

NEUROLOGY

An awakening

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Neuroscientists and engineers are developing ways to help patients overcome paralysis and stroke. But what about mental function itself? Can medical intervention restore consciousness?

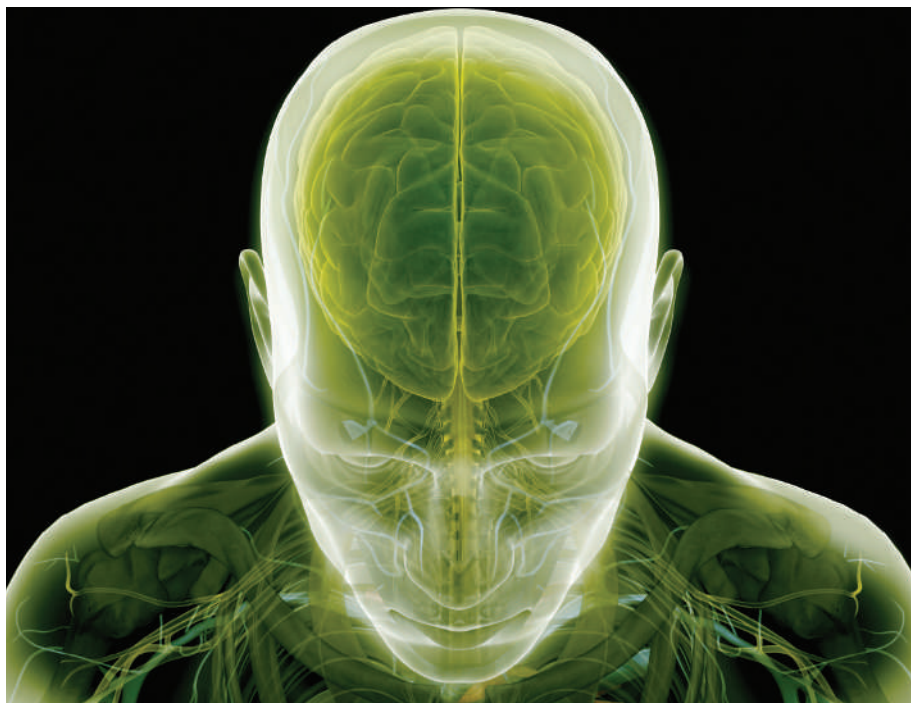
Jean-Paul Sartre wrote¹: “In one sense choice is possible, but what is not possible is not to choose.” To the neurologist, however, gaining consciousness is a decision of the unconscious brain to make choices. Philosophers and scientists may argue about the definition of consciousness^{2,3}, but neurologists have little trouble identifying its absence. Now, physicians are beginning to understand how it can be restored in some patients with severe brain damage. A case report by Schiff *et al.* (page 600 of this issue⁴) raises hope in this area, and sheds light on the neurobiological underpinnings of consciousness. Schiff and his colleagues treated a patient who had been in a ‘minimally conscious state’ (Box 1, overleaf) for several years after a serious brain injury.

Sadly, the vast majority of coma patients do not recover consciousness. The prognosis is determined by the type of injury to the brain, its extent, and the findings from serial neurological examinations⁵. For example, a trained neurologist can predict with near certainty that meaningful recovery will not occur for many patients who remain in a coma for days after a cardiac arrest, in which the brain is deprived of blood flow and oxygen. For other patients, however, the outcome is less certain.

Even after severe brain injury, some patients retain enough of the cerebral cortex to raise hopes that some degree of organized mental function might one day recover. Indeed, some show intermittent signs that are clearly distinguishable from coma, despite an overall level of function that is effectively unresponsive. For these patients, we do not have reliable indicators of prognosis, and we lack treatments that might help the brain restore consciousness.

But advances in basic neuroscience are beginning to reveal the brain systems that are responsible for monitoring and sustaining engagement with the world around us. A key component is the thalamus, which lies between the brainstem and the cerebral hemispheres, and forms the gateway to the brain’s cortex.

The thalamus is organized as a set of nuclei. The best understood of these nuclei are those containing the neurons that relay information



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from the eyes, ears and skin to the appropriate sensory cortex. But much of the thalamus is poorly understood. Anatomical studies in non-human primates have identified a class of thalamic neuron that might operate more generally in activating cortical networks⁶. These neurons, which stain positively for the calcium-binding protein calbindin, are found in all thalamic nuclei. Although we know little about the physiological properties of these calbindin-positive cells, they tend to exhibit a different pattern of connections with the cortex compared with the relay cells. Their axons terminate more broadly both across cortical areas and in layers that the relay cells miss. These calbindin-positive cells comprise a large percentage of the intralaminar nuclei of the thalamus — nuclei that have long been thought to have a role in arousal.

Schiff *et al.*⁴ hypothesized that their patient might express a minimal level of consciousness because of a primary impairment of the arousal system itself. The patient had suffered irreparable damage to much of the cerebral

cortex, but many essential areas were preserved. By stimulating the intralaminar nuclei, the authors hoped to switch on the undamaged areas of cortex. Neurologists and neurosurgeons have previously used electrodes to monitor brain activity in patients with epilepsy and to stimulate deep-brain regions in the treatment of severe Parkinson’s disease. Because the brain itself lacks sensory receptors (after all, it is normally protected by a cranium), these electrodes cause no discomfort. This insight, and extensive experience with stimulation electrodes in animal experiments⁷, made the procedure feasible and relatively safe. Such considerations probably helped to guide the complex ethical debate preceding this experimental trial on a human patient.

The results were dramatic. Within 48 hours of the surgery to place the electrodes, the patient, who had remained in a minimally conscious state for 6 years, demonstrated increased arousal and sustained eye-opening, as well as rapid bilateral head-turning

to voices. Schiff and colleagues allowed 50 days of post-operative recovery before activating the stimulating electrodes again to ascertain that the stimulation by the implanted electrodes — not some unknown aspect of the surgery — was the source of the improvements.

An 18-week 'titration' phase, which involved finding the most effective patterns of stimulation, followed. During this phase, the previously non-verbal patient became capable of naming objects and using objects with his hands — for example, bringing a cup to his mouth. Moreover, he could swallow food and take meals by mouth, meaning he was no longer dependent on a gastrostomy tube.

After the titration phase, the authors turned the stimulation on and off systematically for a better assessment of its effects. The highest state of arousal and the ability to perform functional limb movements were associated with periods of stimulation. But compared with the pre-surgical period, many functions remained improved even without stimulation, indicating carry-over of the stimulation effects to no-stimulation periods.

These results raise hope for some patients with brain injury, but there are two caveats. First, this is a single case report; a carefully controlled clinical trial is needed to answer the remaining questions. What is the spectrum of brain injury that will benefit from thalamic stimulation? What are the clinical, anatomical and functional (neuroimaging) predictors of improvement?

Second, not all patients with disorders of consciousness will benefit from thalamic stimulation. This patient had shown clear signs of interactive behaviour and preservation of many of the important cortical structures before the surgery. Thalamic stimulation presumably increased both the level and consistency of activity in the preserved cortical structures, leading to arousal and behavioural improvements. Such stimulation would not benefit patients who have already lost the critical cortical structures; the condition of persistent vegetative state that often follows deprivation of the brain of oxygen and blood flow (hypoxia and ischaemia) falls into this category.

But besides the hope that this study furnishes for some patients, the observations of Schiff *et al.* may provide clues about the neurobiological underpinnings of consciousness. Cognitive neuroscience is beginning to expose the architecture of information processing that is directed towards goals and actions; we refer to this as an 'intentional framework', but it flies under various banners, including 'affordances' and 'embodied cognition'^{8–10}.

In essence, the brain does not process information in the abstract but instead consults information acquired through the senses and in memory insofar as it bears on the decisions made about potential actions and strategies. Our brains allow us to decide among possible

Box 1 | Disorders of consciousness

To be awake is to be in a state of engaging with the environment. To have agency is to interrogate this environment with some goal or purpose. This capacity to engage and interrogate seems to go awry in various disorders that affect cognition. And nowhere is this incapacitation more patent than in coma and related conditions.

Coma. The patient seems to be asleep and cannot be awoken. There is no spontaneous organized behaviour, not even pushing away of an irritant, and there is no evidence of any awareness of sensory cues — no response beyond reflexes mediated by the brainstem and the spinal cord. Most patients in coma do not recover meaningful neurological function, but many do progress to states that are clearly distinguishable from coma, as described below.

Persistent vegetative state (PVS). This is similar to coma in all respects except that,

at times, the patient does not seem to be asleep. The eyes may be open, and spontaneous, non-purposeful, roving eye movements occur. PVS is probably the result of a return of some of the functions that would govern the sleep-wake cycle, albeit in the absence of a functioning cerebral cortex¹⁴. As a result, it is only the brainstem and perhaps a few islands of dysfunctional (or disconnected) cortex that regain function.

Minimally conscious state (MCS). In contrast to PVS, patients show occasional signs of arousal and organized behaviour. Nevertheless, for the most part, there is a profound deficit in consciousness. Indeed, functional brain-imaging studies¹⁵ indicate that parts of the cortex may be able to function even when the patient seems to be unconscious. This observation and the differential prognosis of MCS and PVS call for more careful classification of patients, which may currently be biased towards PVS¹⁶. **M.N.S. & R.K.**

options — that is, how and in what context to engage with the world around us. The brain makes many such decisions unconsciously. Indeed, the decision to engage at all is, in effect, an unconscious decision to be conscious. Thus, the brain of the sleeping mother queries the environment for the cry of her newborn. We suspect that the normal unconscious brain monitors the environment for cues that prompt it to decide whether to awaken and engage. This mechanism may be disrupted in various disorders of consciousness, including the minimally conscious state, hypersomnolence, concussion, abulia (lack of will) and possibly severe depression.

Previous theories of consciousness have relied on a central executive and magical physiological phenomena (for example, synchronized reverberations) to elevate the subconscious functions of the brain to consciousness. However, viewed as a decision to engage, consciousness can instead be studied in the same framework as other types of decision and the allocation of attention¹¹. Rather than a central executive, there seems to be a network of brain regions that organize the resting state and maintain overall orientation towards context^{12,13}. It is quite possible that they make decisions about whether or not to engage and in what way. They do what Sartre considered impossible: they choose whether to choose or not.

How these networks relate to intralaminar nuclei or the matrix of calbindin-positive thalamic neurons is another question. However, the idea that these areas need to be turned on for consciousness leads us to wonder whether stimulation of the intralaminar thalamus in this patient⁴ worked through the activation of calbindin-positive neurons and these circuits. If so, then the work of Schiff *et al.*⁴ could point the way towards interventions that are more

refined than stimulation with electrodes.

These are loose strands, but neuroscience is beginning to stitch together the neurologist's and the philosopher's ideas of consciousness. It is wonderful to see the fruits of this research help one patient. We hope that further studies will advance our knowledge and help more patients. Meanwhile, our advice is: treat your blood pressure, wear a helmet and read the existentialists. ■

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