NEUROSCIENCE

Hot or not

Electrical stimulation of the human cortex, undertaken for brain surgery, triggers percepts and feelings. A new study documents an ordering principle to these effects: the farther removed from sensory input or motor output structures, the less likely it is that a region contributes to consciousness.

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When Wile E. Coyote, in hot pursuit of Bugs Bunny, invariably ends up being squashed under boulders, anvils and other impossible heavy objects, flashes, stars and birds circle his head. These are an artistic interpretation of 'phosphenes', brief visual percepts that arise due to mechanical, electrical or magnetic stimulation of the eye or visual cortex. These conscious experiences reflect the visual system interpreting activity in its neurons.

Luigi Galvani discovered that the sciatic nerve in a frog's leg caused the attached muscle to spasm when brought into contact with electrical charge in the late 18th century. By 1802, his nephew Giovanni Aldini stimulated the exposed brains of decapitated prisoners during a public event. Since then, researchers have used focal electrical stimulation to infer function from structure. This is how Eduard Hitzig and Gustav Fritsch mapped the motor strip in canine cortex in 1870; a few years thereafter, this technique was attempted in humans, with dubious results. Refined over the following decades, intracranial electrical stimulation (iES) became part of the neurosurgeon's toolbox due to the ground-breaking work of Wilder Penfield at the Montreal Neurological Institute in the 1930s, 40s and 50s, establishing the concept that circumscribed regions of pre- and post-central gyrus represent and control specific muscles, limbs and body parts.

To remove tumours or reduce the incidence and severity of epileptic seizures, neurosurgeons cut, coagulate or otherwise resect brain tissue. How much to remove is a dilemma: cut too much and the participant may become mute, blind or paralyzed; cut too little and tumorous tissue may remain or seizures will continue. To minimize postoperative deficits and maximize beneficial outcome, neurosurgeons implant subdural electrodes that rest on top of the cortical surface or depth electrodes that penetrate into the grey matter to identify functional regions involved in language and speech, motor control, vision and so on. Such functional mapping is part of the routine neurology workup that reveals causal links between specific brain regions and their function.

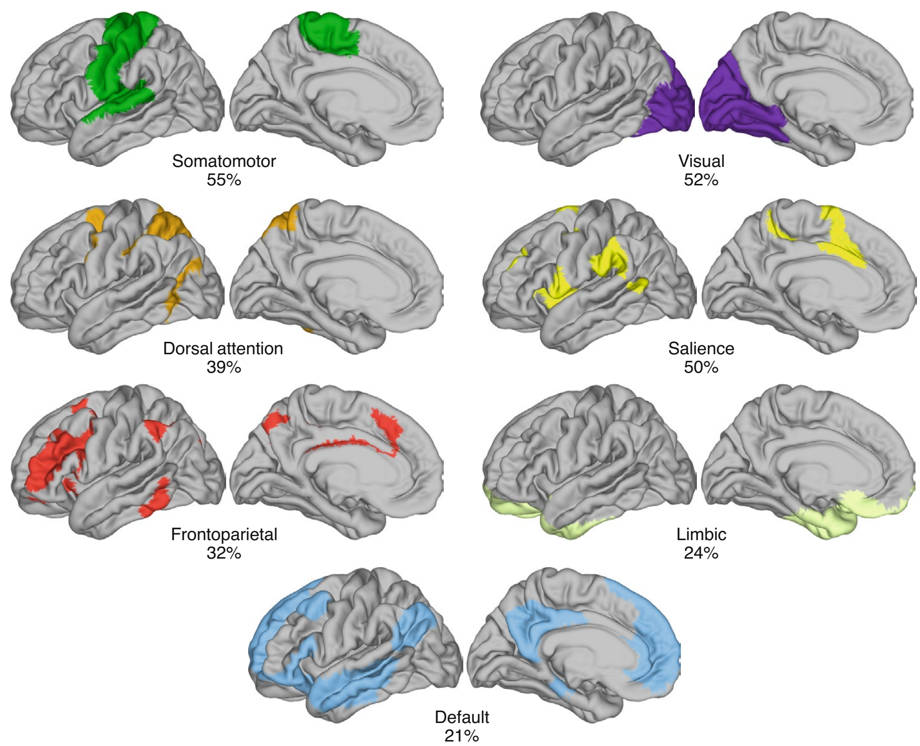

Fig. 1 | Not all cortical regions contribute equally to consciousness . The fraction of responsive electrodes that triggered 573 conscious experiences or motor effects were mapped onto a seven-region parcellation of cortex. This reveals a striking trend: the farther removed from input and output structures a regionis, the less likely its stimulation will be experienced by the patient (modified from ref. [6]).

In this way, Penfield[1] amassed data on experiential responses, rare vivid experiences or hallucinations—previously seen or heard episodes, familiar voices, songs or music—triggered by stimulation of cortex from hundreds of participants. In Penfield's hands, such responses were heavily biased toward the lateral surface of the temporal lobe. Since Penfield's pioneering work, there has been no survey of the litany of sensations, feelings and motor disruptions triggered by iES. This is what Josef Parvizi, professor of neurology at Stanford's medical school, and his team set out to do. Their systematic approach has already yielded bountiful fruits, linking specific cortical sites to specific experiences: seeing flashes[2] and faces[3], mustering courage in the face of feeling ominous threats[4], smelling and tasting[5], and so on.

Their pièce de résistance is published in this issue of *Nature Human Behaviour*[6]. Collecting data from 67 people diagnosed with putative unifocal seizure, the authors recorded from 1,537 sites, primarily with surface-hugging macro-electrodes, registered to a common Montreal Neurological Institute (MNI) space. What they hunted for were 'responsive' electrodes, meaning those that evoked a subjective experience, such as a phosphene, bodily sensation or emotion that the participant could describe or that triggered twitching, limb motion or disrupted speech.

The elicitation rate, the fraction of electrodes the participant can sense when activated (within the safety limits of the stimulation protocol), varies across the accessible cortical surface. It is as high as two out of three electrodes above visual and somatosensory areas and as low as one out of five electrodes above limbic areas or one out of six over the anterior prefrontal regions. When electrode locations were projected onto a 7- or 17-region parcellation of cerebral cortex (derived from functional MRI resting state functional connectivity of a thousand healthy adults), a compelling pattern emerged: the elicitation rate decreased monotonically along a functional-anatomical gradient, starting with sensory regions at the bottom and ending with transmodal, default-mode and limbic networks at the top. The higher up in the cortex a region is, the less likely gentle brain stimulation there will be noticed by the participating brain (Fig. 1). The silence of these frontoparietal, limbic and default mode networks is remarkable as they are thought to be central to much of cognition.

Furthermore, the varieties of distinct experiences (for example, a visual phosphene, a recall of a song, a feeling of unease) increased when ascending this gradient: while the majority of evoked responses in sensorimotor areas reflect the appropriate visual, somatosensory or motor modality, the smaller number of experiences evoked in limbic, midline and the farthest forward prefrontal region were the most diverse across participants. A variety of controls, such as sham trials and varying the amplitude of the iES, ruled out systematic confounds, such as participants having different rates of false alarm or excitability of the underlying tissue varying systematically with location.

While iES is safe and effective, it is also crude: the electrodes are many square millimetres in area and deliver up to 10 mA of bipolar current between adjacent electrodes that can modulate the excitability of a million or more pyramidal neurons and interneurons within a volume given by the resistive spread of the current, supplemented by more remote effects caused by evoking spikes in axons of passage. Still, effects induced by iES can be quite localized, with responsiveness changing from all to none within millimetres or across a sulcus[3,7]. The challenge for the future will be to move towards microstimulation, common in laboratory animals, in which a thousand-fold-smaller current is sent through thousand-fold-smaller electrodes to give rise to ever more specific sensations. Perhaps this will reveal the remarkable absence of auditory percepts when stimulating Heschl's gyri, in the neighbourhood of auditory cortex.

The exacting data collected by Fox and colleagues provides critical causal, not just observational, evidence to identify the neuronal correlates of consciousness. Indeed, whether or not the epicentre of experience is in a postulated posterior hot zone or in prefrontal cortex[8,9] can be addressed in this manner.

Yet that debate should not distract from one of the central mysteries of life: the unexplained daily miracle that exciting cortical tissue triggers subjective, conscious experience. Brains are, after all, a piece of furniture of the universe like any other, subject to the same laws of physics. Yet we have absolutely no evidence that stimulating the liver, the kidney or, for that matter, a tree, a rock or a brass lamp, evokes the djinn of consciousness. What it is about the brain, the most complex piece of active matter in the known universe, that turns its activity into the feeling of life itself[10]? ❐

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Competing interests

The author declares no competing interests.