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
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 increasing sedation,
increasing depth of sedation, they provide evidence that perceptual priming can occur during anesthesia-induced unconsciousness [21–25] (but see [26,27] for divergent results). By contrast, at similar depths of sedation, there is little or no evidence for conceptual priming [22]. Similarly, recent studies using EEG and anesthetic-induced sedation have reported that basic processing of auditory stimuli remains intact (e.g., [28,29]). For example, mismatch negativity and P3a, two event-related potentials, were elicited by an oddball paradigm during sedation, suggesting that some auditory sensory memory and attention-related mechanisms were preserved (but see [30] for divergent results). By contrast, sedation completely abolished an early event-related potential known as right-anterior negativity that is thought to reflect deeper syntactic processing [28]. A recent study of sensory stimulation also found that early responses arising from primary somatosensory cortex persisted during sedation, whereas mid and late responses from temporal and parietal regions disappeared [31].

Overall, these studies are consistent with the notion that sensory information processing in cortex is sequentially impaired from more to less complex, in a dose-dependent manner, by anesthetic-induced sedation. Brain activation declines first in higher-order, or association, cortices before responses in primary cortical areas are attenuated and, at increasing doses, abolished. Crucially, reactivity in sensory cortices appears to persist beyond drug-induced loss of conscious awareness. These studies support a growing body of evidence that simple sensory processes, including the perception of speech stimuli, persist in the absence of, or at reduced levels of, awareness. By contrast, they provide little evidence for complex sensory processing in the absence of awareness because cortical reactivity in association cortices is either absent or significantly attenuated during sedation (Table 1).

**Functional connectivity during anesthesia**

Inherent cerebral connectivity can now be well-characterized by resting-state studies, which are easily conducted in states of unconsciousness. There is now considerable evidence that anesthetics modify functional connectivity within and between resting-state cortical networks ([32–34] for review). Under anesthesia, decreased cortico-cortical connectivity has been reported in higher-order brain networks, including the salience network [35], the default-mode network (DMN) [36–38] (but see [39,40] for divergent results), and the executive control network [36]. In sharp contrast, functional connectivity in low-level sensory cortices is preserved, consistent with the stimulation studies reviewed above that have reported preserved sensory-driven activation in sensory cortex [17,36–39]. In one of the only stimulus-driven fMRI studies of functional connectivity, propofol-induced sedation disrupted functional connectivity between primary auditory cortex and inferior frontal cortex during auditory word stimulation [17]. Conversely, recovery of consciousness following anesthesia is accompanied by the restoration of functional coupling between lower-order areas, including subcortical and limbic regions, and frontal and inferior parietal cortices [41].

One recent study used a novel information-theoretic approach to explore changes in functional connectivity during propofol-induced loss of consciousness [42]. To quantify loss of information integration, six brain networks were defined during resting wakefulness. Following deep sedation, integration was systematically decreased within and between most of these networks; areas became
temporally independent, and exchange of information was reduced, with the loss of integration being most pronounced between frontal or occipital and parietal regions.

The results of EEG studies also suggest that anesthesia disrupts connectivity between higher- and lower-order information-processing areas (but see [43]). For example, one recent study showed that inducing loss of consciousness with propofol led to decreased cortico-cortical connectivity, especially in backward connections between the frontal and parietal cortices [44]. These results have been replicated in other EEG studies that have also shown that connectivity is restored with return of consciousness [38,45,46]. By contrast, feed-forward connectivity has been shown to persist, even at the deepest levels of sedation [45,46].

Similar and contrasting results from anesthesia and psychophysical studies

Despite an increase in the number of studies using pharmacological manipulations to study consciousness, unconscious processing in normal healthy humans has been examined more frequently by using psychophysical techniques. In the visual domain, these include masking, crowding, inattention, or binocular rivalry, all of which allow stimuli to be presented while remaining invisible to participants [1]. When combined with brain imaging, such techniques allow inferences to be made about the boundaries of processing in the absence of conscious awareness. The results of these studies suggest that many cortical areas, including parietal and frontal regions, can be activated by a subjectively unseen stimulus [1–5]. For example, unseen visual words induce activation in both early visual areas and higher-level areas of temporal cortex, whereas unconscious number- and emotion-processing activate parietal cortex and the amygdala, respectively [4]. Using similar techniques, processing without conscious awareness has also been demonstrated for auditory, somatosensory, and olfactory information [3].

Unlike studies of anesthetic-induced sedation, the results of these psychophysical manipulations therefore suggest that unconscious processing is not limited to early sensory cortex. Indeed, there is accumulating evidence that conscious awareness may not be necessary for the full or partial operation of some high-level cognitive functions, including self-monitoring, inhibitory control, error detection, task-switching, and confidence assignment [1–5]. A crucial distinction here is between the level of consciousness, which is typically manipulated during studies of anesthetic sedation, and the contents of consciousness, which are typically manipulated in psychophysical studies. Thus, unlike psychophysical investigations, studies using anesthetic agents invariably lead to concurrent decreases in arousal that might target cognitive functions, including memory, independently of their effects on conscious awareness [47,48]. For example, whereas evidence for perceptual priming during anesthetic sedation is inconsistent, it is a robust finding in the psychophysical literature [47]. Studies using midazolam [49] and propofol [50] have found that doses considerably lower than those causing loss of awareness affect memory and are associated with concurrent decreases in regional cerebral blood flow (rCBF) in areas involved in verbal encoding and working memory, respectively.

Despite the more limited picture of unconscious processing painted by studies of sedation, there are some important points of convergence between these two lines of research. First, although most studies have only documented activation within primary sensory cortex at deeper levels of anesthetic sedation, activation within higher-order association cortex, including frontal and parietal cortices, has been observed in at least one study of light anesthesia [13]. In contrast to an awake condition, however, activation was much more limited and circumscribed. These and other findings caution against the conclusion that frontal or parietal activation constitutes unequivocal evidence of consciousness [1–5].

Clinical relevance of anesthesia research to disorders of consciousness

Detecting vestiges of conscious awareness in non-responsive patients represents a significant challenge to modern medicine [51]. In particular, the clinical assessment of vegetative state (VS) patients is challenging because currently we lack definitive and objective diagnostic measures for consciousness. Diagnosis depends upon subjective interpretation of behavior that can be limited by perceptual, motor, or cognitive compromise [52]. Patients are clinically diagnosed as being in a VS after repeated examinations have yielded no evidence of sustained, reproducible, purposeful, or voluntary behavioral response to visual, auditory, tactile, or noxious stimuli despite preserved sleep–wake cycles [53].

An increasing number of studies have shown that misdiagnosis in this patient group is common, with up to 43% of patients being at least minimally aware [54–57]. Consequences for misdiagnosis can include less-aggressive pain management, inaccurate prognosis, and inappropriate end-of-life decision-making; therefore, discovering a means for more accurate detection of consciousness is of the utmost importance [58]. In several recent studies, so-called active paradigms, which require the willful modulation of neural activity through mental imagery [51] or selective attention [59], have been used to reveal conscious awareness in patients who were previously assumed to be entirely vegetative. Cohort studies employing such paradigms combined with fMRI [52] or EEG [60] have found that a significant minority of patients (16–19%) diagnosed as VS are able to modulate brain activity according to verbal commands, thus providing evidence of conscious awareness. Where available, these tests complement standard bedside assessments that rely on overt behavior [56,61–63]. However, factors such as fluctuations of vigilance, cognitive impairment, or lack of cooperation that can occur after brain injury pose problems both for traditional clinical measures for assessing consciousness [64] and for these active neuroimaging paradigms. So-called passive paradigms (see [65] for a different approach), which involve presenting stimuli (e.g., auditory, visual) to non-responsive patients, and observing the brain response using neuroimaging ([66] for review), circumvent some of these issues, although inferring the presence of consciousness from these brain responses can be problematic. In this context, studies of the effects of anesthetic sedation in
Unlike general anesthesia, VS is characterized by a relative sparing of brainstem functions, leading to preservation of wakefulness (although at preclinical depths of sedation with anesthetics, as is the case in many of the studies reviewed here, brainstem functions may also be preserved [77,99]). By contrast, and in parallel to the effects of anesthesia, VS is often associated with damage to, or altered metabolism in, particular midline structures, including the premotor cortex, the medial prefrontal cortex, the anterior cingulate cortex, and the thalamus [100]. Furthermore, as was the case in many of the anesthesia studies reviewed here, global brain metabolism in VS is diminished by as much as 50–60%, although its relevance to the loss of conscious awareness remains poorly understood [101]. Overall, brain dysfunction in VS appears to be most prevalent within the frontoparietal network [102–104], which is again similar to the effects of some common anesthetic agents, including propofol.

Broadly, the results of fMRI studies of both VS patients and sedated healthy volunteers are consistent with sensory processing in the absence of higher-order, affective components. For example, noxious stimulation in VS yields activation in the brainstem, thalamus, and primary somatosensory cortex, but not in higher-order areas [66,101,105,106]. Basic auditory processing has also been reported in VS patients, including speech-specific activation in superior temporal regions [107–110]. In some cases, identical paradigms have revealed similar patterns of fMRI activity in heavily sedated healthy participants [14]. Finally, CBF changes in response to simple visual stimulation, including pattern flashes, have been reported in the primary visual cortex of VS patients [66].

Studies of functional connectivity in VS patients also mirror findings from the anesthesia literature, and have led to its characterization as a global disconnection syndrome [111,112]; thus, although spontaneous activity persists in the DMN, resting-state connectivity is significantly reduced relative to healthy participants [111]. Numerous studies have documented impaired thalamocortical connectivity [109,112]. Disconnections between distant cortical regions have also been identified, especially between laterofrontal and posteroomedial cortices [113,114]. In an EEG study measuring electrical activity during auditory stimulation in VS, top-down processing from frontal to temporal cortex was impaired [115]. Although backward connections between these regions were absent, feed-forward connectivity was preserved, again mirroring findings from the anesthesia literature. Finally, as with recovery from anesthesia, recovery from VS is associated with functional restoration of both frontoparietal networks and cortico-thalamo-cortical connectivity [113,114].

Other theorists have proposed that conscious access involves a late ‘all-or-none’ ignition of higher-order cortices once the accumulation of information exceeds threshold. In other words, whereas the strength of the perception of a stimulus predisposes it to conscious perception, it is only a precursor to consciousness. Therefore, feed-forward connectivity would be expected to persist despite a lack of awareness resulting in preserved primary cortical activation, but also possibly leading to the circumscribed and evanescent activation that is occasionally observed in frontoparietal regions [1]. In keeping with this view, studies of anesthetic sedation have shown dramatic and sudden increases of activation, especially within parietal, prefrontal, and cingulate areas, when consciousness is regained, as though higher-order cortices are ignited once a threshold is reached (e.g., [41]). By contrast, the point of loss of consciousness during anesthetic sedation is associated with a rapid fragmentation both within and across neuronal networks, especially between lower-order and higher-order cortical regions (e.g., [42]). Finally, EEG studies have documented a conspicuous lack of feedback connectivity during anesthesia-induced loss of consciousness, especially between frontal and parietal cortices, whereas feed-forward connectivity remains intact (e.g., [46]). Prime candidates for mediating this ‘all-or-none’ global ignition are the recurrent N-methyl-D-aspartate (NMDA) connections which allow information to accumulate non-linearly [1,71,72]. Interestingly, the dissociative anesthetics, such as ketamine, induce loss of awareness by antagonizing the NMDA receptor without entailing general sedation, as commonly encountered with more traditional anesthetics (Box 1).

Whereas theories involving global ignition attempt to demarcate the point at which conscious perception of a stimulus might arise, the integrated information theory (IIT) of consciousness [73,74] goes a step further by attempting to define the nature of consciousness itself.
According to this theory, global synchrony (temporarily coincident neural events) and feedback connectivity create an integrated representation of stimulus features, which is consciousness. An empirical prediction from this theory is that changes in the state of consciousness should be accompanied by changes in the ability of a system to integrate information. Some evidence exists to support this notion [75].

Although the details are different, the theory of cognitive unbinding [76] also states that consciousness depends on the synthesis of neural information. However, it does not go so far as to say that consciousness is integration. Rather, this account proposes that information from separate sensory modalities is bound through synchrony, or convergence (coordinated inputs from primary sensory areas to higher-order networks).

Findings from the anesthesia literature reviewed above broadly support both ignition and integration theories of consciousness by demonstrating that loss of consciousness is associated both with a sudden change in the state and connectivity of distributed networks and with a lack of information integration secondary to this change. Moreover, these theories allow for the fact that a significant amount of information processing can occur unconsciously. Thus, even in the absence of conscious awareness, an initial feed-forward sweep allows the identification of the global characteristics of stimuli, even recruiting areas previously thought to be uniquely activated during conscious perception [3].

**Concluding remarks**

The studies that we have highlighted here probe the brain mechanisms of unconscious versus conscious processing. This body of work is important, not only for understanding how anesthetic-induced sedation impacts upon cognition, but also for understanding the patterns of preserved brain activity that are often seen in patients with so-called disorders of consciousness. Studies of healthy participants who are rendered heavily sedated or unconscious in a temporary and controlled manner suggest that activation of specific primary cortical regions and even limited reactivity in association cortices can occur in the absence of consciousness. In disorders of consciousness, therefore, neuroimaging evidence for simple sensory processing does not provide any support for preserved conscious awareness. By contrast, preserved functional connectivity between distant cortical regions, particularly between frontoparietal cortices, and/or activity in association cortices in response to complex cognitive processing, does appear to require conscious awareness. Therefore, when such patterns are observed in non-responsive patients after brain injury, further attempts to detect covert signs of preserved conscious awareness might be warranted.

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