Neuroscience: Signals far and away
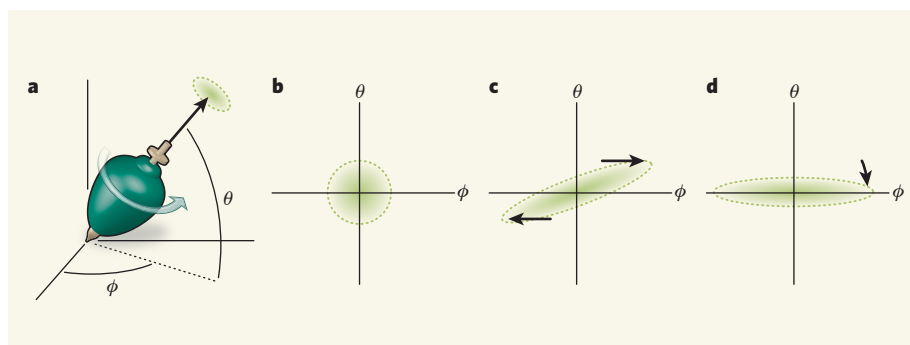
Figure 1 | Spin squeezing. The quantum state of an atom can, in some conditions, be represented as the orientation of a rapidly spinning top. The orientation is defined by two angles, θ and ϕ. Quantum mechanics demands that the orientation is uncertain, so if θ and ϕ are measured a spread of values is obtained. The spread is represented by the green area in **a** and is plotted in **b**. This quantum limit cannot be overcome, but it is possible to reduce the uncertainty in one of the angles while increasing the uncertainty in the other. For instance, **c** shows the effect of interactions between atoms that cause ϕ to increase when the spin axis is pointing up and to decrease when the axis is pointing down. The region of uncertainty is stretched into an ellipse. A subsequent rotation about the centre of the ellipse (**d**) produces a state where θ is known more accurately than is ordinarily possible. Measurements that rely on only one angle can thus be improved through this squeezing technique. Experiments by Riedel et al.[1] and Gross et al.[2] demonstrate this effect using atoms in a Bose–Einstein condensate.

to be redistributed between the vertical and horizontal directions. Even when left alone, the atoms' spin axes are not static: they orbit in a circle around the vertical just as the axis of a toy top does. The rate of this precession is proportional to the energy difference between an atom pointing straight up and one pointing straight down. For independent atoms, the precession doesn't change the orientation uncertainty, but in the experiments of Riedel and colleagues and Gross and colleagues[1,2], the atoms interact with each other. The authors were able to tailor the interactions so that the precession rate increased when the axes were pointed up and decreased when the axes were pointed down. Because the axis orientation was uncertain, the actual precession rate was indefinite: the more upward the axes happened to point, the faster they precessed. This effect caused the uncertainty region to stretch into an elliptical shape (Fig. 1c).

On its own, this leaves the uncertainty in the vertical direction unchanged while that in the horizontal direction increases. After an appropriate interaction time, however, a torque can be applied to rotate the uncertainty region about its centre. If the minor axis is set to be vertical (Fig. 1d), then the uncertainty in that direction is reduced, improving the accuracy of a subsequent measurement of that component of the axis orientation. Because the uncertainty in the horizontal direction is increased, the quantum uncertainty limit remains satisfied. The effect is termed spin squeezing because the uncertainty region is 'squeezed' in one direction. It involves entanglement because the reduction in uncertainty is achieved by correlating the quantum orientation uncertainties of the different atoms.

The more the ellipse is stretched, the smaller the uncertainty becomes, although various technical noise sources add uncertainties of their own and limit the effect. Riedel et al.[1]

achieve a noise reduction of about 25%, whereas Gross et al.[2] achieve about 55%. Gross and colleagues' result improves on the previous record[3] for atomic systems of 45%. The primary difference between the two experiments reported here is the way in which the atomic interactions are controlled to achieve squeezing. Gross et al. use magnetic fields to manipulate the actual interactions, whereas Riedel et al. introduce a further degree of entanglement between an individual atom's spin orientation and its location in space. Because only atoms close to each other can interact, this spatial correlation results in an orientation-dependent interaction, as required. Gross and colleagues' method evidently works better, but Riedel and colleagues' approach has the advantage of being more broadly applicable, because not all

atomic states can be manipulated in the manner that Gross and colleagues' method requires.

The concept of squeezing is not new. It was first developed for photons in the 1970s, and was shown to be applicable to atomic measurements[4–6] in the 1990s. Since that time, squeezing has been observed in several atomic systems. Even in condensates, a variety of squeezing has been observed previously[7], although the noise reduction was not in a variable that was directly applicable to precision measurements. By contrast, Gross et al.[1] already demonstrate a measurement of the energy difference between the spin-up and spin-down states with an accuracy exceeding the normal quantum limit for unentangled atoms. This type of measurement could be used to improve the precision of atomic clocks. Another promising application is atom interferometry, in which the spatial position of the atoms plays a part analogous to the spin-axis orientation discussed here. The resulting measurements can be related to many interesting quantities, from the strength of gravity to Planck's constant[8]. Owing to their controllable interactions and good spatial localization, squeezed condensates could prove particularly useful in such experiments. ■

Charles A. Sackett is in the Department of Physics, University of Virginia, Charlottesville, Virginia 22904, USA.
e-mail: sackett@virginia.edu

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NEUROSCIENCE

Signals far and away

Dirk Feldmeyer

The neocortex of the mammalian brain mediates functions such as sensory perception and ultimately consciousness and language. The spread of local signals across large distances in this brain region has now been clarified.

On page 1155 of this issue, Adesnik and Scanziani[1] report how selective stimulation of neurons in a specific area of the mouse neocortex affects the spatial distribution of excitatory and inhibitory signals both locally and farther afield within the cortex. This study is of value not just for its technical achievement — selective analysis of a single neuronal population in the brain of a live animal — but also because it provides information about the way in which neuronal signals spread within the less widely

explored horizontal plane of the cortex.

Anatomically, the mammalian neocortex consists of up to six horizontal layers (1–6), with layer 1 being the outermost and layer 6 the innermost (Fig. 1). The neocortex is also organized as vertically oriented functional modules[2,3], often referred to as cortical columns. Thousands of neurons constitute each column, and respond similarly to sensory information. Sensory input arrives in layer 4 and is propagated from there in a predominantly

vertical fashion to other cortical layers.

The main excitatory neurons of the neocortex are pyramidal cells. The axons (main output branches) of these neurons project not only vertically through the layers, but also horizontally across several cortical domains. These cells make synaptic contacts with excitatory and inhibitory neurons in both directions, thereby linking cortical domains.

Whereas the local and vertical projections have been investigated in detail[4,5], little is known about the function of horizontal axonal projections[6], or how they connect to other neurons and coordinate the neuronal activity between the cortical columns.

Adesnik and Scanziani[1] used mice to study the somatosensory barrel cortex[4,5], which gets its name from its barrel-shaped appearance in layer 4 (Fig. 1). To selectively stimulate layer 2/3 pyramidal cells (which have prominent horizontal and vertical axonal collateral branches), the authors ingeniously manipulated mice[7,8] in which these cells specifically expressed a light-sensitive protein known as channelrhodopsin-2, so that illuminating the brain or brain slices with light induced the firing of action potentials exclusively in layer 2/3 pyramidal cells.

Indeed, photo-stimulation of layer 2/3 pyramidal cells both in the brain of anaesthetized mice and in brain slices consistently resulted in rhythmic activity (oscillations) of both excitatory and inhibitory synapses in the γ frequency range (~40 hertz), which is thought to be involved in sensory processing and awareness. Activation of these neurons in other neocortical regions, such as the visual cortex and the cingulate cortex, also elicited oscillations, indicating that the results may be generalized to other cortical areas.

To investigate how the oscillating excitatory and inhibitory synaptic activities in layer 2/3 propagate vertically, the authors examined excitatory neurons in layers 2/3, 4, 5 and 6. Oscillations in excitatory and inhibitory synaptic activity were negligible in layers 4 and 6 but were strong in layers 2/3 and 5. The axons of layer 2/3 pyramidal cells branch heavily in layers 2/3 and 5, and so have many horizontal projections within these layers but not in other layers (Fig. 1). Moreover, earlier work[9] has demonstrated that pyramidal cells in layer 2/3 are connected through synapses with those in layer 5.

Investigating the horizontal propagation of rhythmic synaptic activity, Adesnik and Scanziani found that photo-stimulation of a small spot in layer 2/3 results in excitatory and inhibitory synaptic activities to both the left and the right of the spot in layers 2/3 and 5. These activities, which spread within the activated 'home' column and to adjacent barrel columns, decayed with increasing distance from the spot. Surprisingly, however, the spatial distribution of these synaptic activities was similar in layers 2/3 and 5.

But how does the activity of layer 2/3
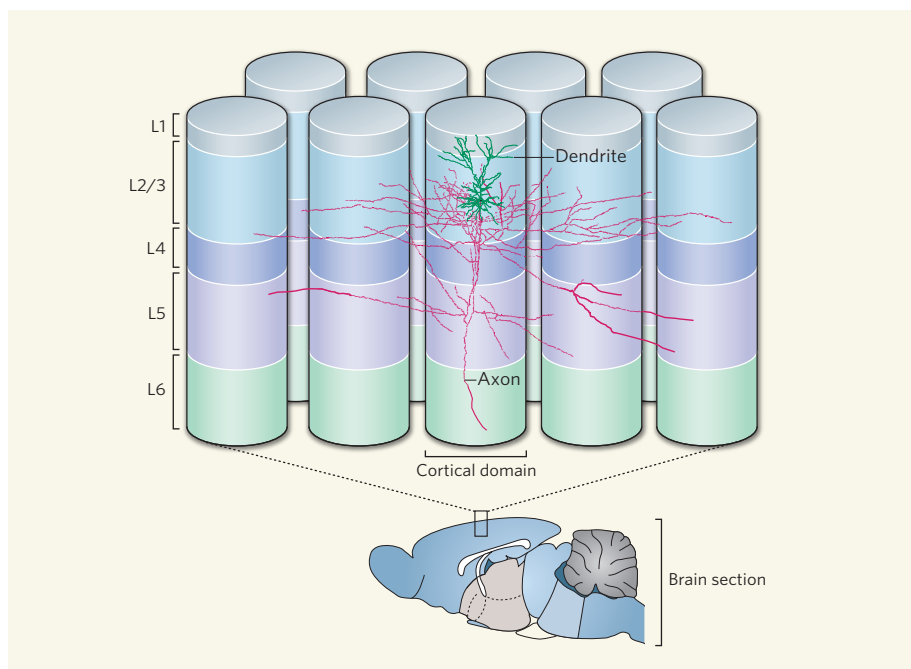
Figure 1 | Layers and domains. The neocortex is divided into up to six anatomical layers (domains L1–L6). Axonal projections (red) of layer 2/3 pyramidal cells branch out not only through their column but also horizontally across layers 2/3 and 5. Adesnik and Scanziani[1] find that this distribution of axonal branches reflects the pattern of signalling from layer 2/3 pyramidal cells within and across layers, and that these neurons differentially modulate the activity of pyramidal cells in layers 2/3 and 5. The barrel shape of the somatosensory cortical domains is extrapolated from the structure of layer 4.

pyramidal cells affect cortical activity? The authors found that light-induced oscillations of the cells' synaptic activity suppressed the firing rate of action potentials in layer 2/3 but facilitated it in layer 5 pyramidal cells. What's more, both of these effects showed similar spatial distributions, being strongest in the home column and weaker — but still significant — in adjacent columns. Thus, oscillations in synaptic activity that are induced by layer 2/3 pyramidal cells enhance firing by layer 5 pyramidal cells in their own and neighbouring cortical domains, but suppress the input to layer 5 by neurons in neighbouring domains. Consequently, the barrel column that is most active dominates the cortical space.

Exploring the mechanism for this layer-specific differential modulation of pyramidal-cell firing, Adesnik and Scanziani found that, whereas pyramidal cells of layers 2/3 and 5 received similar excitatory inputs, the inhibitory input to layer 5 was significantly smaller. This larger excitation-to-inhibition ratio for layer 5 pyramidal cells — and not some intrinsic property of the neurons — seemed to be causally related to the layer-specific modulation. The authors demonstrated this with a clever experiment. When synaptic activity recorded from layer 5 pyramidal cells was mimicked in layer 2/3 neurons, the latter also showed enhanced firing of action potentials. Similarly, layer 5 pyramidal cells displayed action-potential suppression when subjected to layer 2/3-type synaptic input.

These exciting results demonstrate that horizontal axonal projections of pyramidal cells

in one layer differentially modulate the action-potential output of the same and other cortical layers through layer-specific differences in the ratio of synaptic excitation and inhibition. But they also raise important questions. Synaptic inhibition is mediated by a variable class of interneuron that releases the neurotransmitter GABA (γ-aminobutyric acid)[10]. Which types of interneuron are involved in the layer-specific modulation of firing activity? What are their properties? And is the inhibitory input in layer 5 smaller than that in layer 2/3 because fewer interneurons are activated in layer 5?

It is also noteworthy that the photo-stimulation used here[1] results in the activation of a relatively large number of neurons. But coding of sensory stimuli in the neocortex is considered to be sparse — neurons respond only with a low firing activity[11]. Would such sparse activity lead to a different mechanism from that described by Adesnik and Scanziani? And how would the activity of excitatory neurons in other cortical layers affect this mechanism? Whatever the answers, the present study[1] makes one point clearly: for a comprehensive understanding of the cortical microcircuitry and its interactions, researchers must consider not just local connections, but also synaptic interactions via the horizontal collateral branches of neocortical pyramidal cells. ■

Dirk Feldmeyer is at the Institute of Neuroscience and Medicine, INM-2, Research Centre Jülich, and in the Department of Psychiatry and Psychotherapy, RWTH Aachen University, D-52074 Aachen, Germany.
e-mail: d.feldmeyer@fz-juelich.de

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Figure 1 | A stable anion of borole. a, Borole is an unsaturated ring system containing four carbons, one boron atom and two C–C double bonds. Borole itself is intrinsically unstable and has not been isolated. B is boron. **b,** Braunschweig *et al.*[4] have isolated and characterized an anionic borole-containing complex. The complex is stabilized by the presence of an *N*-heterocyclic carbene (red), which donates a lone pair of electrons to the borole (arrow). Ph, phenyl group. **c,** The electrons in the anionic complex are delocalized, but these 'resonance structures' show ways in which the electrons could become localized between the atoms. The double-headed arrow indicates that the real structure of the complex is a hybrid of the resonance structures. The left-hand structure contains a borataalkene group (blue). In the right-hand structure, two negative charges reside on the borole ring. This means that, in this resonance structure, the borole has six π-electrons, which makes it aromatic. The existence of an aromatic resonance structure might help to stabilize the complex.

CHEMISTRY

Not just any old anion

Kyoko Nozaki

Unlike its neighbours on the right-hand side of the periodic table, boron barely forms an anion. A new trick has been established that allows it to do so, enabling a highly unusual complex to be prepared.

The history of boron and its compounds is long and distinguished, with the organoboron compounds — in which organic groups are attached to a boron atom — arguably making the biggest splash. These compounds have many crucial roles as reagents in organic synthesis, especially in carbon–carbon bond-forming reactions[1]. One unusual family of organoboron compounds is the boroles, which contain a relatively unstable ring of atoms (Fig. 1a). These compounds are candidates for a new class of material for organic light-emitting diodes, but synthetic methods for making boroles are rather limited[2,3]. Reporting in *Angewandte Chemie*, Braunschweig *et al.*[4] now describe their preparation of a borole anion. The compound takes part in a surprising chemical reaction, and might open up routes to the preparation of other borole compounds.

Boron belongs to the second row of the periodic table, but its anion chemistry is different from that of most of the other *p*-block elements in that row (fluorine, oxygen, nitrogen and carbon). These elements form anions in alkali–metal salts, such as F⁻ in lithium fluoride, OH⁻ in lithium hydroxide, NH$_2$⁻ in lithium amide and CH$_3$⁻ in methyllithium. For many years, however, there were no direct observations of alkali–metal salts that included the analogous boron anion, R$_2$B⁻ (known as a boryl anion; R can be either hydrogen or an organic group).

This aberrant behaviour is a consequence of boron's inability to fulfil the 'octet' rule of main-group elements (the elements in the periodic table that aren't transition metals). The octet rule states that main-group atoms that have eight electrons in their outermost (valence) shell are particularly stable. These elements therefore tend to form compounds or anions that have eight valence electrons — fluoride, hydroxide, amide and methyl anions are good examples.
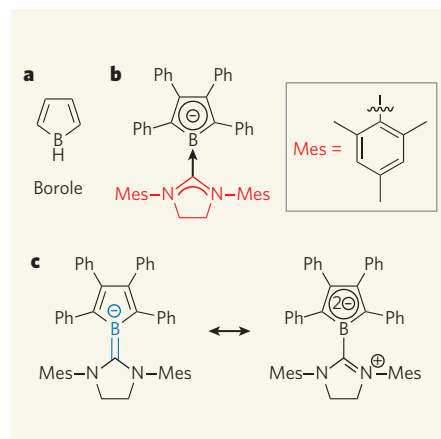
But the boron atom of a boryl anion has only six valence electrons. Boryl anions can get around this problem by accepting two electrons from neighbouring atoms, or by forming a complex with another compound. Several such complexes have been reported[5–7], although the evidence for their existence was indirect. The first boryl anion to be isolated and characterized was described four years ago[8,9]. In that case, the anionic boron atom was stabilized by electron donation from its neighbouring nitrogen atoms.

Braunschweig and colleagues' boryl anion[4] is a different kind of beast, which they describe as a π-boryl anion. Remarkably, it contains a borole ring (Fig. 1b). To understand why boroles can be stable as anions, but not as uncharged molecules, we need to consider another rule of chemistry: Hückel's rule of aromaticity. This defines a formula for the number of π-electrons that a planar, cyclic molecule must have to be aromatic, where π-electrons are those electrons that form π-bonds (such as the double bonds of unsaturated hydrocarbons). The formula is $4n + 2$, where n can be zero or a positive integer. Aromatic molecules can therefore have two π-electrons, or six, or ten, and so on. Delocalization of the π-electrons in aromatic molecules boosts the thermodynamic stability of these compounds, a phenomenon known as the aromatic stabilization effect. Conversely, cyclic planar molecules that have $4n$ π-electrons (four, eight, twelve, and so on) are less stable, and are described as anti-aromatic.

Boroles possess four π-electrons, one from each carbon atom in the ring, and so can be thought of as anti-aromatic. But they also have an empty electron orbital on the boron atom. If that orbital can acquire two extra electrons, then the resulting borole dianion will have six π-electrons, thus becoming aromatic. Such borole dianions are known, and have often been incorporated into complexes with metal atoms[10–12].

But Braunschweig and colleagues' borole[4] flouts convention, because it is a monoanion — a new class of boryl anion. The monoanion has only five π-electrons, and so isn't as stable as the aromatic borole dianions. It makes up

for this lack of stability by forming a complex with a compound known as an *N*-heterocyclic carbene (Fig. 1b). Such carbenes are known to donate two electrons to other boron-containing molecules[13], but this is the first time that one of these compounds has been used to stabilize a borole species.

The structure of the authors' borole[4] can be drawn in several different ways (known as resonance structures; Fig. 1c), which can be used to help to explain electron distribution in the molecule. One of these structures contains a borataalkene group — a negatively charged carbon–boron double bond. These groups usually react with electrophiles (molecules that contain areas of positive charge) so that the electrophile becomes attached to the carbon atom of the group. But Braunschweig *et al.* found that their compound reacts with an electrophile only at the boron atom. The borole monoanion is therefore the first example of a borataalkene whose typical polarity has been reversed.

Another resonance structure of the borole monoanion might help to explain the reversed reactivity of the borataalkene. In this structure, the borole ring harbours two negative charges (Fig. 1c), rendering it aromatic. Because the