neurons called neural networks. The dynamic and malleable nature of these networks, a feature often referred to as neuroplasticity, forms the basis for development and learning[3] and also serves other functions, including recovery from brain injury. The most basic unit of neuroplasticity is the point of contact between two neurons – and this connecting structure, called a synapse, allows information to propagate inside the brain and to the rest of the body. All human thoughts, actions, emotions and memories exist in a meshwork of electrochemical signals mediated by the synapse.

Before the presentation of this work by Krishna and colleagues, it was widely thought that gliomas compromise neurological and cognitive function in one of a few ways: by infiltrating and affecting brain tissue; by compressing adjacent tissue; by inducing swelling around the tumour[4]; or potentially by competing for blood supply through 'vascular steal' (Fig. 1). The authors now reveal a previously unknown mechanism, in which gliomas modify brain circuitry to meet their own needs – by hijacking neuroplasticity through synaptic remodelling and thereby actively altering the architecture of the brain. The ability to capitalize on this induced neuroplasticity enables gliomas to receive extra neuronal signalling and to proliferate.

A compelling body of work has demonstrated that neurological activity can enable gliomas to grow. It was previously reported that working synapses (those that are electrophysiologically functional) form between neurons and gliomas[5]. Depolarizing currents, which are the fundamental foundations of neuronal activation and information flow in the brain, promote robust glioma proliferation[5]. Neuronal activity in the visual pathways seems to promote tumour growth (tumorigenesis) in the setting of the disease neurofibromatosis[6]. Krishna and colleagues' work indicates that conscious thought, and the activity of the mind itself through speech mechanisms, also seems to promote tumorigenesis, demonstrating an unexpected connection between the brain and the mind. The mechanisms by which these tumours engage with neuronal circuits to promote synaptic plasticity are explored by Krishna and colleagues.

The authors began these studies showing that gliomas infiltrating the brain hijack network plasticity and use voluntary mental activity to grow. This was demonstrated during language tasks in which people who were awake during brain surgery were asked to name items in pictures, and their brain-surface activity was recorded during the surgery. Tumour-infiltrated brain regions that were distant from recognized language areas and presumably regions normally uninvolved in language networks nevertheless demonstrated task-related increases in brain activity. This parasitized plasticity offered no extra computational power to distinguish between simple and more complex words.

"These findings are relevant for understanding associated symptoms in people who have gliomas."

Carrying out a multiscale analysis that linked synaptic formation to large-scale networks in the brain, the authors used the technique of magnetoencephalography (MEG) to detect small magnetic fields that are generated by the electrical activity of large populations of neurons. Brain regions that show correlated fluctuations in these magnetic fields are said to be functionally connected. The authors evaluated the connectivity of different subregions of gliomas by studying how MEG signals from various regions of tumour-infiltrated brain tissue correlate with other regions of the brain. Parts of tumours were classified as possessing high or low functional connectivity (HFC or LFC).

In HFC regions, genes involved in neural-circuit assembly, including the gene encoding the protein TSP-1, were expressed more highly than usual. TSP-1 is a protein involved in synapse formation and is normally secreted by healthy cells called astrocytes[7]. Regions of the glioma that induced synaptic changes at the molecular level were found to show alterations in their wiring to the entire brain.

To study the formation of synapses in the HFC regions in more detail, Krishna and colleagues performed a set of experiments involving techniques such as the use of 3D cultured cells called organoids that contained tumour cells. Cells from HFC regions of gliomas were found to be better integrated with co-cultured neurons and showed more electrical activity compared with cells from LFC regions. These findings are relevant for understanding associated symptoms in people who have gliomas. These symptoms can include epileptic seizures, which might be triggered through the action of this emergent subregion of glioma that regulates synapse formation at the cellular level[8].

Consistent with the authors' hypothesis that TSP-1 has a key role in glioma-mediated synapse formation, the authors report that when TSP-1 was added to LFC regions of gliomas co-cultured with neurons, the organoid model behaviour resembled the behaviour associated with organoids co-cultured with cells from the HFC region of the tumour. Conversely, when the TSP-1 inhibitor gabapentin was added to the co-cultures, glioma proliferation was reduced. Furthermore, glioma-infiltrated brain tissue enriched in TSP-1 formed synapses when grafted into the hippocampal region of the mouse brain *in vivo*.

After exposure to liquid that bathed neural samples (neuronal conditioned medium), HFC glioma cells showed greater invasive properties and developed cellular outgrowths called tumour microtubes that link tumour cells together. These microtubes might amplify

the effects of the input currents from neural activity[5]. The implications of these findings are far-reaching, given that microtube-connected glioma cells can evade the cell death that usually arises from radiation therapy[9].

In mice and humans, the gliomas that were enriched for functional connectivity were associated with poorer survival and with cognitive decline. The study shows that gliomas hijack computational power from the brain by parasitizing neural plasticity, so as to grow at the expense of cognitive function. Cognitive decline in individuals with glioma might therefore be an independent predictor of poor survival[10]. This electrical conversation in the brain between the physiological mind and the tumour is a frankly startling and astounding concept. Through this hijacking, gliomas demonstrate a unique form of plasticity that is perhaps appropriate only for an intrinsic tumour of the mind.

These two ghosts in the machine, the mind and the tumour, whispering to each other in the dark recesses of the brain, engage in a conversation that could be well worth eavesdropping on. Doing so could lead to innovative approaches to improving the lives of people with brain tumours.

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Medical research

Childhood hepatitis outbreak under scrutiny

Frank Tacke

Since 2022, more than 1,000 cases of childhood hepatitis with no known cause have been reported. The discovery of adeno-associated virus 2 in the blood and livers of such children might provide an explanation. **See p.555, p.564 & p.574**

Paediatricians first began to report a concerning wave of acute severe hepatitis — a disease involving liver inflammation — in children in spring 2022. This spate of cases, which now numbers more than 1,000 (see go.nature.com/42dpfv4), had no known cause, unlike most cases of paediatric hepatitis. The cases were often serious, with 7.3% of affected children needing a liver transplant[1]. Three groups now independently provide evidence that infection by adeno-associated virus 2 (AAV2) is linked to this wave[2–4]. Their work is likely to spark debate, and could influence disease management.

Two previous analyses[5,6] of this wave of acute severe hepatitis found an association with human adenovirus (HAdV), particularly the HAdV-F41 strain. However, this result has puzzled clinicians because, although adenovirus-induced hepatitis is a known phenomenon, it is rare and usually restricted to people with severely compromised immune systems. Moreover, the studies identified various HAdV strains, even in children from the same geographical region, implying that a single strain could not explain these hepatitis outbreaks. Furthermore, adenovirus-induced hepatitis is characterized by virus-derived structures, called inclusions, in the nucleus — something that has not often been detected in the current outbreak[7].

Controversy therefore remained around whether the outbreak was caused by HAdV or another virus. The previous studies identified HAdV using targeted genetic-sequencing approaches. By contrast, the current studies involved an untargeted approach called clinical metagenomics, in which all nucleic acids from a sample are sequenced, to discover which viruses might be present. All three identified AAV2 — a virus known to replicate in the liver, but not known to cause hepatitis[8].

In the first of the papers, Ho *et al.*[2] (page 555) report high levels of AAV2 in blood and liver samples from 26 (81%) out of 32 affected children in the United Kingdom. By contrast, the researchers detected only low AAV2 levels in 5 (7%) of 74 members of a control group consisting of healthy children, children who had HAdV infection but not hepatitis, or children who had other diseases or other forms of acute hepatitis. The authors found that 93% of the affected group carried a gene variant that predisposes an individual to autoimmune diseases involving immune cells called T cells. Liver biopsies were available for five infected children. Analysis using a tissue-staining approach (histology) revealed AAV2 in abnormally swollen liver cells (hepatocytes) surrounded by T cells, suggesting a causative role of AAV2 in acute hepatitis.

In the second study, also from the United Kingdom, Morfopoulou *et al.*[3] (page 564) report high levels of AAV2 in 27 of 28 affected children, and only low levels of AAV2 in a control group, which included immunocompromised children who had acute hepatitis due to other causes, and children with normal immune systems who had fever. The authors used several techniques to demonstrate that the disease was not due to direct damage

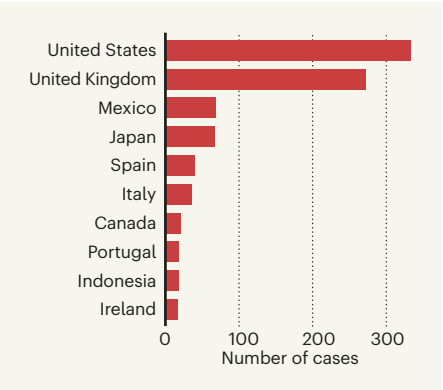

Figure 1 | Hepatitis outbreak around the world. As of July 2022, 35 countries had reported cases of severe acute paediatric hepatitis that had no known cause, according to the World Health Organization (see go.nature.com/42dpfv4). Numbers for the 10 countries with most reported cases are shown here. Three groups[2–4] now provide evidence that adeno-associated virus 2 has a role in this outbreak.