CONSCIOUSNESS AND NEUROSURGERY

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THE NEURONAL BASIS of consciousness is the greatest challenge to the scientific worldview. Much relevant empirical work is carried out on the minimal neuronal mechanisms underlying any one specific conscious percept. Two broad approaches are popular among brain scientists: electrophysiological recordings from individual neurons in the cortex of behaving monkeys or behavior combined with functional brain imaging in humans. However, many aspects of consciousness are problematic or remain off-limits to the former approach, while the latter one lacks sufficient spatial and temporal resolution to monitor individual neurons that are key to perception, thought, memory, and action. It is here that neurosurgeons, probing the living human brain on a daily basis, can play a decisive role. This article explores the contributions of neurosurgeons to this quest and outlines some of the results that have already been achieved.

KEY WORDS: Cerebral cortex, Consciousness, Electrical stimulation, Medial temporal lobe, Neuronal correlates of consciousness, Single-neuron recordings, Visual awareness

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n a rough way, we all know what it is like to be conscious. The neurosurgeon uses the terms "conscious" and "unconscious" in daily practice. The presence of consciousness and, more importantly, the absence or impairment of consciousness have immediate implications for the neurological assessment of the patient. The clinician realizes that between the extreme states of consciousness and coma stand a variety of intermediate states, or altered states of consciousness. Like the Eskimo's vocabulary for snow, neurologists and neurosurgeons have developed a detailed vocabulary and numerical scales for impaired or altered consciousness. The clinician uses such terms as clouding of consciousness (reduced wakefulness and awareness), delirium, obtundation, and stupor (40) as well as a numerical scale for coma, the Glasgow Coma Scale. These terms do little to further scientific understanding of consciousness. They are arguably useful in communicating a patient's neurological status, but appearances may be misleading. The patient in a persistent vegetative state may seem conscious but has no real interaction with the environment, whereas the "lockedin" patient may seem unconscious but only lacks effective means of communicating his conscious self to the observer. The Glasgow Coma Scale uses motor responsiveness, speech, and eye opening as measures to assess

consciousness. But none of these faculties is necessary or sufficient for consciousness.

Despite the more pressing need to treat the patient with impaired consciousness, neurosurgeons through the ages have realized that their work on the human brain poses a specific challenge. Some have taken this challenge beyond the immediate clinical question to ask how the brain gives rise to consciousness. Wilder Penfield addressed this question by observing his epilepsy patients during periods of behavioral automatism and by applying electrical stimulation to sites in the brain during neurosurgical procedures under local anesthesia (38, 39). His observations on alteration in the content of consciousness have captured the imagination of generations of neuroscientists. In a lecture delivered in 1936 and published in the Harvey Lectures, Penfield addressed the neurosurgical community in the following words:

The neurosurgeon has a unique opportunity for psychological study when he exposes the brain of a conscious patient, and no doubt it is his duty to give account of such observations upon the brain to those more familiar with the mind. He may find it difficult to speak the language of psychology, but it is hoped that material of value to psychologists may be presented, the application

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being left to them. It seems to me quite proper that neurologists should push their investigations into the neurological mechanism associated with consciousness and inquire closely into the localization of that mechanism without apology and without undertaking responsibility for the theory of consciousness. (35)

Few neurosurgeons know that Walter Dandy's last article (8) was about "the location of the consciousness center in the brain." Dandy was intrigued by the case of a patient with a bilateral frontal glioma who underwent extirpation of the right frontal lobe, followed 3 weeks later by resection of the left frontal lobe for the remaining tumor. The procedure led to immediate loss of consciousness that persisted until the patient's death 7 days later. Dandy then analyzed a series of cases including seven frontal lobe resections in which both anterior cerebral arteries were sacrificed at the genu of the corpus callosum. In all cases, consciousness was "totally lost immediately" and did not return for up to 51 days, the longest period of survival. Interestingly, Dandy's conclusion was that it was damage to the corpus striatum, rather than to the frontal lobes, that was responsible for loss of consciousness, leading him to the conclusion stated in the title of the article: "The location of the seat of the conscious center in the brain: The corpus striatum" (8).

The neurosurgeon can contribute to an understanding of consciousness in various ways. One is simply by observation of clinical states involving alteration of consciousness, which might teach us something about the nature of consciousness. Another way is by recording bulk brain activity (electroencephalogram [EEG]), single-neuron and multiple-neuron activity, and local field potentials directly from the human brain when clinical opportunities to do so arise. Finally, direct manipulation of brain activity by electrical stimulation, which has proved useful in brain mapping for neurosurgical decision making, may also be useful in gaining insight into the nature of consciousness.

One of us (FC) gave a keynote address at the Annual Meeting of the Congress of Neurological Surgeons that took place in October 2001 in San Diego, CA, on the topic of "Consciousness and Neurosurgery" (6). The text of this address has been expanded, and background material has been added, to better convey the unique contributions that neurosurgeons and associated clinical disciplines can make to the ongoing search for the neuronal basis of the conscious mind. For more background material, see the article by Crick and Koch (7) as well as the book by Koch for a general medical and scientific audience (21).

CLINICAL OBSERVATIONS

Much processing in the normal nervous system, even in the cerebral cortex, is unconscious. A rather striking example is the retina. Of course, without the retina, normal vision is not possible (although if the retina is lost in later life, we may be able to imagine things visually), yet the evidence shows rather clearly that what goes in the retina does not completely correspond to what is seen. Examples of discrepancies between retinal processing and visual perception include the blind spot, the absence of short-wavelength photoreceptors at the fovea, the precipitous drop-off of cone photoreceptors and the corresponding loss of color vision outside the fovea, and blurring caused by incessant eye movements and blinks. What needs to be discovered, in the first instance, are the neuronal correlates of consciousness (now widely known as the NCC), and it seems fairly certain that these are not in the retina.

People are not conscious of much of what is going on in their digestive systems, but can they be unconscious of their external actions? Much indirect evidence suggests that this happens—that a runner starts to run before he consciously hears the starting pistol—but one example of brain damage gives stronger evidence (32). One patient with diffuse brain damage produced by carbon monoxide poisoning, can see motion, color, and texture but neither the shape of objects nor their orientation. Nevertheless, she can post a letter accurately in an inclined slot, although she is at chance in describing its orientation. Interestingly, she cannot "post" it correctly if there is a short delay. She can only perform this action correctly "on line." The observations of patients with visual agnosias reveal the extent to which unconscious visual processing goes on.

Other cases of apparent on-line action familiar to the neurosurgeon appear during partial complex seizures. The patient can perform various stereotyped responses yet have no recollection of them afterward. Penfield and Jasper called these responses automatism, indeed implying that the patient is not conscious. But these patients do pose a considerable problem for the observer, who, much like the protagonist of "The Tales of Hoffman," cannot tell whether Olympia is just an automaton. They seem capable of negotiating obstacles in the environment, they grasp objects, and they respond to movement and speech-yet, they are unable to report their experiences. A striking example is the patient who reported to one of us (IF) seizures that occurred while he was riding his bicycle to work. After setting out for work, he would occasionally find himself riding back home. Apparently, during a complex partial seizure, he was able to turn around and operate a bicycle (12). What compounds the problem of assessing consciousness here is the involvement of the medial temporal lobe system of declarative memory: these patients are unable to encode their behavior into memories that can be consciously recollected. Koch and Crick (22) have called these seemingly automatic activities "zombie modes." In everyday life, these zombie modes, such as reaching for and grasping an object, are involved in a good portion of our behavior. They seem to act in parallel with consciously seeing the object, but they may be significantly faster.

THE GENERAL NATURE OF VISUAL CONSCIOUSNESS

Why is our brain not just a whole series of unconscious zombie systems? The answer is that there would have to be a vast number of them to replicate all of human behavior. It looks as if the function of consciousness is to provide a general-purpose mode of perception that can cope with complicated situations and select one of very many possible reactions, including silent thought. There would be a considerable evolutionary advantage to a creature having these two interacting modes: one to provide a limited number of rapid, stereotyped unconscious responses and the other, parallel but slower, for more measured conscious responses to more complex situations. There is evidence that these two modes interact somewhat.

What is the general nature of visual consciousness? As is well known, the information coming into the two eyes is not enough, by itself, to interpret the visual scene. The brain must form the best guess it can about what is out there. It does this by using previous experience, both from past interactions with the world and also from the experience of our ancestors, embodied in the genes. For example, each retina gets a twodimensional snapshot of the visual scene. Visual perception (usually) corresponds to a three-dimensional interpretation of this, in terms of objects, actions, and their relationships.

Observers seem to see the whole visual scene equally distinctly, but this is an illusion. In fact, only a small central region is clearly seen in detail. A wider picture is built up by the constant movements of the eyes. Such eye movements are initiated by a shift in visual attention, either by an act of will or because of especially salient inputs, such as a sudden movement or loud noise. One can be clearly conscious of what one is attending to, and one can easily remember recently attended items, but consciousness for the other, nonattended parts of the scene is only vague, if present at all. This has been demonstrated quite powerfully by visual psychologists using such illusions as "inattentional blindness" (30) or "change blindness" (34). If this sounds rather abstract, recall how it feels to drive a car along a familiar highway.

We believe that attention biases the competition between different possible interpretations of objects and actions in the visual scene so that the brain can either act rapidly or think about what is the best action to take. How does the visual system do all this? Most of the information from the retina goes to the occipital lobe via the lateral geniculate bodies. In the past, these cortical areas were called Areas 17, 18, and 19. Area 17 is indeed a single area, now called the primary visual cortex (V1). Area 18 includes several visual areas, and there are now many subdivisions of Area 19. We have known for some time that the retina is interested primarily in small spots of light and their exact position and in the wavelength of the light. Area V1 is more interested in oriented lines and edges, together with movement, disparity (the differences between the visual images in the two eyes), wavelength, and so on. There is a loose hierarchy of visual areas. Ascending the hierarchy, starting from V1, the features each neuron responds to become more complex, so that there are neurons in higher areas beyond V1 that respond, for example, to faces (strictly, certain aspects of a face), to hands, to houses, and so on. The neurons also become less fussy about the exact location and

appearance of the feature they are responding to, so that a "face neuron" will respond in much the same way if the image of the face is bigger or smaller or if the angle of view of the face is a little different.

CEREBRAL CORTEX AND CONSCIOUSNESS

Consciousness almost certainly involves the cerebral cortex and some of its associated structures, such as the thalamus. Within the cortex, approximately 80% of the neurons are excitatory. Their connections are primarily within the cortex, many of them with neighboring neurons, so there is much rather specific mutual excitation.

Most excitatory neurons also project out of their cortical area. Each neuron makes and receives some thousands of connections. The resulting mutual excitation of cortical areas is held in a precarious balance by the various types of inhibitory neurons. The whole system is a highly evolved, very intricate, balanced network, on several different scales.

The main job of a neuron in any cortical area is to respond to the significant correlations in its inputs and, gradually, to learn them, so that it can build the appropriate feature detectors (such as those for faces). It probably does this primarily by modulated Hebbian (or pseudo-Hebbian) learning mechanisms (19). Early cortical areas discover simple, local correlations, whereas later areas look for correlations of these correlations, and so on, in a hierarchical manner.

With any visual input, the cortical areas attempt to find the best past correlations that will fit the input. This may involve, simultaneously, more than one tentative interpretation of the input, so that an unconscious competition develops between them to gain control of wide and powerful regions of the network. We believe that what becomes conscious, after approximately several hundred milliseconds of activity, is the winner of the competition. The winner is strong enough to sustain much of this activity for at least several hundred milliseconds, so that the neuronal coalitions representing the winner can produce a powerful effect on the cortical regions involved in thinking and planning.

It may help to make a crude political analogy. The early discussions of an election and the primaries would correspond roughly to the preliminary unconscious processing. Consciousness would correspond to the winning party, which would remain in power for some time and would attempt to influence and control future events. "Attention" would correspond to the efforts of journalists and others to focus on certain issues rather than others and thus attempt to bias the electorate in their favor. One could even argue that the large pyramidal neurons in cortical layer V, which project to the superior colliculus and the thalamus (both involved in visual attention), correspond to the polls. These progress from early tentative polls to later, rather better polls as the election approaches. However, it is unlikely that all this happens in the brain in a fixed time sequence. The brain may resemble more closely the British system, in which the time between one election and the next can be irregular. Such an analogy should not be pressed too far. Like all analogies, it should be regarded as a possible source of ideas, which, of course, will have to be confirmed by experiment.

Thus, in this picture, seeing involves unconscious competition between various tentative interpretations, a winner-takeall process involving many cortical areas; the neural activity associated with this winning coalition would be sufficient to mediate the specific content of consciousness at that time. After an interval, another winning coalition emerges, based in part on the ongoing input.

This makes consciousness sound like a very global phenomenon, but it has local aspects. For example, local brain damage in humans can lead to achromatopsia: the patient sees the visual world in black and white, with little or no color (31, 44). This (and other evidence from brain damage) suggests that there are *essential nodes* in the network, to borrow a term from Semir Zeki (45). If an essential node is removed, then the particular feature represented at that node cannot become conscious. Put another way, to see some aspect of the visual scene, there must be at least one essential node for it somewhere in the cortex. Of course, no one is suggesting that if the entire cortex were destroyed except for, say, the nodes for color, then the patient could see color. A node is a node, not a whole network.

Although consciousness seems to be a widespread network activity, this does not mean that there may not be crucial local elements. For example, certain gap junctions, or electrical synapses, between subclasses of inhibitory cortical neurons (4) might be essential for conscious but not for unconscious stereotyped responses. If something like this were true, it would make the experimental attack on consciousness much easier. It is also possible that certain cortical oscillations, such as the much-debated 40-Hz oscillations, may be essential for consciousness, although they may also be used for unconscious operations (11).

It is not easy to see how to approach these complex network properties. One might speculate that unconscious stereotyped reactions correspond to a traveling netwave of activity, whereas consciousness corresponds to some sort of standing netwave, involving the so-called back-connections (7).

EXPERIMENTAL APPROACHES

Single-Neuron Recordings in Nonhuman Primates

What experiments are being performed to help delineate the NCC? Although it is desirable to study the widespread activity of the brain, it will be crucial to investigate the firing of individual neurons, and of as many of them as possible simultaneously. Because we know that humans are conscious, it would obviously be better if all such experiments could be performed in humans. For obvious ethical reasons, such invasive methods cannot be used in humans, except in a few special cases. They can be performed on macaque monkeys, but monkeys cannot talk, although they can respond by pressing buttons or moving their eyes. It is extremely laborious to train them to perform the chosen task, whereas humans can easily learn what the experimentalist wants them to do. Clearly, we have to study both humans and monkeys and hope that we can make useful comparisons between the two species.

How could one go about looking for the NCC? An ingenious experimental paradigm provides a constant visual input that produces a variable percept, as in bistable perception of a Necker cube. One popular method to do this in a controlled manner is to project one image into one eye and simultaneously a quite different input into the other, in such a way that the two images overlap. The observer does not see the two images superimposed except very briefly, because this makes little sense to the brain. Instead, the observer sees first one image, then the other, then the first one, alternating irregularly every few seconds or so. This "binocular rivalry," as it is called, is easily demonstrated in humans. Macaque monkeys seem to react in a very similar way (3).

Leopold and Logothetis (28) and Logothetis (29) studied neurons in several visual areas, from V1 to the inferotemporal cortex. Which of these neurons tended to follow the input (which was constant), and which followed the monkey's percept (which was changing)? The experimentalists found that only approximately 10% of the neurons in V1 (weakly) followed the percept, whereas as much as 95% of the relevant neurons in the inferotemporal region, near the top of the visual hierarchy, did so in an almost all-or-none manner. That is, when the monkey signaled that it saw the stimulus, the cell fired. When the preferred stimulus of the cell was present on the retina but the monkey signaled that it did not perceive it, the cell remained silent. This hints that neurons in the inferotemporal cortex may be a significant part of the NCC.

A phenomenon closely related to binocular rivalry is called "flash suppression." If an image is projected into just one eye, with nothing into the other eye, the observer naturally sees this image. If a second image is now suddenly projected into the other eye, the observer sees only this second image and is quite blind to the first image, although it is still coming into one of the eyes (43). This effect is highly reproducible. The situation can be reversed, such that in one situation, one image is perceived, but in a different situation, the other image is perceived. This manipulation dissociates the physical input from the subjective percept.

Monkeys can also be trained in this procedure while the activity of single neurons in the visual cortex is monitored (41). As seen in *Figure 1*, a neuron in the superior temporal sulcus of the monkey responds to the percept. This particular neuron responds vigorously to the ape's face by itself (*left*) but not to the sunburst pattern in isolation (*right*). If the image of the ape's face is in the right eye and the sunburst pattern is suddenly switched on in the other eye, this neuron follows the percept the monkey signals and fails to fire for the ape's face, although its image is still present in the right eye. That is, the neuron's firing is then highly correlated with the monkey's percept. The large majority of cells in this region, part of the



FIGURE 1. Recording of a neuron that follows the monkey's percept. In this experiment by Sheinberg and Logothetis (41), the picture of a young ape evokes a vigorous response from a neuron in the superior temporal sulcus if shown by itself (left panel, far left). When the picture of sunburst is flashed into the other eye, the monkey signals that it sees this pattern and that the face becomes invisible. This is reflected at the cellular level, with a loss of response from the neuron in the superior temporal sulcus. Conversely, if the monkey fixates on the sunburst pattern for a while and the image of the face is flashed on, the animal sees the face and the cell fires strongly (right). Neurons in earlier areas are largely unaffected by such perceptual changes (from, Koch C: The Quest for Consciousness: A Neurobiological Approach. Englewood, Roberts & Co., 2004 [21]).

inferotemporal cortex, follow the percept rather than the stimulus.

Electrical Stimulation in Humans: "Doubling of Consciousness"

The monkey cannot directly tell us whether it is conscious. A few neurosurgeons have realized that certain questions, particularly those pertaining to consciousness, can be answered only in humans and have proceeded to use clinical opportunities to make observations. Indeed, there are two ways for the neurosurgeon to be actively involved in such endeavors. The first involves electrical stimulation of the brain. This well-established method of brain mapping, often used during neurosurgical procedures or via chronically implanted electrodes, has already yielded striking observations about the nature of consciousness.

It has been established by Penfield and Perot (39) and later clinical neuroscientists that electrical stimulation can alter the content of consciousness (1, 12, 17, 18). Of particular interest are the so-called "experiential responses." These include alteration of perception in the form of various illusions as well as new percepts superimposed on or superseding the ongoing content of consciousness. A striking example is provided in the case of a patient in whom stimulation in the anterior part of the supplementary motor area elicited robust laughter (14). The patient found herself executing the motor activity of laughter and at the same time feeling mirth, yet had to provide the meaning or reason for the laughter. This changed according to what she happened to attend to at the time, which then became the "funny" object. Penfield (36, 37) referred to the experiential responses elicited by stimulation of the cerebral cortex as a "stream of consciousness" that can be electrically reactivated and faithfully reenacts past experience. In contrast, Gloor (16) noted that these experiences, although vivid, often lack detail and do not possess a continuous flow of time. Clearly, electrical stimulation of the cerebral cortex does not abolish consciousness, nor does it completely replace its content. Despite the compelling immediacy of the "experiential responses," patients are usually aware that these responses are unreal, leading to a feeling of "being there" yet accompanied by the realization that these events are not actually occurring at the present time. This coexistence of being and not being "there" has been described by Jackson (20) as "doubling of consciousness" or "mental diplopia." A striking example is the phenomenon of déja vu that can be elicited by stimulation of the temporal cortex in humans and also arises spontaneously at the onset of some complex partial seizures of temporal lobe origin. Here, the patients find it bizarre that they



FIGURE 2. A, magnetic resonance imaging scan of an electrode track with the electrode superimposed over the track to illustrate the position of a recording microelectrode within entorhinal cortex (EC). H, hippocampus. B, enlarged Nissl-stained section of entorhinal cortex (obtained from unrelated autopsy material) with orientation similar to the magnetic resonance imaging scan in A and with a superimposed electrode image. Arrows point to the contacts for EEG recordings along the electrode shaft. Note that the microwires can be staggered at various lengths, allowing each microwire to record from different cells at different layers of entorhinal cortex (from, Bragin A, Wilson CL, Staba RJ, Reddick M, Fried I, Engel J Jr: Interictal high frequency oscillations (80–500 Hz) in the human epileptic brain: Entorhinal cortex. **Ann Neurol** 52:407–415, 2002 [5] © 2002 John Wiley & Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.).

should think that the present situation has happened before, even though they know, at the same time, that it has not (1).

Single-neuron Recordings in Humans

The opportunity to record directly from the human brain exists today in the context of a few neurosurgery procedures. These include recordings of intracranial EEG, local field potentials, multiple-neuron activity, and the activity of individual neurons. The ability to use a clinical opportunity for expanding our knowledge about brain function in general and consciousness in particular rests first with the neurosurgeon. There are only few clinical opportunities in neurosurgery to study single neurons, but these represent our only access to single-neuron activity in humans. Single- and multipleneuron activity have been recorded both intraoperatively during epilepsy surgery (see summary in Reference 33) and during surgery for movement disorders (see Reference 27 and many others) and extraoperatively through chronically indwelling electrodes for treatment



FIGURE 3. Histograms of enhanced response of a neuron in the entorhinal cortex of a patient to pictures of animals. A, average activity of the neuron (poststimulus time histogram) in response to images from different categories of stimuli (total number of presentations is shown next to the category name). The stimuli were presented for 1000 milliseconds (onset and offset are indicated by vertical dashed lines). The horizontal dashed line shows the average neuronal activity over the whole experiment. B, responses of the same neuron to the seven different pictures of animals presented in this experiment (from, Kreiman G, Koch C, Fried I: Category-specific visual responses of single neurons in the human medial temporal lobe. Nat Neurosci 3:946–953, 2000 [25]).

of epilepsy (13). Ojemann et al. have recorded intraoperatively from lateral temporal neocortical neurons during a variety of language and memory tasks (see summary in Reference 33). Recordings of single units in the thalamus, basal ganglia, subthalamic nucleus, substantia nigra, and anterior cingulate have been reported in patients with movement and other disorders undergoing stereotactic procedures for ablation or for placement of deep brain stimulators (see References 2, 9, 27, and others).

Fried and his colleagues at the University of California, Los Angeles, have performed a series of studies recording from single neurons in the medial temporal lobe to examine visual perception and memory. Some of these studies have direct relevance to the NCC. They used multiple-depth electrodes to pick up, extracellularly, the firing of single neurons over a period of several days. The electrodes are placed in an attempt to localize the seizure focus in a subset of patients with intractable epilepsy in whom noninvasive methods have failed to provide concordant localization of a resectable focus (15). The electrodes are placed stereotactically using magnetic resonance imaging and angiographic guidance. Each probe (*Fig. 2*) is 1.3 mm in diameter

and, in addition to contacts for EEG recordings, they are also fashioned with eight microwires, which allow recordings of multiple- and single-unit activity at the tip of the electrodes (13, 15). After implantation of the electrodes, the patients are monitored on the ward for a period of 1 to 2 weeks, until a sufficient number of spontaneous seizures are captured. It is during this period that a variety of perceptual and memory tasks can be presented to the patients who are awake and conscious. Once the electrodes are inserted, they cannot be moved. In the majority of patients, the probes are inserted bilaterally into medial temporal lobe structures, such as the amygdala, the hippocampus, the entorhinal cortex, and the parahippocampal gyrus, selected for clinical reasons. These areas of the medial temporal lobe receive input from the higher stages of visual processing and are critical in transforming percepts into lasting memories for future conscious recollection (10, 42).

In collaboration with Gabriel Kreiman from Koch's group at Caltech, Fried recorded from more than 1000 neurons in these patients, establishing that single neurons in the medial temporal lobe have specific responses to stimulus attributes and to catego-

ganization

categories.

the medial temporal lobe and that these responses reflect the or-

of stimuli

The situation in which the

same retinal input may lead to different percepts has already been investigated in monkeys by

use of binocular rivalry and flash

suppression, as described above. Kreiman et al. (24) used flash suppression to examine this

question, recording from human

medial temporal lobe neurons.

An example is provided in Figure

4. The input was a line drawing of President Clinton. Although in both cases (*top left* and *top right*), Clinton's image is projected on

the retina of one eye, the neuron

responds only when Clinton is perceived (*top right*) but not when perception of Clinton is suppressed (*top left*). Approximately

two-thirds of visually selective neurons tested followed the per-

ceptual alternations rather than

the retinal input. The other onethird did not correlate with the percept but in fact never fired

Another finding, revealed in *Figure 4*, although only sugges-

tive, is really surprising. The neuron responds to the drawing

of Clinton's face but also to a

very different image of the President, this time in color and in

the company of two other per-

sons. This amygdala neuron

also responds to a third and dif-

ferent image of Clinton, yet to

no other of 50 stimuli, including

the pictures of three other pres-

idents or other men. Whether

this neuron would respond to

all images of Bill Clinton or to

other sensory inputs related to

him is not known.

during the flash period.

into



FIGURE 4. Histograms of responses of a neuron located in the amygdala of a patient during the flash suppression paradigm. We show here the responses of this neuron to two different images of former President Bill Clinton (a black-and-white drawing and a photograph amid other people). For each picture, we show the stimuli projected to the retina (A and D, respectively), the subject's percept (B and E, respectively), and the neuronal response (C and F, respectively). Left, the image of Clinton is shown monocularly, and a black-and-white pattern is flashed to the other eye, suppressing the percept of Clinton. The neuron increases in activity during the monocular period but reduces its firing rate when Clinton is suppressed. Right, the black-and-white pattern is shown monocularly, and the image of Clinton is flashed to the other eye. The neuron responds only during the flash period when the subject sees Clinton (from, Kreiman G, Fried I, Koch C: Single neuron correlates of subjective vision in the human medial temporal lobe. **Proc Natl Acad Sci U S A** 99:8378–8383, 2002 [24] © 2002 National Academy of Sciences, U.S.A.).

ries of stimuli (13, 23, 25). A neuron can, for example, respond to pictures of animals but not to human faces or to outdoor scenes or other objects such as cars or food items (*Fig. 3A*). A detailed look at the responses to animals reveals that the neuron responds to a variety of animals, including a tiger, a scorpion, and an eagle (*Fig. 3B*). This experiment shows that stimuli leaving different imprints on the retina generate similar responses at the level of

Medial temporal neurons respond to percepts rather than to stimulus projections on the retina. But what if all retinal input is removed? How will these cells respond to imagery? In other experiments, when a neuron was found to respond to a particular object, such as a face, the patient was asked to close his eyes and imagine that object (26). As seen in *Figure 5*, the response to an imagined object, when no retinal input was

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FIGURE 5. Comparison of neuronal responses during vision and visual imagery. The responses of a neuron located in the entorhinal cortex while the subject observed or imagined the images shown above. Each vertical tick shows a spike from this neuron; the green horizontal lines indicate presentation of the dolphins, and the red horizontal lines indicate presentation of the pictures, demonstrating that the neuron responds to the pictures of the dolphins (green lines) and not to the pictures of the face (red lines). Bottom, when the subject was asked to close his eyes and imagine the same stimuli in alternate manner, the neuron also modulated its activity in a selective manner, with the same stimulus preferences observed during vision, i.e., the neuron fired during imagery of dolphins but only weakly during imagery of the face. Another example can be found in Kreiman G, Koch C, Fried I: Imagery neurons in the human brain. **Nature** 408:357–361, 2000 (26).

present, was comparable to that of the real object, both in selectivity and in firing rate. Of the neurons that fired selectively during both vision and imagery, the majority (88%) had identical selectivity. The firing rate during imagery was approximately 85% of that during actual vision. These experiments can hardly be performed in nonhuman primates and demonstrate the unique opportunity provided by neurosurgical patients to access conscious experience and correlate it with neuronal activity.

These are not the only examples of neurosurgeons studying the activity of individual neurons in the alert human brain, but they are probably the ones most relevant for visual consciousness. We urge the neurosurgeons to ask: could I study single neurons during my work, to help unravel some of the detailed neural activity of the human brain, consciousness included? We realize that, for ethical reasons, this can be performed in only a minority of patients. However, if compelling enough, such discoveries may change our view of the problem and its ultimate solution in a decisive manner. As in the collaboration between Fried and Koch, it helps to have a neurosurgeon and other neuroscientists join forces to optimize resources, methods, and techniques.

Returning to the question of consciousness, one can ask: what of the future? At the moment, we are all groping for answers. Our present ideas may have to change radically (7, 21). History has shown that new experimental results are often decisive. Obviously, we need better tools and techniques to monitor and interfere delicately, reversibly, transiently, and deliberately with populations of identified neurons. Multichannel recordings may afford examination of coalitions of neurons, rather than isolated single neurons. By applying electrical microstimulation more locally, we can alter perception. In addition, the recent developments in molecular biology may allow selective targeting of specific neuronal networks.

Consciousness remains one of the major unsolved scientific problems of this new century. The solution of it may well change our whole view of ourselves. We hope very much that neurosurgeons, with their priv-

ileged access to the human brain, will join in the search for the NCC in one way or another.

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COMMENTS

This article by Crick and Fried is an expansion of a talk at the Congress of Neurological Surgeons (CNS) given by Crick. In this article, the authors review some of the background concerning ideas related to visual consciousness and provide examples from human and nonhuman primates of neuronal responses associated with perception. Of interest is that the percept can be generated by real or imagined stimuli. The unstated but real assumption in this article is that perception is equivalent to consciousness or selfawareness. Our group has been particularly interested in this subject and has demonstrated by use of functional magnetic resonance imaging that real and imagined cutaneous stimulation activates similar areas of primary and higher-level somatosensory areas.

This article avoids the work performed on the basic anatomy and mechanisms of the on-off quality of consciousness that is related to reticular activating system control of thalamic gating mechanisms. The on-off mechanisms have obviously been of great interest to neurosurgeons, because destruction of their anatomic substrate is related to failure of treatment with resultant coma and even death. Here, the authors challenge neurosurgeons to become involved in one of the great human questions, the mechanisms of awareness or consciousness. Although the authors' work uses visual mechanisms as the platform for evaluating awareness, there are clearly other forms of sensory, imaginary, or motor processing that could be invoked as well.

This is a stimulating article that can help to generate thoughtful contributions by neurosurgeons to understanding brain function. The hope is that with some thought, more neurosurgeons will become involved in unraveling the mysteries of human brain function. We have a unique opportunity and obligation to contribute to these questions.

Charles J. Hodge, Jr. *Syracuse, New York*

More than a year before the 51st Annual Meeting of the CNS, planned to be held in San Diego in September 2001, I contacted Francis Crick to gauge his interest in being an Emeritus

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Special Lecturer. Beyond Crick's well-known contributions to the foundation of molecular genetics, the CNS Annual Meeting Committee was intrigued by his more recent work in the neuroscience of consciousness, with his book *The Astonishing Hypothesis*, his published collaborations with Koch on the neurobiology of the visual system and with Fried, a neurosurgeon at the University of California, Los Angeles, in intraoperative recordings from the human brain. Because he was a resident of San Diego County, we hoped that the CNS Meeting venue would least inconvenience Professor Crick.

His response to my invitation was prompt and flatteringly considerate. While cautioning me about inviting a man his age so far ahead of a planned meeting, he expressed his "intrigue" at the possibility of addressing a scientific meeting of America's brain surgeons. A few months later, a delegation of the CNS leadership visited Professor Crick at the Scripps Institute in La Jolla, and he delighted us by his insight and focus on the question of consciousness, a riddle at the interface of biology and philosophy since the dawn of human scholarship.

And we learned in subsequent months that Professor Crick had applied all the ingenuity of mind that discovered DNA structure and the genetic code to a problem at the core of neurosurgical science. We discovered a scholar committed to integrative and translational research at their most elegant and rigorous levels. Undaunted by the dizzying trauma of the tragic events only weeks earlier in September 2001, Professor Crick delivered a splendid lecture that mesmerized and inspired the neurosurgical audience. It is a mark of honor on our field for Professor Crick to now publish a scientific review based on that elegant lecture, synthesizing his rigorous investigations in this field of neuroscience. The organization of this work is truly extraordinary, and its relevance to neurosurgery incising, both reflecting an unmatched clarity of vision by one of the great conceptualizers of modern biology.

> **Issam A. Awad** *Evanston, Illinois*

At the request of the 2001 CNS Annual Meeting Committee, Francis Crick agreed to address our membership and share his passion and research on the topic of consciousness. He framed it within the context of neurosurgery and challenged neurosurgeons to investigate the detailed workings of the mind whenever possible. Clearly, our specialty has so much room to grow and so many mountains to climb. As they read this report, it is my hope that neurosurgeons will be energized in a manner similar to those who attended the San Diego meeting weeks after September 11, 2001.

Douglas Kondziolka

Pittsburgh, Pennsylvania

The authors review a fascinating topic in addressing human consciousness and make a compelling plea for the value of and necessity for contributions from neurosurgeons to this topic. In fact, neurosurgeons have much to contribute to studies of cognitive function in general. Cognitive neuroscience is a field that has come into maturity over the past decade, and one of the more intriguing aspects of this field is the study of consciousness. This is a very complex topic, and one facet of consciousness, visual perception, is reviewed by the authors.

Interestingly, the phenomenon described for object perception has parallels in visual perception of shape and color and is seen in studies of auditory and tactile cortex as well (1). This has been described as "top-down" modulation and seems to be a general property of sensory systems. The anterior cingulate, among other areas, seems to play a key role in directing attentional mechanisms and giving rise to modulations such as those described by the authors. Thus, "consciousness" is much broader than merely alteration of perception. Just as the observation that northern North American native languages may have more words for snow is probably an illusion of early, imperfect translations, so too the field of consciousness is clouded by confusions in terminology (4).

The authors also point out the complex visual processing that can happen without consciousness. This complexity is not limited to merely visual processing. A great deal of literature on the process of priming demonstrates that complex language processing, spatial processing, motor learning, and even pattern recognition can occur without conscious awareness (2). Thus, many levels of cognitive processing can occur without requiring consciousness.

The nature of consciousness has been debated extensively, and one particular theory is worth mention. As the authors point out, consciousness may be based on a series of nodes, no particular one (especially perceptual regions) being necessary or sufficient. One philosophy of consciousness holds that what we call consciousness is an emergent property of brain function and interaction between regions (3). In this model, finding nodes of consciousness in the brain makes no more sense then finding properties of "wetness" within molecules of water. Simplistically, this model might compel us to look at the interaction between regions as being equally important as the function of the regions themselves.

Neurosurgeons often enter the field because of intense desire to learn how the brain works. Modalities of functional imaging, stimulation mapping, and microelectrode recordings are tools the neurosurgeon may take advantage of. But even "mere" observation and more complex neuropsychological study of neurosurgical patients and their day-to-day deficits can be a source of invaluable contributions from our field to cognitive neuroscience. We should heed the authors' entreaties and act with haste.

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