43 GHz is located only 14 to 23 Schwarzschild radii from the black hole. (The Schwarzschild radius is the distance between the black hole's centre and its event horizon if the black hole does not spin, and up to twice this distance if it spins rapidly.) This value is surprisingly small, because estimates[4,5] of the black-hole-to-core distance in quasars, which are more-luminous cousins of M87, are more than 100,000 times the Schwarzschild radius.

Hada and colleagues' results[1] show that the jet flows into a broad angle between the black hole and core before becoming tightly focused farther out (Fig. 1). This agrees with predictions of some theoretical models[6,7] that explain jets as the products of magnetic fields twisted by the differential rotation of the ionized gas swirling around the black hole. In such models, the flow accelerates and narrows over hundreds to about 100,000 Schwarzschild radii, with faster jets requiring greater distances.

How are we to reconcile the short black-hole-to-core distance of M87 with the much longer distance inferred in some quasars? Perhaps jets spread out more rapidly in lower-luminosity objects because there is less hot ionized gas in the nucleus to confine the flow. Another possibility is that the jet consists of an ultra-fast (99% of the speed of light) spine surrounded by a slower (perhaps 90% of the speed of light) sheath. In quasars with bright jets, the spine points almost right at us, so we see the radiation beamed in our direction, whereas emission from the sheath is too weak to be noticed. The jet of M87 is more inclined to our line of sight, by 15–25°, so the spine is relatively dim, allowing us to see the slower sheath. The images of M87 thereby reveal slower regions of the jet that are close to the black hole, whereas in quasars the jets become bright only where the spines reach their terminal velocity at much greater distances from the black holes.

The ability to image jets on such small scales in M87 implies that very-long-baseline interferometry can explore phenomena even closer to black holes by observing at higher frequencies of 86, 230 or even 350 GHz, at which the resolution is two to eight times finer than at 43 GHz. In combination with monitoring of time variations in the radiation at infrared, visible, X-ray and γ-ray frequencies, such observations would act as an 'event-horizon telescope'[8]. ■

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NEUROSCIENCE

When lights take the circuits out

Circuit-level perturbations in the brain's electrical activity may underlie social-interaction deficits seen in people with schizophrenia and autism. A new optogenetic tool was instrumental in making this discovery. SEE ARTICLE P.171

JOÃO PEÇA & GUOPING FENG

On page 171 of this issue, Yizhar *et al.*[1] add to our understanding of the neuronal circuits that control mammalian behaviour. By tuning neuronal activity with light, they show that 'hijacking' specific brain circuits in the mouse prefrontal cortex (but not the visual cortex, for example) can selectively disrupt the normal responses to social stimuli and social interaction.

Information processing across neuronal circuits in the brain determines thoughts, shapes emotions and regulates behaviours. It will therefore come as no surprise if dysfunctions affecting synaptic communication between neurons and neuronal circuits reside at the core of several neuropsychiatric disorders. This assumption has led to considerable efforts to explore how circuit activity and information processing might differ between the healthy and the diseased brain. In recent years, one particular theory has gained substantial traction — that disorders such as autism and schizophrenia arise from imbalances in the ratio of excitatory to inhibitory synaptic inputs (E/I balance) in discrete neuronal populations[2,3].

Symptoms of various psychiatric disorders may arise from common features at cellular and circuit levels. These common features could therefore account, at least in part, for the convergence seen in the traits of broad-spectrum disorders such as autism that have a varied range of causes. Yizhar *et al.*[1] set out to directly test the hypothesis that an increase in E/I balance may underlie some of the common symptoms of neuropsychiatric diseases.

For this investigation, the authors made use of a novel optogenetic tool. Optogenetics is based on the expression of a light-sensitive ion channel in the membrane of discrete populations of neurons. Light is usually delivered through the skull to those neurons by an optical fibre, causing the channels to open. Optogenetics has allowed researchers to directly and rapidly manipulate neuronal firing, probe neuronal-circuit function and control behaviour on very fast timescales — within milliseconds. For example, in disorders in which the underlying neural-circuit dysfunction is well understood, optogenetics has been used successfully not only to mimic the expected behavioural deficiencies, but also to positively modulate symptoms in animal models of the relevant disorder[4] (Fig. 1).

Recently, Yizhar and colleagues[5] introduced step-function optogenetic channels. Tools of this new generation have been modified to remain open for longer periods of time (seconds to minutes) after light activation. This allows the induction of successive, subthreshold neuronal activation to bring cells close — although not all the way — to firing. The functional consequence of this is modulation of the properties of endogenous neuronal circuits as a whole, without 'overloading' or overriding normal neuronal firing.

For their latest study[1], the authors developed step-function optogenetic channels with improved temporal stability to prime distinct populations of neurons in the prefrontal cortex of the mouse brain so that these could more readily become active in response to native neural-network activity over long periods of time. They were thus able to manipulate neuronal E/I ratios in this brain region: when the targeted populations were excitatory neurons, the functional network output corresponded to an increase in E/I ratio; when they were inhibitory neurons, the E/I ratio decreased. On the basis of these manipulations, Yizhar *et al.* report that increased — but not reduced — E/I balance in the prefrontal cortex leads to well-defined behavioural impairments and a striking perturbation in sociability in mice.

Although these data provide strong evidence that alterations in the cortical E/I balance directly affect social behaviour in mice, we should avoid adopting a simplistic view of the implications of changes in this ratio. Recent genetic and genomic studies have identified a large number of candidate genes for autism, many of which encode proteins crucial to

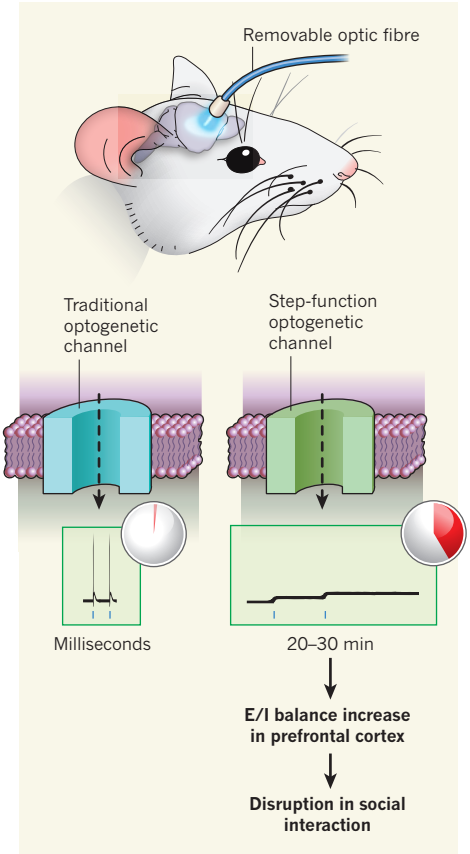

Figure 1 | Optogenetics and analysis of social dysfunction. Yizhar *et al.*[1] used step-function optogenetic channels to analyse the excitation–inhibition (E/I) balance in specific neural circuits within the prefrontal cortex of the mouse brain. Like traditional optogenetic channels, this latest tool is activated in response to light delivered by optic fibres through the animal's skull; this in turn allows ions to enter the neuron (dashed arrows). Step-function optogenetic channels, however, do not necessarily induce immediate firing by their host neuron. Instead, they cause a gradual increase in neuronal depolarization, increasing the probability of the neuron firing in response to endogenous stimuli over 20–30 minutes. This gave the authors sufficient time to perform behavioural analysis on the animals without the optic fibre being attached. They found that increasing the E/I balance in the prefrontal cortex disrupts social interaction between mice.

synaptic development and function[6]. Moreover, introduction of a mutation seen in patients with autism (the R451C mutation in the protein neuroligin-3) into the equivalent mouse protein increases inhibitory synaptic transmission[7]. So to clarify the significance of E/I ratios in disease states, future studies should traverse the added level of complexity arising from relevant human mutations in relation to regional and cell-type-specific gene expression. Such studies should also consider whether the broader circuits affected have an inhibitory or an excitatory effect on their downstream neuronal targets.

Yizhar and colleagues' paper[1] highlights a notable point — to unravel the complexity of the mammalian brain, it is essential to understand the functioning of circuits in both healthy and diseased brains. Combining information arising from observation, and control, of neuronal circuits will also be crucial in such efforts[8]. Together, these approaches should not only magnify our ability to predict how changes in circuit function may lead to abnormal behaviours, but also give a glimpse of how circuit-level manipulations might ultimately be used for the treatment of neuropsychiatric disorders. ■

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METABOLISM

Let them eat fat

A specialist neuron uses an intriguing process to help control the body's response to hunger. A lipid pathway involving the breakdown of cellular components regulates the expression of a neuropeptide that affects feeding and body weight.

SCOTT M. STERNSON

When resources become scarce, we tighten our belts and make do with what we have. This is also true for our bodies, which in the absence of food intake start to consume themselves. In a paper published in *Cell Metabolism*, Kaushik *et al.*[1] describe how, when mice are deprived of food, a specialized starvation-sensitive neuron dines on fat released from body stores. Strikingly, the authors find that disrupting this process in these neurons results in leaner, lighter mice, even when food is freely available.

Hunger results from food deprivation and leads to food seeking and consumption. An internal sensory system detects signals of energy deficit circulating in the blood and modulates neural circuits that regulate these behaviours. A neuron that is crucially involved in this system is defined by its expression of the gene Agouti-related protein (*Agrp*), which encodes the AgRP neuropeptide.

The AgRP neuropeptide increases feeding and body weight when injected into the brain. Furthermore, AgRP-expressing neurons have properties expected of a starvation-sensing system: they alter their firing rate and gene expression in response to signals from hormones and metabolites such as ghrelin, leptin, glucose and fatty acids. Without these neurons, mice stop eating[2]. Conversely, voracious eating can be induced in well-fed mice by increasing the electrical activity of these neurons[3,4]. It is therefore clear that the regulation of AgRP-neuron function is important for controlling hunger-related behaviour.

During food deprivation, changes occur in the body to conserve energy and to signal the need to replenish energy levels by eating. The body switches to using stored fat as a fuel, releasing free fatty acids into the blood that can be sensed by the brain. Kaushik *et al.*[1] examine the influence of this process on AgRP neurons in cell culture and in mice.

The authors explore an unusual mechanism for modulating *Agrp* gene expression by investigating the role of macroautophagy (here termed autophagy) in fatty-acid utilization. Autophagy is a regulated, cannibalistic process in which cells consume and recycle their components (such as damaged organelles) and use their internal structures as a fuel source during starvation. In autophagy, cellular components are enveloped in a membrane-bounded vesicle called an autophagosome for transport to an organelle known as the lysosome for degradation. Some of the authors of the current study previously discovered an intriguing mechanism in liver cells whereby the autophagy pathway can mobilize stored fat as a fuel source[5].

Kaushik *et al.*[1] report that a similar pathway operates in AgRP neurons, with consequences that seem to extend beyond fuel utilization. They propose that AgRP neurons accumulate free fatty acids from the blood during food deprivation and that these fatty acids are then quickly converted into triglyceride fats and stored in lipid droplets (Fig. 1). These lipids are rapidly remobilized through autophagy of the lipid droplet, and free fatty acids are re-formed for use as fuel. The authors suggest that this circuitous pathway provides a mechanism for regulatory control over the accumulation of free fatty acids in the cell, so that they can be used in an orderly fashion. It remains to be seen