Review

CellPress

Anesthesia and neuroimaging: investigating the neural correlates of unconsciousness

Alex A. MacDonald[1], Lorina Naci[1], Penny A. MacDonald[2], and Adrian M. Owen[2]

[1] Undergraduate Medical Program, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[2] The Brain and Mind Institute, The Natural Sciences Centre, University of Western Ontario, London, Ontario, Canada

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

Corresponding author: Owen, A.M. (adrian.owen@uwo.ca).
Keywords: anesthesia; unconscious processing; awareness; disorders of consciousness.

1364-6613/
 http://dx.doi.org/10.1016/j.tics.2014.12.005

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

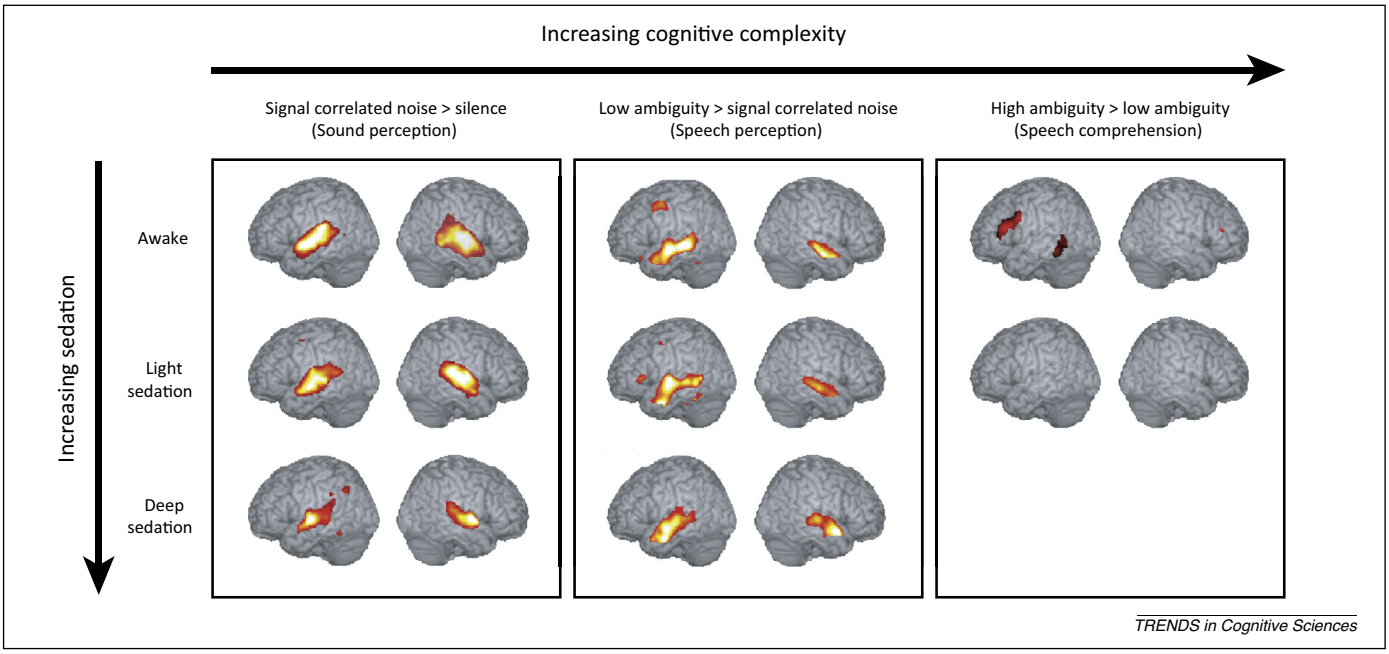

Figure 1. fMRI response to auditory stimulation during sedation with Propofol. fMRI response at three levels of sedation to increasingly complex stimulation, adapted from Davis *et al.* {[14]; © (2007) National Academy of Sciences, USA}. Evidence for speech comprehension, assessed by contrasting high- 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.

Table 1. Studies of cortical reactivity during anesthetic sedation

Modality	First author and year	Anesthetic	Contrast	Changes in cerebral activation
Tactile				
	Antognini *et al.* 1997 [6]	Isoflurane	Tactile stimulation vs rest	Loss of cortical activation
	Bonhomme *et al.* 2001 [7]	Propofol	Vibro-tactile stimulation vs rest	Loss of cortical activation
	Hofbauer *et al.* 2004 [8]	Propofol	Painful heat vs warmth	Decrease of intensity and extent of stimulation
	Mhuircheartaigh *et al.* 2010 [95]	Propofol	Pain stimuli vs rest	Decrease of intensity and extent of stimulation
Auditory				
	Heinke *et al.* 2004 [13]	Propofol	Sentences vs pseudo-word sentences	Decrease of intensity and extent of stimulation
	Kerssens *et al.* 2005 [10]	Sevoflurane	Word stimuli vs silence	Decrease of intensity and extent of stimulation
	Veselis *et al.* 2005 [12]	Propofol, Thiopental	Word stimuli vs silence	Decrease of intensity and extent of stimulation
	Dueck *et al.* 2005 [11]	Propofol	Musical stimuli vs silence	Decrease of intensity and extent of stimulation
	Plourde *et al.* 2006 [16]	Propofol	Words vs scrambled words	Loss of cortical activation
	Davis *et al.* 2007 [14]	Propofol	Low-ambiguity sentences vs high-ambiguity sentences	Loss of cortical activation
	Liu *et al.* 2012 [17]	Propofol	Words vs silence	Decrease of intensity and extent of stimulation
	Adapa *et al.* 2014 [15]	Propofol	Low-ambiguity sentences vs high-ambiguity sentences	Loss of cortical activation
Visual[a]				
	Martin *et al.* 2000 [18]	Pentobarbital	Visual stimuli vs rest	Decrease of intensity and extent of stimulation
	Heinke *et al.* 2001 [20]	Isoflurane	Moving stimuli vs stationary stimuli	Decrease of intensity and extent of stimulation
	Ramani *et al.* 2007 [19]	Sevoflurane	Pattern stimuli vs rest	Decrease of intensity and extent of stimulation

[a]Visual studies were conducted at sub-anesthetic doses of pentobarbital, isoflurane, or sevoflurane. Adapted from Boveroux [98].

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, persists 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

Box 2. Vegetative state (VS) and anesthesia: similarities and contrasts

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, rCBF 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 posteromedial 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].

healthy human participants have been particularly helpful. Based on the evidence reviewed here, they suggest that intact fMRI responses to simple sensory processes, including the perception of speech, in patients who have been diagnosed as VS cannot be taken as evidence of preserved awareness, particularly where passive cognitive tasks are used ([17], also Box 2). By contrast, complex sensory processing (e.g., in active cognitive tasks), reflected by cortical reactivity in association cortices, may reflect undetected consciousness in non-responsive patients [17].

Relevance of anesthesia to models of consciousness

There are multiple frameworks of consciousness within which the literature reviewed here can be interpreted. Importantly, these theoretical accounts are not entirely mutually exclusive. We briefly review some models of consciousness and the empirical evidence from studies that support them.

Information processing is often thought of as comprising a number of distinct but interrelated stages. First, an early feed-forward sweep of information processing involves propagation of sensory information from lower- to higher-level sensory areas, accompanied by an increasingly complex analysis of global stimulus features. Subsequently, stimulus processing is refined through the recruitment of connections within sensory-specific regions and through feed-back connections to early sensory areas from higher-order cortical regions [1,3,4,67].

Within this general framework, multiple attempts have been made to identify the point at which consciousness emerges. For example, based on early observations that conscious awareness of a stimulus varies according to the strength of initial sensory activation (e.g., [68]), one model has proposed that conscious perception arises quickly following stimulus onset and is conveyed by the strength of the evoked sensory activity [69]. More recent studies cast doubt on this model. For example, there is accumulating evidence from studies of healthy volunteers that similar activity in sensory areas can lead to differences in conscious experience (e.g., [70]). Moreover, preserved activation in primary cortex can occur in response to sensory stimulation in the absence of awareness (e.g., [10]). EEG studies have also documented preserved early response components to stimulation in primary cortex following anesthesia (e.g., [31]).

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 (temporally 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

Acknowledgments

This work was supported by the Canada Excellence Research Chairs (CERC) Program (A.M.O).

References

1 Dehaene, S. *et al.* (2014) Toward a computational theory of conscious processing. *Curr. Opin. Neurobiol.* 25, 76–84
2 Boly, M. *et al.* (2013) Consciousness in humans and non-human animals: recent advances and future directions. *Front. Psychol.* 4, 625
3 van Gaal, S. and Lamme, V.A. (2012) Unconscious high-level information processing: implication for neurobiological theories of consciousness. *Neuroscientist* 18, 287–301
4 Sergent, C. and Naccache, L. (2012) Imaging neural signatures of consciousness: 'what', 'when', 'where' and 'how' does it work? *Arch. Ital. Biol.* 150, 91–106
5 van Gaal, S. *et al.* (2012) The role of consciousness in cognitive control and decision making. *Front. Hum. Neurosci.* 6, 121
6 Antognini, J.F. *et al.* (1997) Isoflurane anesthesia blunts cerebral responses to noxious and innocuous stimuli: a fMRI study. *Life Sci.* 61, 349–354 PL
7 Bonhomme, V. *et al.* (2001) Propofol anesthesia and cerebral blood flow changes elicited by vibrotactile stimulation: a positron emission tomography study. *J. Neurophysiol.* 85, 1299–2308
8 Hofbauer, R.K. *et al.* (2004) Dose-dependent effects of propofol on the central processing of thermal pain. *Anesthesiology* 100, 386–394
9 Heinke, W. and Koelsch, S. (2005) The effects of anesthetics on brain activity and cognitive function. *Curr. Opin. Anaesthesiol.* 18, 625–631
10 Kerssens, C. *et al.* (2005) Attenuated brain response to auditory word stimulation with sevoflurane: a functional magnetic resonance imaging study in humans. *Anesthesiology* 103, 11–19
11 Dueck, M.H. *et al.* (2005) Propofol attenuates responses of the auditory cortex to acoustic stimulation in a dose-dependent manner: a FMRI study. *Acta Anaesthesiol. Scand.* 49, 784–791
12 Veselis, R.A. *et al.* (2004) Thiopental and propofol affect different regions of the brain at similar pharmacologic effects. *Anesth. Analg.* 99, 399–408
13 Heinke, W. *et al.* (2004) Sequential effects of propofol on functional brain activation induced by auditory language processing: an event-related functional magnetic resonance imaging study. *Br. J. Anaesth.* 92, 641–650
14 Davis, M.H. *et al.* (2007) Dissociating speech perception and comprehension at reduced levels of awareness. *Proc. Natl. Acad. Sci. U.S.A.* 104, 16032–16037
15 Adapa, R.M. *et al.* (2014) Neural correlates of successful semantic processing during propofol sedation. *Hum. Brain Mapp.* 35, 2935–2949
16 Plourde, G. *et al.* (2006) Cortical processing of complex auditory stimuli during alterations of consciousness with the general anesthetic propofol. *Anesthesiology* 104, 448–457
17 Liu, X. *et al.* (2012) Propofol disrupts functional interactions between sensory and high-order processing of auditory verbal memory. *Hum. Brain Mapp.* 33, 2487–2498
18 Martin, E. *et al.* (2000) Effect of pentobarbital on visual processing in man. *Hum. Brain Mapp.* 10, 132–139
19 Ramani, R. *et al.* (2007) Sevoflurane 0.25 MAC preferentially affects higher order association areas: a functional magnetic resonance imaging study in volunteers. *Anesth. Analg.* 105, 648–655
20 Heinke, W. and Schwarzbauer, C. (2001) Subanesthetic isoflurane affects task-induced brain activation in a highly specific manner: a functional magnetic resonance imaging study. *Anesthesiology* 94, 973–981
21 Lubke, G.H. *et al.* (1999) Dependence of explicit and implicit memory on hypnotic state in trauma patients. *Anesthesiology* 90, 670–680
22 Andrade, J. and Deeprose, C. (2007) Unconscious memory formation during anaesthesia. *Best Pract. Res. Clin. Anaesthesiol.* 21, 385–401
23 Deeprose, C. *et al.* (2007) Unconscious learning during surgery with propofol anaesthesia. *Br. J. Anaesth.* 92, 171–177
24 Deeprose, C. *et al.* (2005) Unconscious auditory priming during surgery with propofol and nitrous oxide anaesthesia: a replication. *Br. J. Anaesth.* 94, 57–62
25 Kerssens, C. *et al.* (2009) Preserved memory function during bispectral index-guided anesthesia with sevoflurane for major orthopedic surgery. *Anesthesiology* 111, 518–524
26 Kerssens, C. *et al.* (2002) Memory function during propofol and alfentanil anesthesia: predictive value of individual differences. *Anesthesiology* 97, 382–389
27 Kerssens, C. *et al.* (2005) No evidence of memory function during anesthesia with propofol or isoflurane with close control of hypnotic state. *Anesthesiology* 102, 57–62

28 Koelsch, S. *et al.* (2006) Auditory processing during deep propofol sedation and recovery from unconsciousness. *Clin. Neurophysiol.* 117, 1746–17459
29 Ypparila, H. *et al.* (2002) Evidence of auditory processing during postoperative propofol sedation. *Clin. Neurophysiol.* 113, 1357–1364
30 Simpson, T.P. *et al.* (2002) Effect of propofol anaesthesia on the event-related potential mismatch negativity and the auditory-evoked potential N1. *Br. J. Anaesth.* 89, 382–388
31 Supp, G.G. *et al.* (2011) Cortical hypersynchrony predicts breakdown of sensory processing during loss of consciousness. *Curr. Biol.* 21, 1988–1993
32 Bonhomme, V. *et al.* (2012) Neural correlates of consciousness during general anesthesia using functional magnetic resonance imaging (fMRI). *Arch. Ital. Biol.* 150, 155–163
33 Hudetz, A.G. (2012) General anesthesia and human brain connectivity. *Brain Connect.* 2, 291–302
34 Di Perri, C. *et al.* (2014) Functional neuroanatomy of disorders of consciousness. *Epilepsy Behav.* 30, 28–32
35 Guldenmund, P. *et al.* (2013) Thalamus, brainstem and salience network connectivity changes during propofol-induced sedation and unconsciousness. *Brain Connect.* 3, 273–285
36 Boveroux, P. *et al.* (2010) Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. *Anesthesiology* 113, 1038–1053
37 Greicius, M.D. *et al.* (2008) Persistent default-mode network connectivity during light sedation. *Hum. Brain Mapp.* 29, 839–847
38 Jordan, D. *et al.* (2013) Simultaneous electroencephalographic and functional magnetic resonance imaging indicate impaired cortical top-down processing in association with anesthetic-induced unconsciousness. *Anesthesiology* 119, 1031–1042
39 Martuzzi, R. *et al.* (2010) Functional connectivity and alterations in baseline brain state in humans. *Neuroimage* 49, 823–834
40 Stamatakis, E.A. *et al.* (2010) Changes in resting neural connectivity during propofol sedation. *PLoS ONE* 5, e14224
41 Langsjo, J.W. *et al.* (2012) Returning from oblivion: imaging the neural core of consciousness. *J. Neurosci.* 32, 4935–4943
42 Schrouff, J. *et al.* (2011) Brain functional integration decreases during propofol-induced loss of consciousness. *Neuroimage* 57, 198–205
43 Barrett, A.B. *et al.* (2012) Granger causality analysis of steady-state electroencephalographic signals during propofol-induced anaesthesia. *PLoS ONE* 7, e29072
44 Boly, M. *et al.* (2012) Connectivity changes underlying spectral EEG changes during propofol-induced loss of consciousness. *J. Neurosci.* 32, 7082–7090
45 Lee, U. *et al.* (2013) Disruption of frontal–parietal communication by ketamine, propofol, and sevoflurane. *Anesthesiology* 118, 1264–1275
46 Ku, S.W. *et al.* (2011) Preferential inhibition of frontal-to-parietal feedback connectivity is a neurophysiologic correlate of general anesthesia in surgical patients. *PLoS ONE* 6, e25155
47 Andrade, J. (1996) Investigations of hypesthesia: using anesthetics to explore relationships between consciousness, learning, and memory. *Conscious. Cogn.* 5, 562–580
48 Deeprose, C. and Andrade, J. (2006) Is priming during anesthesia unconscious? *Conscious. Cogn.* 15, 1–23
49 Reinsel, R.A. *et al.* (2000) Midazolam decreases cerebral blood flow in the left prefrontal cortex in a dose-dependent fashion. *Int. J. Neuropsychopharmacol.* 3, 117–127
50 Veselis, R.A. *et al.* (2002) A neuroanatomical construct for the amnesic effects of propofol. *Anesthesiology* 97, 329–337
51 Owen, A.M. *et al.* (2006) Detecting awareness in the vegetative state. *Science* 313, 1402
52 Monti, M.M. *et al.* (2010) The vegetative state. *BMJ* 341, c3765
53 The Multi-Society Task Force on PVS (1994) Medical aspects of the persistent vegetative state. *N. Engl. J. Med.* 330, 1499–1508
54 Andrews, K. *et al.* (1996) Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. *BMJ* 313, 13–16
55 Childs, N.L. *et al.* (1993) Accuracy of diagnosis of persistent vegetative state. *Neurology* 43, 1465–1467
56 Gill-Thwaites, H. (1997) The Sensory Modality Assessment Rehabilitation Technique – a tool for assessment and treatment of patients with severe brain injury in a vegetative state. *Brain Inj.* 11, 723–734
57 Schnakers, C. *et al.* (2006) Does the FOUR score correctly diagnose the vegetative and minimally conscious states? *Ann. Neurol.* 60, 744–745
58 Guldenmund, P. *et al.* (2012) Mindsight: diagnostics in disorders of consciousness. *Crit. Care Res. Pract.* 2012, 624724
59 Naci, L. *et al.* (2013) The brain's silent messenger: using selective attention to decode human thought for brain-based communication. *J. Neurosci.* 33, 9385–9393
60 Cruse, D. *et al.* (2011) Bedside detection of awareness in the vegetative state: a cohort study. *Lancet* 378, 2088–2094
61 Giacino, J.T. *et al.* (2004) The JFK Coma Recovery Scale – Revised: measurement characteristics and diagnostic utility. *Arch. Phys. Med. Rehabil.* 85, 2020–2209
62 Shiel, A. *et al.* (2000) The Wessex Head Injury Matrix (WHIM) main scale: a preliminary report on a scale to assess and monitor patient recovery after severe head injury. *Clin. Rehabil.* 14, 408–416
63 Wijdicks, E.F. *et al.* (2005) Validation of a new coma scale: The FOUR score. *Ann. Neurol.* 58, 585–593
64 Majerus, S. *et al.* (2005) Behavioral evaluation of consciousness in severe brain damage. *Prog. Brain Res.* 150, 397–413
65 Casali, A.G. *et al.* (2013) A theoretically based index of consciousness independent of sensory processing and behavior. *Sci. Transl. Med.* 5, 198ra105
66 Monti, M.M. (2012) Cognition in the vegetative state. *Annu. Rev. Clin. Psychol.* 8, 431–454
67 Dehaene, S. and Changeux, J.P. (2011) Experimental and theoretical approaches to conscious processing. *Neuron* 70, 200–227
68 Ress, D. and Heeger, D.J. (2003) Neuronal correlates of perception in early visual cortex. *Nat. Neurosci.* 6, 414–420
69 Zeki, S. and Bartels, A. (1999) Toward a theory of visual consciousness. *Conscious. Cogn.* 8, 225–259
70 Haynes, J.D. and Rees, G. (2005) Predicting the stream of consciousness from activity in human visual cortex. *Curr. Biol.* 15, 1301–1307
71 Flohr, H. (2000) NMDA receptor-mediated computational processes and phenomenal consciousness. In *Neural Correlates of Consciousness* (Metzinger, T., ed.), pp. 245–259, MIT Press
72 Andrade, J. (2000) NMDA receptor-mediated consciousness: a theoretical framework for understanding the effects of anesthesia on cognition? In *Neural Correlates of Consciousness* (Metzinger, T., ed.), pp. 271–278, MIT Press
73 Tononi, G. (2004) An information integration theory of consciousness. *BMC Neurosci.* 5, 42
74 Tononi, G. and Koch, C. (2008) The neural correlates of consciousness: an update. *Ann. N. Y. Acad. Sci.* 1124, 239–261
75 Lee, U. *et al.* (2009) Propofol induction reduces the capacity for neural information integration: implications for the mechanism of consciousness and general anesthesia. *Conscious. Cogn.* 18, 56–64
76 Mashour, G.A. (2013) Cognitive unbinding: a neuroscientific paradigm of general anesthesia and related states of unconsciousness. *Neurosci. Biobehav. Rev.* 37, 2751–2759
77 Brown, E.N. *et al.* (2010) General anesthesia, sleep, and coma. *N. Engl. J. Med.* 363, 2638–2650
78 Franks, N.P. (2006) Molecular targets underlying general anaesthesia. *Br. J. Pharmacol.* 147 (Suppl. 1), S72–S81
79 Hemmings, H.C., Jr *et al.* (2005) Emerging molecular mechanisms of general anesthetic action. *Trends Pharmacol. Sci.* 26, 503–510
80 Franks, N.P. (2008) General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. *Nat. Rev. Neurosci.* 9, 370–386
81 Rudolph, U. and Antkowiak, B. (2004) Molecular and neuronal substrates for general anaesthetics. *Nat. Rev. Neurosci.* 5, 709–720
82 Campagna, J.A. *et al.* (2003) Mechanisms of actions of inhaled anesthetics. *N. Engl. J. Med.* 348, 2110–2124
83 Heinke, W. and Schwarzbauer, C. (2002) In vivo imaging of anaesthetic action in humans: approaches with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). *Br. J. Anaesth.* 89, 112–122
84 Franks, N.P. and Zecharia, A.Y. (2011) Sleep and general anesthesia. *Can. J. Anaesth.* 58, 139–148
85 Fiset, P. *et al.* (1999) Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. *J. Neurosci.* 19, 5506–5513

86 Veselis, R.A. *et al.* (1997) Midazolam changes cerebral blood flow in discrete brain regions: an $H_2{}^{15}O$ positron emission tomography study. *Anesthesiology* 87, 1106–1117
87 Alkire, M.T. *et al.* (1997) Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anesthesia. *Anesthesiology* 86, 549–557
88 Alkire, M.T. *et al.* (1995) Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. *Anesthesiology* 82, 393–403
89 Uhrig, L. *et al.* (2014) Cerebral mechanisms of general anesthesia. *Ann. Fr. Anesth. Reanim.* 33, 72–82
90 Kaisti, K.K. *et al.* (2003) Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology* 99, 603–613
91 Kaisti, K.K. *et al.* (2002) Effects of surgical levels of propofol and sevoflurane anesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. *Anesthesiology* 96, 1358–1370
92 Alkire, M.T. *et al.* (2000) Toward a unified theory of narcosis: brain imaging evidence for a thalamocortical switch as the neurophysiologic basis of anesthetic-induced unconsciousness. *Conscious. Cogn.* 9, 370–386
93 Velly, L.J. *et al.* (2007) Differential dynamic of action on cortical and subcortical structures of anesthetic agents during induction of anesthesia. *Anesthesiology* 107, 202–212
94 Schroter, M.S. *et al.* (2012) Spatiotemporal reconfiguration of large-scale brain functional networks during propofol-induced loss of consciousness. *J. Neurosci.* 32, 12832–12840
95 Mhuircheartaigh, R.N. *et al.* (2010) Cortical and subcortical connectivity changes during decreasing levels of consciousness in humans: a functional magnetic resonance imaging study using propofol. *J. Neurosci.* 30, 9095–9102
96 Liu, X. *et al.* (2013) Differential effects of deep sedation with propofol on the specific and nonspecific thalamocortical systems: a functional magnetic resonance imaging study. *Anesthesiology* 118, 59–69
97 Monti, M.M. *et al.* (2013) Dynamic change of global and local information processing in propofol-induced loss and recovery of consciousness. *PLoS Comput. Biol.* 9, e1003271
98 Boveroux, P. *et al.* (2008) Brain function in physiologically, pharmacologically, and pathologically altered states of consciousness. *Int. Anesthesiol. Clin.* 46, 131–146
99 Alkire, M.T. *et al.* (2008) Consciousness and anesthesia. *Science* 322, 876–880
100 Damasio, A. and Meyer, K. (2009) Consciousness: an overview of the phenomenon and of its possible neural basis. In *The Neurology of Consciousness* (Laureys, S. and Tononi, G., eds), pp. 3–14, Elsevier
101 Laureys, S. *et al.* (2002) Brain function in the vegetative state. *Acta Neurol. Belg.* 102, 177–185
102 Thibaut, A. *et al.* (2012) Metabolic activity in external and internal awareness networks in severely brain-damaged patients. *J. Rehabil. Med.* 44, 487–944
103 Laureys, S. *et al.* (2004) Brain function in the vegetative state. *Adv. Exp. Med. Biol.* 550, 229–238
104 Laureys, S. *et al.* (1999) Cerebral metabolism during vegetative state and after recovery to consciousness. *J. Neurol. Neurosurg. Psychiatry* 67, 121
105 Kassubek, J. *et al.* (2003) Activation of a residual cortical network during painful stimulation in long-term postanoxic vegetative state: a ^{15}O-H_2O PET study. *J. Neurol. Sci.* 212, 85–91
106 Laureys, S. *et al.* (2002) Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage* 17, 732–741
107 Laureys, S. *et al.* (2000) Auditory processing in the vegetative state. *Brain* 123, 1589–1601
108 Boly, M. *et al.* (2004) Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. *Arch. Neurol.* 61, 233–238
109 Fernandez-Espejo, D. *et al.* (2008) Cerebral response to speech in vegetative and minimally conscious states after traumatic brain injury. *Brain Inj.* 22, 882–890
110 Coleman, M.R. *et al.* (2007) Do vegetative patients retain aspects of language comprehension? Evidence from Fmri. *Brain* 130 (Pt 10), 2494–2507
111 Vanhaudenhuyse, A. *et al.* (2010) Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain* 133, 161–171
112 Fernandez-Espejo, D. *et al.* (2010) Combination of diffusion tensor and functional magnetic resonance imaging during recovery from the vegetative state. *BMC Neurol.* 10, 77
113 Laureys, S. *et al.* (1999) Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. *Neuroimage* 9, 377–382
114 Laureys, S. *et al.* (2000) Restoration of thalamocortical connectivity after recovery from persistent vegetative state. *Lancet* 355, 1790–1791
115 Boly, M. *et al.* (2011) Preserved feedforward but impaired top-down processes in the vegetative state. *Science* 332, 858–862