Conscious awareness underlies important aspects of cognitive behavior. Understanding the neurobiological basis of conscious awareness has proved to be one of the most elusive problems for neuroscientists. Progress in recent years, however, allows for the development of theories of conscious awareness through integration of evidence from physiological, anatomical, and behavioral studies.

This review focuses on conscious awareness: the state in which external and internal stimuli are perceived and can be intentionally acted on. Much investigative effort has been directed at testing theoretical constructs dealing with general as well as specific characteristics of conscious awareness. We address 3 general questions: Where in the brain does consciousness occur? When does it occur in relation to external and/or internal stimuli? How are the underlying neural mechanisms involved in the emergence of consciousness? Experimentally obtained answers to these questions, although at times not definitive, narrow the list of possible hypotheses, provide new insights into conscious mechanisms, and guide future research.

WHERE

Considering the dispersed nature of various sensory centers in the brain and the resultant complexity of consciousness, it is likely that the interaction between different cerebral areas gives rise to consciousness. In their classic studies, Plum and Posner\(^1\) analyzed clinical records of comatose patients across a period of several decades. Coma was found to result from diffuse cerebral dysfunction, extensive damage to both cerebral hemispheres, diffuse demyelination of the hemispheric subcortex, destruction of the thalamus, or lesions of the upper brainstem. Coma may be induced by relatively focal subcortical damage to the diencephalon or midbrain. In contrast, unilateral lesions of the cerebral hemispheres, unless augmented by secondary lesions, are incapable of permanently affecting all consciousness but may cause transient loss of awareness. Focal cortical lesions may produce deficits in circumscribed aspects of conscious perception. In the right parietal cortex, for example, such lesions may impair perception of stimuli from the left hemispace.

Lesion studies such as those described previously are limited to identifying areas that when damaged or dysfunctional lead to lack of conscious awareness. However, localization of dysfunction does not imply localization of function. A given behavioral deficit may be the result of damage to a specific area mediating a behavior, but it can also be due to disruption in a distributed functional network. In the latter case, the spared but denervated network components may all play a role in the observed symptoms. Identification of a precise number of neural structures dealing exclusively with consciousness is thus unlikely to be fruitful. Much more likely, disrupted communication between subcortical and distributed cortical regions is what affects consciousness most profoundly; the anatomical position of any such disruption may reflect the type and severity of the impairment.

A recent study comparing ictal and interictal single-photon emission computed tomography has demonstrated that patients with partial seizures associated with loss of awareness have increased blood flow in the thalamus and upper midbrain during these seizures compared with patients with simple partial seizures who retain awareness\(^2\) (Figure 1). These results suggest that complex partial seizures impair conscious awareness by spread or dias-
chotic effects on these central structures. This observation is consistent with functional imaging reports that abnormal or disrupted activity in these regions impairs consciousness and that marked attentional effort is associated with increased metabolism in the thalamus and upper midbrain. The role of the centrencephalic core is likely not that of a simple on/off switch for consciousness but involves interactions with cortical structures, similar to the interplay observed in electrophysiological studies.

It has been postulated that consciousness is mediated by high-order association areas, whereas primary sensory regions are suggested to play only an indirect role. Final conclusions, however, are premature. Studies of conscious perception that report differences of evoked activity in the primary and association regions often use tasks that require high-level processing (eg, identifying an object or a face); activation of association areas in these studies is hardly surprising. Experiments using simple sensory stimuli suggest that the primary sensory areas may be involved in certain forms of consciousness. For example, Meador et al report differences in coherent gamma activity in the primary somatosensory cortex in response to perceived vs nonperceived stimuli. Although these findings do not provide a definitive answer, they show that the primary sensory regions may actively contribute to conscious perception. The extent of this contribution may (and should) be argued.

WHEN

When do humans become conscious of external stimuli? The seminal studies of Libet et al provide insights into the timing of conscious awareness. Using trains of electrical stimuli to the human cortex, Libet and colleagues demonstrated that perceptual threshold decreases as the train duration is extended up to about 300 to 500 milliseconds and that longer train durations do not further lower the perceptual threshold. They called this 300- to 500-millisecond window the utilization time and suggested that it was the time necessary for a stimulus to reach conscious awareness. They argued that once conscious awareness was achieved, it was referred back in time to the primary evoked potential (EP) that served as a timing element. The finding that peripheral stimulation of the hand is perceived before cortical stimulation has been attributed to the absence of primary EPs during cortical stimulation and the resultant failure of time referral. Consistent with this theory, Libet and colleagues described a patient with a parietal stroke who exhibited reduced contralateral tactile perception and lacked the primary somatosensory EP on the side of the stroke. When given simultaneous bilateral stimuli, the patient perceived stimuli to the hand ipsilateral to the stroke first. Stimuli were perceived as simultaneous if the ipsilateral hand was stimulated about 400 milliseconds after the contralateral hand.

Masking experiments have been instrumental in further defining the temporal gap between stimulus presentation and its conscious perception. Masking refers to the suppression of conscious perception of a target stimulus by another stimulus. The masking effect is enhanced in some patients with focal cerebral lesions (eg, neglect syndrome), but it can also be produced in healthy subjects. In the somatosensory modality, a mask given 50 to 100 milliseconds after the target stimulus to the opposite hand is actually more effective in blocking the target than if presented simultaneously with the target. These findings demonstrate not only that conscious perception is delayed but also that the mechanisms leading to conscious perception are particularly sensitive to dis-
neuronal firing, increase cerebral blood flow, and elicit gamma-oscillatory responses.\textsuperscript{3,10} Lesions in the medial reticular formation, nucleus reticularis of the thalamus, superior colliculus, intralaminar complex, and parietal lobes have all been associated with decreased attentional responses to external stimuli. Decreased attention is among the symptoms of many neurological disorders of consciousness, including blindsight, neglect, prosopagnosia, pure alexia, and optic aphasia.\textsuperscript{2} Lesions in many of these cases lead to only a partial loss of consciousness and are thus qualitatively different from lesions associated with comatose states. The existence of a gradient suggests that consciousness is a state regulated by specific neuronal processes rather than an epiphenomenon of coordinated brain activity.

Can regional activity differences accommodate the dissociation between conscious and unconscious states? The idea dates back to the concept of the Cartesian theater and is hardly novel. The phenomenon of blindsight, for example, is sometimes suggested to constitute residual visual processing by subcortical structures failing to communicate with higher visual areas. A functional magnetic resonance imaging experiment by Moutoussis and Zeki\textsuperscript{11} found no overall differences in distribution of regional cerebral blood flow (rCBF) in the conditions of conscious vs unconscious processing of brief (50-millisecond) visual stimuli. Depending on the presentation method, the perception of 2 simultaneous images occurred either unconsciously (when a single image was seen) or consciously (when both images were seen). In both conditions, the activity foci were the same; conscious perception, however, elicited larger percentage increases of rCBF than did unconscious perception. Although the results may imply consciousness as a function of intensity of neuronal response, intense neuronal activity also occurs in conditions that impair consciousness (eg, generalized seizures).

In another provocative study, Balkin et al\textsuperscript{12} reported rCBF changes during awakening, which appears to model transition from an unconscious to a conscious state. An initial rCBF increase in subcortical areas (brainstem, thalamus, or basal ganglia) subsequently declined as cortical areas (notably prefrontal cortices and regions of the temporal lobe) and the caudal orbital cortex of the basal forebrain became active. These results may suggest several neuronal activators of consciousness.

Could specific patterns of neural activity lead to conscious awareness? Crick and Koch\textsuperscript{3} proposed that coherent gamma activity may underlie consciousness. Gamma oscillations at this specific time interval. Results of the masking studies suggest that conscious awareness must occur more than 100 milliseconds after the stimulus; the train duration studies argue further that it occurs no later than 300 to 500 milliseconds after the stimulus. It is interesting to note that the time period between these 2 restraints is associated with gamma synchronization in response to perception of simple somatosensory stimuli.\textsuperscript{3}

A temporal framework for some salient features of conscious mechanisms is suggested in Figure 2. Contingent negative variation is a slow negative wave occurring after a cue and prior to a target stimulus. Contingent negative variation is associated with focusing of attention and may serve as a state-dependent predictor of conscious awareness. N20 is an early EP associated with conscious and unconscious processing of somatosensory stimuli; early EPs can also be seen during processing of stimuli in other sensory modalities. Although always preceding conscious awareness in normal conditions, conscious perception can occur in the absence of early EPs in abnormal states. Maximal masking of somatosensory stimuli occurs later, 50 to 100 milliseconds poststimulus, suggesting a critical time period for conscious awareness in the somatosensory modality. A unique electrical signal, gamma coherence, can be seen in the cortex 170 to 270 milliseconds after somatosensory stimuli, which are consciously perceived. Conclusive evidence for the role of gamma coherence in the brain has yet to be presented. Reduction of the perceptual threshold by trains of stimuli up to 300 to 500 milliseconds has been suggested to reflect the final stages of neuronal processing leading to conscious awareness.

The “when” of consciousness is subject to much debate and reinterpretation, all of exceptional intellectual interest.\textsuperscript{9} Regardless of credibility and persuasiveness of any particular theory, however, the experimental data demonstrate that (1) some stimuli elicit neuronal response yet are not consciously perceived; (2) there is a time delay between stimulus-evoked cortical activity and conscious awareness of the stimulus; and (3) a mechanism must exist to link the delayed conscious processing to the initial subconscious neural response.

**HOW**

The third problem is vital and perhaps the most complex. Attention has been suggested as a mediator of conscious states. Focusing of attention has been shown to increase
synchronization has been observed in several sensory modalities, yet its correlation with awareness of the sensory stimuli is still uncertain. However, because oscillatory gamma discharges are increased with directed attention, gamma synchronization may serve as a neuronal amplifier of the sensory stimuli. Of particular interest is the fact that attention-mediated gamma increases are accompanied by simultaneous decreases of low-frequency firing. A special value of these observations is that they make way for the study of within-network interactions thought to underlie all complex processing.

Gamma coherence has also been proposed as an essential component of temporal synchronization or binding of distributed neural processes. The need for spatial and temporal synchronization arises because the receptive fields of individual neurons cannot accommodate the entirety of a sensory landscape and because the distinct features of different sensory stimuli are processed with different latencies. For example, perception of color occurs before perception of motion; likewise, orientation, depth, and other stimulus attributes are perceived at different times. Temporal synchronization may be necessary to perceive sensory stimuli as singular events rather than as a disjointed sequence of their various characteristics.

Llinas and Ribary hypothesized that the mechanism underlying consciousness involves a pair of coupled oscillators, both of which connect the thalamus and cortex. One oscillator connects the intralaminar nuclei of the thalamus across a broad distribution of the cortex. The second oscillator connects modality-specific nuclei in the thalamus with modality-specific cortical areas. Forty-hertz waves traveling across the cortex during wakefulness and dreaming were reported in the magnetoencephalography studies by Llinas and Ribary. Recordings using intracranial electrodes, however, have thus far failed to reproduce these magnetoencephalographic findings, and scalp electroencephalographic findings have been inconsistent, possibly owing to artifacts such as muscle activity.

Although gamma coherence is an attractive candidate for a neuronal mechanism underlying consciousness, its ubiquity in the nervous system invalidates somewhat its unique specificity for all of conscious processing. Because of the uncertainty of the extent to which gamma coherence reflects integrative processes underlying consciousness, alternative hypotheses must be considered. Firing rate modulations may tag a signal for conscious vs unconscious processing, or re-entrant loops may organize sensory input into unified percepts. The organizing power of such mechanisms appears more limited and presents a less elegant explanation of feature integration. However, feature integration itself may not require conscious processing; implicit learning exemplifies one of the better known cases of feature integration without consciousness.

CONCLUSIONS

Although many cognitive and behavioral processes occur without awareness, consciousness plays a critical role in cognitive mechanisms and forms the basis of our experience. An improved understanding of conscious mechanisms will provide insights into a variety of neurological disorders and new therapeutic approaches. Consciousness appears to depend on distributed neuronal components acting in a functionally integrated way. The anatomical location of these components may vary with time and depend on the stimuli and the task. Interactions of the neocortex with the thalamus and possibly the upper midbrain may be instrumental in these mechanisms. Attention plays a regulatory role in modulating the intensity of neural activation and influencing conscious mechanisms. Aspects of neuronal code, such as high frequency coherence, other types of oscillatory activity, firing rate, or iterative feedback-forward loops, might underlie functional integration, although the specificity of such mechanisms to consciousness cannot be determined with present data. The human brain’s capacity for functional integration may be a trait evolutionarily selected for and thus effectively the purpose of consciousness. Whether or not functional integration is the sole purpose of consciousness and just how purposeful this human characteristic really is remain unanswered.

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REFERENCES


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