Review

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Anesthesia and neuroimaging: investigating the neural correlates of unconsciousness

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In the past 15 years, rapid technological development in the field of neuroimaging has led to a resurgence of interest in the study of consciousness. However, the neural bases of consciousness and the boundaries of unconscious processing remain poorly understood. Anesthesia combined with functional neuroimaging presents a unique approach for studying neural responses as a function of consciousness. In this review we summarize findings from functional neuroimaging studies that have used anesthetic drugs to study cognition at different levels of conscious awareness. We relate the results to those of psychophysical studies of cognition and explore their potential usefulness in interpreting clinical findings from studies of non-responsive patients.

Consciousness and anesthesia

A first, and perhaps pragmatic, step to understanding consciousness is to define what it is not. Studies of unconscious processing play a pivotal role in establishing the necessary and sufficient conditions for consciousness. If a cognitive computation or neural marker is assumed to be specific to conscious processing, its absence must also be established under non-conscious conditions [1].

Studies of the neural correlates of consciousness in the healthy adult brain often manipulate the contents of sensory awareness, while the level of wakefulness is held constant [2]. From these experiments, which employ stimulus-manipulation paradigms such as masking, attentional blink, or binocular rivalry, there is accumulating evidence that many cognitive processes can occur in the absence of awareness, arguing for a dissociation of consciousness and many high-level cognitive functions ([1–5] for reviews). Considerably fewer studies, however, have attempted to manipulate the global level of consciousness directly to study cognitive processing in various states of wakefulness. As an experimental paradigm, anesthesia allows consciousness to be reliably and reproducibly abolished in healthy individuals. Coupled with neuroimaging techniques, findings from graded sedation using anesthetic agents both complement and extend results from traditional psychophysical studies.

In the following we summarize findings from functional neuroimaging studies that have used anesthetic agents to study changes in brain activation at reduced levels of awareness, both with sensory stimulation and at rest. We then relate these results to those obtained with brain imaging (i) using traditional psychophysical manipulations of awareness, and (ii) in behaviorally non-responsive patients. In the latter case, we discuss how studies that have used anesthetic drugs to modulate the level of awareness might inform diagnoses in disorders of consciousness. We focus on cognitive systems that have been studied thoroughly using both anesthetic agents and neuroimaging, separately or in combination, to identify areas of convergence between these fields of research.

Cortical reactivity during anesthetic sedation

With increasing understanding of the mechanisms by which anesthetics induce loss of consciousness (Box 1), a number of studies have probed the effects of anesthetic sedation on brain activation during cognitive processing of sensory stimuli. One early fMRI study found that mild and moderate sedation with isoflurane abolished evoked blood oxygen level-dependent (BOLD) responses to innocuous tactile stimulation in primary and secondary somatosensory cortices [6]. Similarly, using positron emission tomography (PET), vibrotactile stimulation failed to elicit cerebral blood flow (CBF) changes in sensory cortex at a propofol concentration sufficient to induce unconsciousness [7]. Noxious stimuli, however, did lead to increased CBF in somatosensory cortex at this propofol concentration [8], suggesting that cortical activity following anesthetic-induced loss of consciousness varies as a function of the nature or intensity of the tactile stimulus used [9].

More recent research has focused on the limits of auditory processing during anesthetic-induced sedation. Following light anesthesia with sevoflurane, activation to auditory word stimuli relative to silence was preserved in bilateral superior temporal gyri, right thalamus, bilateral parietal, left frontal, and right occipital cortices [10]. Parallel results have been found with both propofol and the short-acting barbiturate thiopental, suggesting that basic auditory processing remains intact during reduced or absent conscious awareness [11,12]. Increasing

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Box 1. Mechanisms of anesthesia

General anesthesia is a reversible drug-induced state involving amnesia, analgesia, and loss of consciousness [77]. Within the clinical context, loss of consciousness is generally defined as the loss of ability to respond to loud noise or rousing shakes [77]. Within a research setting, loss of consciousness most commonly refers to a loss of responsiveness to verbal command, which occurs at a much lower dose than general anesthesia. However, the effects of these two approaches are simply on a continuum; progressively increasing sedation through the use of anesthetic agents results eventually in clinical anesthesia. Although effects at the cellular level may be heterogeneous, all anesthetic agents are similar in decreasing neuronal firing, either through the enhancement of inhibitory currents or the reduction of excitatory currents within the brain [74,78]. γ-Amino-butyric acid type A ($GABA_A$) and *N*-methyl-D-aspartate (NMDA) receptors in the cortex, thalamus, brainstem, and striatum appear to be the most important targets of anesthesia [77, 79–81]. Given that nearly all anesthetics decrease global cerebral metabolism in a dose-dependent manner [7,77,80,82–86], early studies posited that a general (e.g., non-specific) reduction in metabolism was the common mechanism for producing anesthesia-induced loss of consciousness [87,88]. Accumulating research, however, has shown that anesthetic agents differ in their specific targets, against a background of general cellular depression ([89] for review). For example, the intravenous anesthetic propofol preferentially suppresses activity within frontoparietal cortex [12,85], as does the inhalational anesthetic sevoflurane [90,91]. The thalamus is a second common site of action for most anesthetics [92], and early reports suggested that the thalamus was the primary region mediating loss of consciousness during anesthesia. However, using EEG data from a group of patients with Parkinson's disease, one study [93] provided convincing evidence that the decreased thalamic activity during induction of anesthesia follows both cortical depression and loss of consciousness. Moreover, whereas some studies have reported decreased thalamocortical connectivity with anesthesia-induced loss of consciousness [17,36,94], others have not [95]. Although this inconsistency might relate to the anatomical complexity of the thalamus [96], accumulating evidence suggests that unconsciousness during anesthesia arises as a consequence of the disruption of cortico-cortical connections [97]. Indeed, it is now widely held that the cortex is the primary site of anesthetic action, whereas subcortical structures are suppressed secondary to decreased excitatory cortico-thalamic feedback ([33,89] for review).

the anesthetic dose of sevoflurane abolished all reactivity to these stimuli [10].

By contrast, light anesthesia impairs more complex auditory processing [13–17]. For example, in one study the characteristic bilateral temporal-lobe responses to auditorily presented sentences were preserved during propofol-induced sedation (Figure 1) [14], whereas 'comprehension-related' activity in inferior frontal and posterior temporal regions to ambiguous versus non-ambiguous sentences was abolished. The authors interpreted their results as indicating that more basic aspects of speech processing (perception) were left intact by sedation, while higher-level processes, such as semantic decoding and mnemonic processing, were abolished. Studies using visual stimulation have also reported that activation in higher-order association cortices is preferentially affected by anesthetic-induced sedation [18–20]. For example, in one study, isoflurane-induced decreases in activation during performance of a visual search task were observed in bilateral parietal cortex and right insula [20]. Subcortical structures and primary visual and motor cortices, however, were not affected (Table 1).

Broadly speaking, studies using behavioral measures and electroencephalography (EEG) have reported similar findings. For example, patients are significantly more likely to use a word on a post-operative word-stem completion task if it has been presented auditorily during surgery involving anesthesia. Although these priming effects decrease with

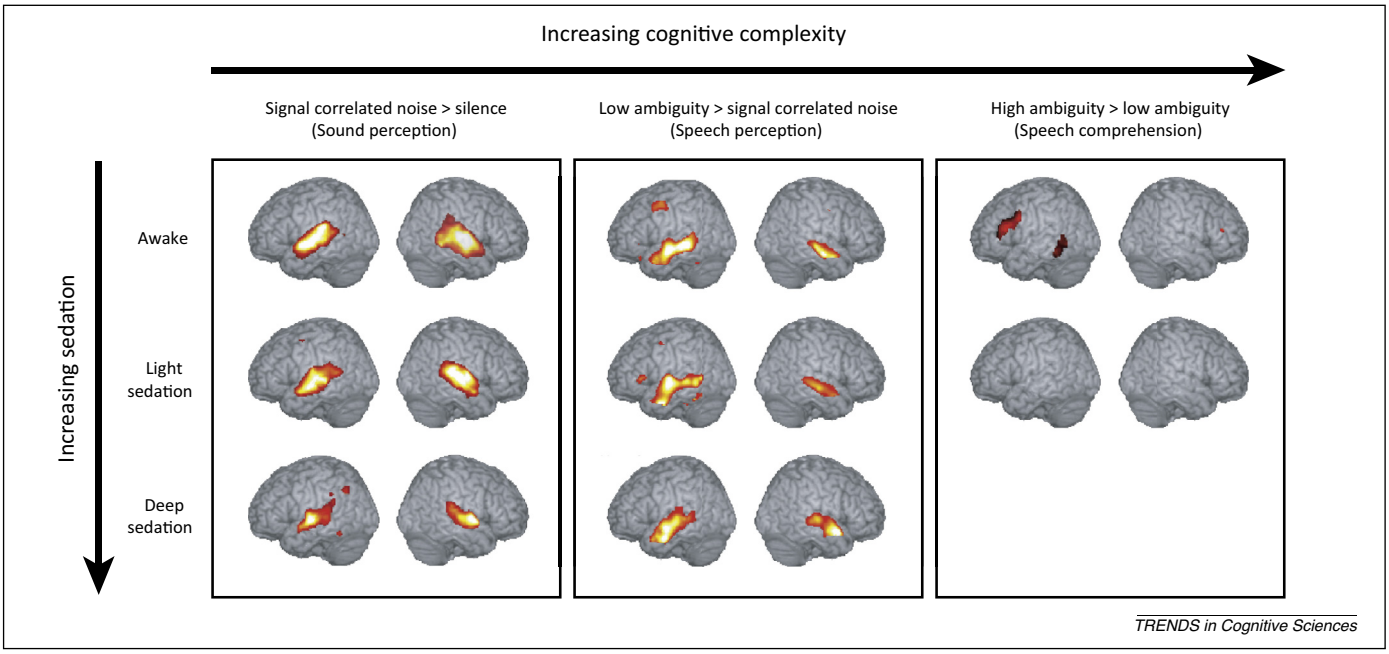

Figure 1. fMRI response to auditory stimulation during sedation with Propofol. fMRI response at three levels of sedation to increasingly complex stimulation, adapted from Davis *et al.* {[14]; © (2007) National Academy of Sciences, USA}. Evidence for speech comprehension, assessed by contrasting high- and low-ambiguity speech, is not evident during either light or deep sedation. By contrast, the robust temporal-lobe response to speech versus signal correlated noise at all levels of sedation suggests that preserved sound and speech perception are preserved at reduced levels of awareness.