surface (Fig. 1). A standard digital camera takes a photograph of this pattern and feeds the information into a computer algorithm that has substantial improvements over previous algorithms in the analysis of areas containing shadows.

The algorithm can estimate the position of the obscuring structure and produce an image of the hidden target. Furthermore, from a single photograph, brightness and colour variations in the target can be reconstructed with unprecedented resolution. By analysing a series of photographs, any motion of the target could be observed and displayed on a monitor.

The authors' approach can extend the perception range of ordinary cameras, and therefore enhance the equipment's sensing capabilities. Future improvements to the technique might enable the shape of the obscuring structure to be determined and allow a 3D reconstruction of the hidden scene. Because we can see objects only in our direct field of view, such non-line-of-sight imaging could revolutionize how we think about our perception of the environment.

Saunders and colleagues' work could lead to improvements in microscopy and in medical-imaging devices such as endoscopes. Moreover, their approach might find applications in the monitoring of hazardous or inaccessible areas such as chemical or nuclear plants, and in the industrial inspection of, for example, turbines and enclosed areas. Finally, the technique could be used by vehicles to avoid collisions, and by firefighters and first responders to look into burning or collapsed structures. The results of this work will therefore have a large impact on the development of imaging devices that have extended perception ranges. ■

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STRUCTURAL BIOLOGY

A chatty brain receptor

The $GABA_A$-receptor family has a crucial role in neural inhibition in the human brain. New structures of a $GABA_A$ receptor highlight the mechanisms of crosstalk between its binding sites. SEE ARTICLE P.454 & LETTER P.516

MICHAELA JANSEN

The activity of the central nervous system is regulated by excitatory and inhibitory molecules called neurotransmitters, which mediate communication between neurons. The main inhibitory neurotransmitter in the human brain is γ-aminobutyric acid (GABA), which binds to several receptors, including the $GABA_A$ receptor. Mutations affecting $GABA_A$ receptors can cause neurological disorders such as epilepsy. $GABA_A$ receptors also have binding sites for many other ligand molecules, some of which are widely used therapeutic drugs. Binding of ligands to non-GABA sites can alter communication between different binding sites and affect the receptor's conformation in ways that stimulate or inhibit its function (allosteric modulation). Laverty *et al.*[1] (page 516) and Masiulis *et al.*[2] (page 454) now report the 3D high-resolution structures of an isoform of the $GABA_A$ receptor bound to different ligands in physiologically relevant conformations. Their work sheds light on the intricate network of short- and long-distance crosstalk between distinct binding sites of the receptor, and is likely to stimulate drug-discovery research.

The $GABA_A$ receptors are a family of protein complexes that span the cell membrane of neurons. They are composed of five subunits (most often two α, two β and one γ subunit) arranged in a nearly symmetric fashion around a central channel. Each subunit has three domains: the extracellular, transmembrane and intracellular domains. GABA binds to the extracellular part of the receptor, at the interfaces between the α and β subunits. This leads to conformational changes that cause the channel to open and chloride anions to flow through. Benzodiazepines — a group of drugs that includes several widely used sedative and anti-anxiety therapeutics — bind to an extracellular site between the α and γ subunits, whereas the transmembrane part of the receptor harbours binding sites for alcohols, anaesthetics and neurosteroids[3–5].

Laverty *et al.* and Masiulis *et al.* used cryo-electron microscopy (cryo-EM) to study a $GABA_A$ isoform that contains two α1, two β3 and one γ2 subunits arranged in the order α1-β3-γ2-α1-β3 (Fig. 1 of ref. 1). This is one of the most abundant isoforms of the $GABA_A$ receptor in the human brain. Although the receptor's overall architecture was known, the studies provide new insight into the molecular details of subunit architecture and assembly, location of modulator binding

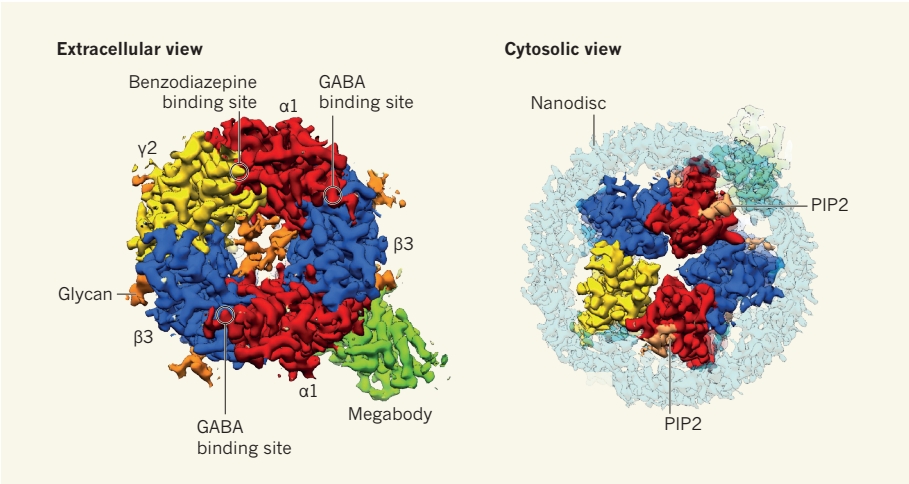

Figure 1 | Structure of a $GABA_A$ receptor composed of two α1, two β3 and one γ2 subunits. Laverty *et al.*[1] and Masiulis *et al.*[2] determined the structures of one of the most abundant $GABA_A$-receptor isoforms in the human brain, alone or bound to various ligands, using cryo-electron microscopy. Before imaging, they reconstituted the receptor within a lipid membrane (nanodisc) that mimics the cell membrane of neurons, the receptor's natural environment. The receptor was also coupled to an enlarged antibody (megabody) to enable better orientation during imaging. The extracellular portion of the receptor contains binding sites for γ-aminobutyric acid (GABA), a natural ligand, and for benzodiazepines, which are widely used therapeutic drugs. The structure also indicates the sites of some molecules usually associated with the receptor, such as phosphatidylinositol 4,5-bisphosphate (PIP2) and glycans (sugars attached to the receptor). (Adapted from Fig. 1 of ref. 1.)

sites and conformational changes initiated by ligand binding.

The study by Laverty *et al.* has three new methodological aspects. First, the authors used full-length $GABA_A$ subunits, not the truncated subunits used in previous studies[6,7]. Second, they reconstituted the receptors in discoidal membranes (nanodiscs) composed of a double layer of lipid molecules girdled by scaffold proteins, an environment similar to their natural cell-membrane surroundings (Fig. 1). This contrasts with the detergent environment that has been used in the vast majority of previous studies of this group of receptors. Third, the receptors were coupled to a synthetically enlarged antibody (called a megabody) to aid receptor orientation and alignment during cryo-EM imaging. Using this methodology, Laverty *et al.* solved the structure of the receptor bound to GABA, and Masiulis *et al.* solved five additional structures with different ligands or ligand combinations: picrotoxin (an agent that blocks the open channel of the receptor); picrotoxin and GABA; bicuculline (a drug that induces epilepsy symptoms); alprazolam (a benzodiazepine) and GABA; and diazepam (another benzodiazepine) and GABA.

$GABA_A$ receptors are notorious for requiring a particular lipid environment to undergo functional conformational transitions. Recently, two breakthrough studies[6,7] determined the first heterotrimeric $GABA_A$-receptor structures. In both studies, the transmembrane domain of the receptor was in an unnatural conformation, which might have been caused by the replacement of the natural membrane environment with a detergent. Given the allosteric nature of the $GABA_A$ receptor, any conformational alterations of the structure of the transmembrane domain of one or a few subunits might affect the transmembrane domains of other subunits, and potentially also the extracellular domains. Therefore, the new structures obtained in a membrane environment might be a closer representation of the natural conformations of the binding sites of the receptor. Notably, Laverty *et al.* demonstrated that their method of receptor reconstitution preserved the physiological long-distance crosstalk between different ligand-binding sites: varying the amount of a given ligand bound to the receptor modulated the binding of a different, radioactively marked ligand to a distant site (Fig. 1f and Extended Data Fig. 2d of ref. 1).

The authors of both studies incubated the $GABA_A$-receptor-nanodisc samples with the megabody to orient the $GABA_A$-megabody complexes during cryo-EM imaging in such a way that snapshots from different angles could be obtained. The use of megabodies might also be a technological advance because it can increase the size of protein complexes that would otherwise be too small for their structures to be determined using cryo-EM.

The findings show how the binding of a given ligand to its site leads to conformational and functional changes throughout the $GABA_A$ receptor, including changes to the binding sites of other ligands. For example, one structure shows that binding of GABA to both of its sites in the extracellular domain causes a conformational change that contracts and closes these sites (Fig. 3 of ref. 1). Another structure shows that picrotoxin, which binds to the transmembrane domain, stabilizes the receptor in a closed-channel conformation (Fig. 1 of ref. 2). However, a third structure reveals that when GABA and picrotoxin are both present, one of the two GABA-binding sites is incompletely closed (Fig. 2 of ref. 2), indicating that picrotoxin binding influences the GABA-binding sites. Intriguingly, structures obtained when both GABA and a benzodiazepine are present indicate that these compounds strengthen the interactions between the otherwise weakly associated extracellular portions of the α and γ subunits (Figs 5 and 6 of ref. 2). This might explain how benzodiazepines promote the activity of the receptor when GABA is present.

The studies also give clues about the cytosolic parts of the receptor. Only short fragments of the large intracellular domains could be resolved, even though full-length $GABA_A$ subunits were imaged. This is in stark contrast to the well-resolved structures of the intracellular segments of full-length cation-conducting nicotinic acetylcholine- and serotonin-receptor channels, which are members of the same superfamily of pentameric neurotransmitter channels as the $GABA_A$ receptor[8–11]. The present findings might be the first experimental hint that the intracellular segments of $GABA_A$ and other anion-conducting pentameric channels might not have a defined secondary structure, whereas the intracellular domains of cation-conducting pentameric channels are structured even when expressed in the absence of the extracellular and transmembrane domains[12]. The diversity in length and amino-acid composition of the intracellular domain remains a challenge in the structural and functional characterization of $GABA_A$ and related receptors.

"Binding of ligands to non-GABA sites can alter communication between different binding sites."

In theory, the involvement of specific combinations of $GABA_A$-receptor subtypes in particular normal and disease processes holds promise for precise pharmacological interventions. In practice, the large number of different $GABA_A$ subunits (19 subunits) that have substantially similar amino-acid sequences renders subunit-specific drug targeting tedious, if not impossible. The detailed structural insights reported in the two papers discussed here, as well as a

50 Years Ago

While he was working on the various biological problems that obsessed him, Charles Darwin relentlessly bombarded friends and acquaintances with requests for information and specimens. In a correspondence that lasted more than twenty years, W. B. Tegetmeier, one of his most valuable contacts, was continually questioned about such topics as breeds of fowls, length of cats' teeth, sex ratio at birth and race horse records … Sometimes Darwin reached a wider public by publishing his requests in journals … One of these, *Questions about the Breeding of Animals*, has been reprinted in facsimile … The questions are concerned largely with the outcome of crosses involving wild and domesticated animals, and the likeness of the hybrid progeny to parents and grandparents.
From *Nature* 25 January 1969

100 Years Ago

In an interesting essay on "Camouflage" … Mr Abbott H. Thayer illustrates his well-known conclusions in regard to the cryptic coloration of animals that hunt or are hunted. In their "superhuman perfection" the concealing coats of wild animals have become the models for the camouflage corps of armies … What is practically universal is background–imitation … Mr. Thayer illustrates this by interesting views of brook-scenes and wood-scenes photographed through a stencil of bird or beast. The creature has the garment of invisibility because its "costume is pure scenery". "All the patterns and brilliant colours on the animal kingdom, instead of making their wearers conspicuous, are, on the contrary, *pure concealing coloration*, being the *actual colour notes of the scene in which the wearer lives*, so that he really is Nature's utmost *picture* of his background."
From *Nature* 23 January 1919

better understanding of the highly diverse intracellular domain, will probably provide a solid framework for structure-guided drug design and open up new avenues for drug-discovery research. ■

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MATERIALS SCIENCE

Gel sandwich smartens up windows

Polymeric gel particles have been used to make windows that highly effectively allow or block heat-generating wavelengths of sunlight in response to temperature. Such windows might increase the energy efficiency of buildings.

MICHAEL J. SERPE

Smart polymers can sense and react to environmental conditions, and have been used in myriad technologies for decades[1]. Writing in *Joule*, Li *et al.*[2] report that such polymers can be used to make smart windows that strongly modulate the amount of ultraviolet, visible and — most notably — near-infrared light that enters a building. Because these components of sunlight can generate heat, this regulation could reduce the monetary and energy costs associated with heating and cooling buildings.

Estimates show that about half of the energy used in a typical US home is for heating and cooling (see, go.nature.com/2c4ypxw), making temperature control the most energy-consuming process in residential properties. It therefore follows that the heating and cooling of homes in the United States contributes more to greenhouse-gas emissions, and hence global warming, than any other process associated with household maintenance. The discovery and use of energy-efficient building materials, including windows, could thus have a profound impact for society.

A common approach to reduce heating and cooling demand in buildings is to open or close window coverings such as blinds and curtains. To begin to make this process less dependent on human intervention and hence more efficient, 'electrochromic' windows, which darken in response to the application of small electrical potentials, have been developed. Such windows are used on the Boeing 787 Dreamliner aeroplane, for example. The windows still require someone to decide when to darken them, but a simple feedback mechanism could be used to allow the windows to be darkened in response to room temperature.

Electrochromic windows are effective, but have several drawbacks[3–5]: they require the application of an electrical potential, are expensive to make, have inconsistent light-blocking efficiency and are unlikely to be durable in the long term. As a result, 'thermochromic' smart-window technologies that directly respond to the local temperature by changing their ability to allow sunlight into a space are highly desirable. Such technologies exist, but have limitations. For example, films of the thermochromic compound vanadium dioxide show promising sunlight-modulating properties, but are activated (darkened) at impractically high temperatures of up to 90 °C (ref. 6). Furthermore, the amount of light they allow through — their transmittance — in the inactivated, transparent state is relatively low, on the order of 50% (refs 6, 7).

Li and co-workers now report a useful advance in the development of thermochromic smart windows that depend on smart polymers for their function. The authors' system consists simply of a thin layer of a concentrated solution of polymeric gel particles (known as microgels), trapped between two glass layers (Fig. 1). The resulting windows had an infrared transmittance of up to 81.6% in their inactivated transparent state, but a much lower transmittance of about 6% when activated — which represents an extremely high modulation of solar energy. In addition, the authors' windows are activated at about

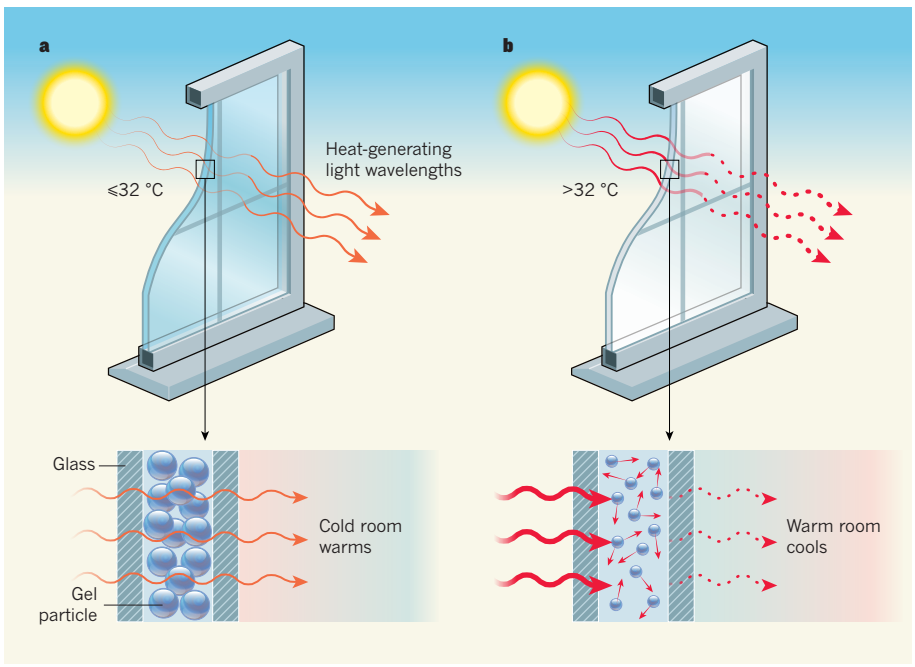

Figure 1 | Smart windows that incorporate temperature-sensitive polymeric gel microparticles. Li *et al.*[2] have made windows in which a solution of precisely prepared, microscopic polymer particles in water is sandwiched between two panes of glass. **a**, At or below about 32 °C, the gel particles are swollen by water. This makes them essentially transparent to the heat-generating components of sunlight (near-infrared, visible and ultraviolet light), which can, therefore, pass through the window and warm up any space on the other side. **b**, Above 32 °C, the particles collapse and expel water. The collapsed particles scatter the heat-generating components of sunlight, preventing them from passing through the window and limiting the temperature increase on the other side. The glass also becomes visually opaque.