NEUROSCIENCE

A picture of diversity

A single-cell sequencing study reveals how different types of neuron are distributed in the brain. An analysis then demonstrates how these data can improve our understanding of neuronal functions. SEE ARTICLES P.72 & P.79

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Imagine an art curator preparing for an exhibition. Paintings in the gallery can be arranged into various ensembles — for example by artist, medium, style or theme. Similarly, neurons can be categorized according to a variety of features, such as their size, shape or location in the brain. Writing in *Nature*, Tasic *et al.*[1] (page 72) and Economo *et al.*[2] (page 79) delve deep into the gallery of neuronal types in the cortex of the mouse brain, and use cutting-edge technologies to uncover previously unknown facets of these cells.

Around the turn of the twentieth century, Spanish neuroscientist Santiago Ramón y Cajal created a 'portrait gallery' of neurons by carefully examining slices of brain tissue to produce detailed drawings of the cells that captured their diverse shapes. Since then, neurons have been further characterized using measurements of shape, physiology or function. Now, technologies to analyse the gene-expression profile of single cells enable unbiased exploration of cell types.

The brain's cerebral cortex is responsible for cognition and memory, and contains regions involved in sensory and motor functions. Tasic and colleagues used single-cell sequencing to profile the gene-expression landscapes of more than 20,000 cells, mostly neurons, from two anatomically distinct cortical areas in adult mice — the visual cortex, which processes visual sensory information from the eye, and the anterior lateral motor cortex, which is involved in movement. By doing so, they could compare cells of the same type located in regions with different functions (Fig. 1).

Broadly speaking, neurons of the cortex can be classified as excitatory or inhibitory, depending on the type of neurotransmitter molecule they produce and whether their activation leads to increased or decreased activity of neural circuits. The authors identified more than 100 different cell types, including 61 types of inhibitory neuron and 56 types of excitatory neuron. They found that most cell types were present in both cortical areas — with the exception of excitatory neurons.

These cells are the primary activity-generating units of cortical circuits, and have long been hypothesized to be identical across all cortical areas[3]. But Tasic *et al.* found that nearly every subtype of excitatory neuron was specific to either the visual or the anterior lateral motor cortex. The authors injected the cells with fluorescent tracers to track their neuronal projections into distant brain areas. Surprisingly, neurons with different gene-expression profiles also showed different patterns of long-range projection, suggesting that molecular definitions of cell types based on gene expression can provide information about multiple properties of an excitatory neuron.

A study published last year[4] also found area-specific excitatory neurons in the developing human cortex, even before the cortical circuits begin to process sensory information. This, together with Tasic and colleagues' observations, suggests the need to revise our framework for understanding how cortical areas process diverse types of information. In particular, these findings suggest that the functional specialization of cortical areas might rely not only on differences in microcircuits and connectivity patterns, but also on the use of different cell types to process information. Future work is needed to sample cells from more cortical areas to establish how many area-specific excitatory-neuron types exist and how their distribution affects cortical function.

Whereas Tasic and colleagues present an entire gallery of cortical neurons, Economo *et al.*[2] zoom in to look at nuanced differences between neurons in one layer of the cortex — much like studying paintings of the same style on one gallery floor. Excitatory pyramidal tract neurons, which reside in a region called layer 5 in the anterior lateral motor cortex, communicate with other neurons located many thousands of cell diameters away by establishing physical contacts. Pyramidal tract neurons were presumed to all have similar functions[5]. However, Tasic and colleagues' analysis revealed that these cells fall into different subtypes on the basis of their gene-expression profiles. Economo and colleagues sought to

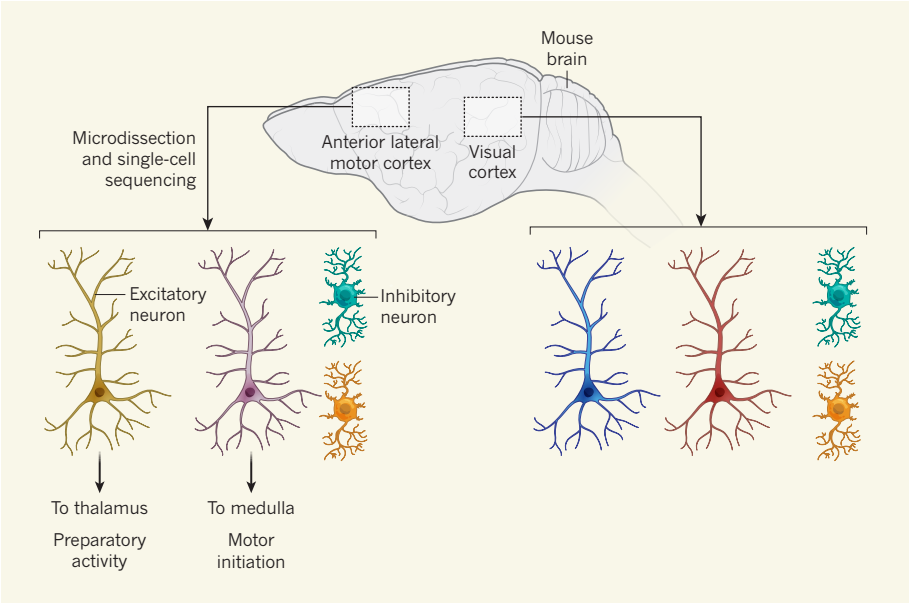

Figure 1 | Cell-type diversity in the mouse cortex. Tasic *et al.*[1] microdissected the anterior lateral motor cortex and the visual cortex of the mouse brain, and subjected neuronal cells from these regions to single-cell sequencing. The authors identified 133 cell types on the basis of gene-expression profiles. The analysis revealed that types of inhibitory neuron are shared between regions (colours indicate cell types), but that types of excitatory neuron are area-specific. Economo *et al.*[2] performed in-depth characterization of two subpopulations of excitatory neurons in the motor cortex. They found that the two connect to distinct brain regions (the thalamus and medulla) and perform different functions in respectively preparing and initiating motion.

dissect the differences between subgroups.

Pyramidal tract neurons located primarily in the upper part of layer 5 send signals to a brain region called the thalamus that sends projections back to the cortex, forming a loop involved in preparing for motor activity. Tasic *et al.* demonstrated that these neurons are molecularly distinct from those located in a lower portion of layer 5 that project to the medulla, which is associated with the execution of movement. Economo *et al.* engineered each subpopulation of neurons to express the protein channelrhodopsin — a light-sensitive ion channel. This enables neuronal activity to be precisely controlled using light (a method known as optogenetics), and so allowed the authors to dissect the roles of the upper and the lower layer-5 neurons in different types of motor function.

Economo and colleagues used light to independently activate the pyramidal tract populations in mice, and simultaneously monitored both the activity patterns of the cells and the behaviour of the animals as they engaged in a motor-learning exercise. These experiments confirmed that the two populations of pyramidal tract neurons have separate roles: one in preparing for motor activity and the other in initiating movement. The authors' results also provide a compelling demonstration of how understanding the molecular taxonomy of the brain can lead us to an understanding of how neurons connect and function.

Together, the two studies highlight the transformative potential of atlas-scale data sets in modern neuroscience[6,7]. They make a strong case for conducting similar studies of more cell types and of the brains of animals of different species, including humans, at various ages. In support of the need for data from different species, a recent single-cell sequencing study[8] has reported a greater diversity of neurons in a cognition-associated region of the human cortex than has been described for mice — this might explain our ability for higher-order cognition. Further characterization of both neuronal and non-neuronal cell classes could also yield fresh insights into their selective vulnerabilities to disease states, and instruct the development of protocols to generate these cell types from stem cells *in vitro*, for use as disease models and for drug testing.

In the future, researchers will undoubtedly make use of the genetic markers of specific neuronal populations identified by Tasic and colleagues' cell atlas. For example, these markers could be used to design more optogenetic experiments that target specific neuronal populations; to investigate whether 'area-specific' cell types can be found in other cortical regions; and to isolate populations of cells for further functional characterization.

However, translating the cellular composition of the brain into biologically meaningful insights will require new strategies for interrogating neuronal function. Technologies to manipulate cell types currently being developed through the support of the US National Institutes of Health BRAIN Initiative[9] might enable these analyses. In doing so, they could allow us to fully appreciate the portrait gallery of cells that control brain function. ■

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QUANTUM PHYSICS

Mechanical quantum systems controlled

The control of quantum systems offers great potential for advanced information-processing and sensing applications. An approach has been demonstrated that enables such control over the motion of mechanical oscillators. SEE ARTICLE P.53

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People tend to behave differently when they are being watched. It turns out that objects in the quantum world do, too, and that the very act of measurement can modify their behaviour. This effect is a consequence of Heisenberg's uncertainty principle, which states that, if we measure the position of a moving object precisely, we cannot simultaneously know the object's momentum. On page 53, Rossi *et al.*[1] report an experiment that beautifully demonstrates this tenet of quantum physics. The authors use their measurements to apply a feedback force to a mechanical oscillator — an object akin to a vibrating drumhead — to greatly suppress the oscillator's motion. The work opens up an avenue for controlling mechanical quantum systems by continuously monitoring and manipulating their dynamics.

The use of measurements and feedback to stabilize a system is a well-developed technique in engineering and is applied in many everyday technologies. For example, the technique is used to stabilize the motion of lifts, and is also used to reduce the effects of turbulence during flights in many types of aircraft. Researchers have now extended these concepts so that measurement and feedback can be used to control the properties of individual quantum systems[2].

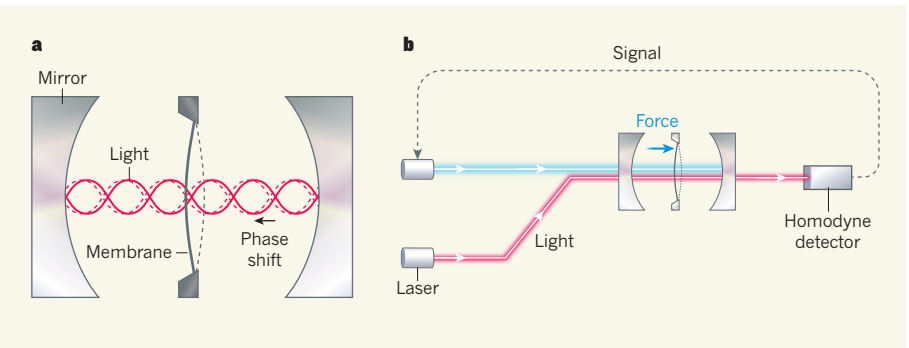

Figure 1 | Quantum measurement and feedback. a, Rossi *et al.*[1] report an experiment in which a millimetre-sized mechanical membrane interacts with light that bounces back and forth between a pair of mirrors known as an optical cavity. The drumhead-like motion of the membrane causes the light to acquire a phase shift that depends on the position of the membrane. The black and red dashed lines indicate a mechanical displacement and such a phase shift, respectively. **b**, The authors continuously supplied the cavity with light (red) from a laser. They monitored the phase shift of light that was transmitted through the cavity using a device called a homodyne detector, thus enabling a continuous measurement of the membrane's position. The signal from the detector was then used to control the intensity of a second laser. The light (blue) from this laser applied a feedback force to the membrane that brought the membrane's motion close to its ground state — a convenient starting point for future quantum experiments.