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Review Article

NEUROSCIENCE AND NEUROANAESTHESIA

Comparison of anaesthetic- and seizure-induced states of unconsciousness: a narrative review

Benjamin F. Gruenbaum

Department of Anesthesiology, Yale School of Medicine, New Haven, CT, USA

E-mail: benjamin.gruenbaum@yale.edu

Summary

In order to understand general anaesthesia and certain seizures, a fundamental understanding of the neurobiology of unconsciousness is needed. This review article explores similarities in neuronal and network changes during general anaesthesia and seizure-induced unconsciousness. Both seizures and anaesthetics cause disruption in similar anatomical structures that presumably lead to impaired consciousness. Despite differences in behaviour and mechanisms, both of these conditions are associated with disruption of the functionality of subcortical structures that mediate neuronal activity in the frontoparietal cortex. These areas are all likely to be involved in maintaining normal consciousness. An assessment of the similarities in the brain network disruptions with certain seizures and general anaesthesia might provide fresh insights into the mechanisms of the alterations of consciousness seen in these particular unconscious states, allowing for innovative therapies for seizures and the development of anaesthetic approaches targeting specific networks.

Keywords: awareness; general anaesthesia; mechanism; seizure; unconsciousness

Editor's key points

- When explaining general anaesthesia to patients and families, anaesthetists often state that we are putting people to sleep, which is fundamentally inaccurate.
- General anaesthesia, unlike sleep, is not a restorative and easily disrupted state of unconsciousness, but is rather a dangerous neurophysiological perturbation more akin to coma; although with highly trained anaesthetists, modern drugs, and sophisticated monitors it has become much safer.
- Both the cortical and subcortical brain regions and networks that are affected with generalised seizures appear to be similarly targeted and disrupted with general anaesthesia.
- Studying the unconscious states associated with seizures might shed light on states of general anaesthesia, and might also improve our understanding of the neurobiological and dynamic underpinnings of both consciousness and unconsciousness.

The study of consciousness has important scientific and philosophical implications. Despite difficulties with definitions, most people inherently understand the concept of being conscious or aware of one's experience. In clinical practice, unconsciousness with general anaesthesia is casually equated with the term 'asleep' and contrasted with the term 'awake', as patients losing consciousness after receiving anaesthetic agents appear to be falling asleep.[1–3] Anaesthesiologists often tell patients to 'pick out a good dream' and colloquially refer to general anaesthesia as 'putting patients to sleep,' a soothing turn of phrase for anxious patients and families who worry about relinquishing control over their minds and bodies.[4,5] Sleep is a universally understandable and familiar state popularly associated with the positive connotations of restfulness, relaxation, and rejuvenation. The concept of sleep as an unconscious state was popularised by Steriade and colleagues and others, and more recently the similarities to coma have been noted.[3,6–9] While sleep shares several behavioural and neuronal mechanisms with loss of

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consciousness under anaesthesia, they are different brain states with distinct neurobiological processes.[3,10–15]

An alternative model for general anaesthesia is seizures associated with loss of consciousness, although a comparison between seizures and anaesthesia would probably not calm nervous patients preoperatively. Seizures are divided into two main categories, generalised and focal, which refer, respectively, to the seizure originating from the whole brain or from a localised region. Three types of both generalised and focal seizures impair consciousness: 1) focal onset impaired awareness seizures (previously called complex partial seizures), 2) absence seizures, and 3) generalised tonic-clonic seizures.[16,17] In focal onset impaired awareness seizures, seizures originate most often in the temporal lobe.[18] These seizures produce automaton-like behaviour, with sudden impaired consciousness.[18] Absence seizures are generalised non-convulsive seizures that consist of characteristic brief episodes of unconsciousness, with transient staring spells.[19] Generalised tonic-clonic seizures typically involve profound unresponsiveness, resembling coma during the seizure and postictal periods.[16] Electroconvulsive therapy electrically induces generalised tonic-clonic seizures to treat patients with certain mental health disorders.[20,21]

Despite differences in behaviour and physiology, these three seizure types associated with unconsciousness involve disruptions of a common set of brain structures, including the frontoparietal association cortex and the subcortical arousal systems in the thalamus and upper brainstem.[16,17] The cortex, thalamus, and other subcortical structures appear to be involved in changes of arousal during general anaesthesia as well.[22–29] This common involvement of anatomical structures allows for a useful comparison relating the state of unconsciousness under general anaesthesia to the loss of consciousness caused by seizures. Both states consist of a short and often reversible loss of consciousness with similar side-effects, which are represented by comparable electrophysiological features and directed by the corticothalamic network. In this review, a thorough analysis of the mechanisms of both seizure and anaesthesia-induced unconsciousness reveals neurophysiological similarities that elucidate fundamental new insights into the conscious mind.

Thalamocortical structures and mechanisms of consciousness

Beyond a colloquial understanding of awareness, a more precise definition of consciousness consists of two underlying aspects: 'level', described by wakefulness or arousal and alertness, and 'content', described by awareness to

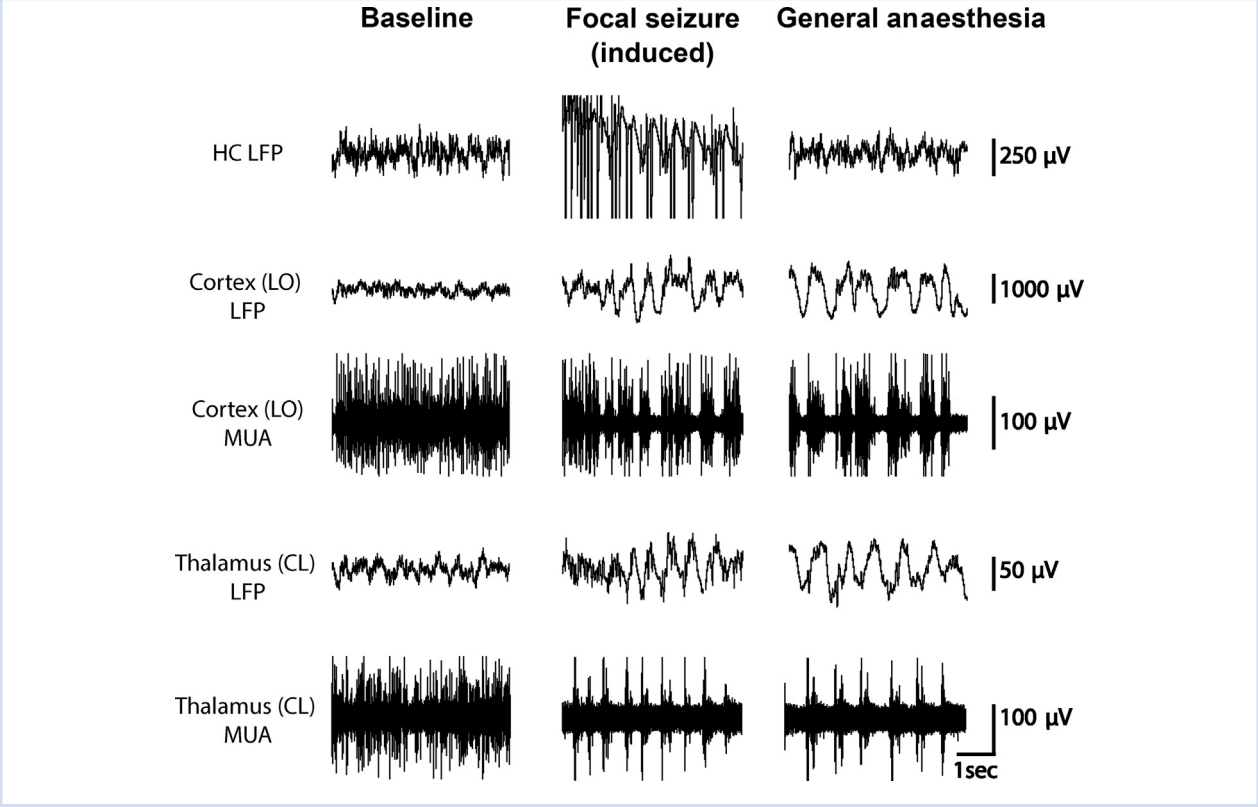

Fig 1. Comparison of neuronal changes seen in the unconscious states of general anaesthesia and focal onset seizures in a rodent model. Note similar electrophysiologic patterns in the cortex and thalamus in the deeply anaesthetised and seizure states. Data used to produce this figure were obtained by permission from Feng and colleagues.[67] Seizures were induced by hippocampal stimulation with a 2 s current injection of 200 micA in the hippocampus with 60 Hz frequency. General anaesthesia was induced with ketamine-xylazine (90/15 mg kg^{-1}) and doses were reduced to establish baseline periods. Local field potential (LFP) filter 0.1–100 Hz. Multi-unit activity (MUA) filter 400 Hz–10 KHz. CL, central lateral nucleus of the thalamus; HC, hippocampus; LO, lateral orbital frontal cortex.

stimuli.[30–32] These two functions are mediated by certain anatomical structures of the brain that are important for changes in consciousness, referred to as the 'consciousness system', including the reticular formation of the brainstem, hypothalamus, basal forebrain, thalamus, and cerebral cortex.[16,26,30,33]

Recent progress in consciousness research has determined the involvement of the thalamocortical network on several key features of consciousness.[6,34–41] It is possible that an interference in the higher order association cortex and related subcortical regions, including the thalamus, causes loss of consciousness through either aberrant excitation or inhibition.[42,43] The relationship between cortical and thalamic regions to loss of consciousness is complex, but recent literature has suggested various ways that those regions are modulated.

The role of the frontoparietal cortex

The frontoparietal cortex serves an important function in unconscious states such as general anaesthesia and seizures.[44] It has been established that the dorsolateral prefrontal and superior/posterior parietal association cortex are implicit in various cognitive functions such as attention, perception, working memory, and consciousness.[33,45,46] In various models of epilepsy and anaesthesia, cortical changes observed in the regions of the frontoparietal cortex are crucial in regulating consciousness.[33,47]

Despite a global reduction in neuronal activity under general anaesthesia, specific regions in the cortex, including the parietal and frontal association cortex, have been shown to have markedly decreased activity.[48–52] This cortical decrease is associated with characteristic slower-wave oscillatory changes on EEG.[53,54] Evidence in the literature has not conclusively established whether anaesthetics target the cortex directly,[55–58] or indirectly by thalamocortical disruption,[3,7,59–62] hypothalamic inhibition,[63,64] microtubule interaction,[65] or a combination of all three.

Electrophysiological monitoring of the frontoparietal cortex during focal seizures and under general anaesthesia shows similar slow-wave formations (1–3 Hz delta or slower, see Fig 1). Rodent models have demonstrated similar patterns of cortical slow waves and decreased cortical neuronal activity during focal seizures and under general anaesthesia administered by ketamine and xylazine (Fig 1).[66–78] In general, slow wave oscillation is characterised on EEG by rhythmic fluctuations in membrane potentials with cycles of synaptically-driven depolarisation and action potentials (Up states), followed by a reduction in synaptic inputs, membrane hyperpolarisation, and cessation of activity (Down states).[76] During Up states, recurrent network activity is initiated and moderated by an exact balance between excitatory and inhibitory inputs that likely influences the neuronal response.[76,79–83] During focal onset impaired awareness seizures, neocortical slow waves demonstrate increases and decreases in neuronal firing that resemble Up and Down states observed under general anaesthesia.[73] The electrophysiological measurements of Up and Down states during these types of seizures and under general anaesthesia, specifically membrane potential, firing rate, and input resistance, are significantly similar.[84] Thus, though the electrical activity in the region of origin in focal onset impaired awareness seizures does not resemble activity under general anaesthesia, the neuronal activity looks very similar in areas outside of origin, such as in the frontal or parietal cortex.[66,73–75,84]

Despite the classification of both absence seizures and generalised tonic-clonic seizures as generalised, recent evidence has suggested that these seizures do not necessarily occur throughout the whole brain and instead spare some brain regions.[85,86] EEG and neuroimaging techniques have demonstrated that these seizures preferentially affect focal bilateral regions in the brain involved in the conscious system.[16] Certain anaesthetics have also been demonstrated to selectively target comparable brain regions.[87–90] During absence seizures, decreases in cortical activity appear in the medial frontal, medial parietal, anterior and posterior cingulate, and lateral parietal cortices, and both increases and decreases in cortical activity are observed in the lateral frontal cortex.[16,91,92] Just as uncertainty persists about the predominant brain region of anaesthetic action, it is debated whether absence seizures are generated in the thalamus or cortex.[16] However, animal studies favour a cortical origin, suggesting that populations of hyperexcitable deep somatosensory cortical neurones initiate the spike-and-wave discharge.[93,94] During generalised tonic-clonic seizures, increases in cortical activity have been demonstrated in the lateral, frontal, and medial parietal cortices, with postictal decreases in the medial and lateral frontoparietal association cortices.[21,95,96] Thus, these types of seizures (absence, generalised tonic-clonic, and focal) and general anaesthesia have all been associated with analogous cortical changes.[91,92,95,96]

Subcortical involvement

There is strong evidence to suggest that subcortical areas, such as the thalamus and the brainstem, are critical to maintaining consciousness. Neurones within the central thalamus have been identified for restoring function at the network level for patients with consciousness disorders.[97] Consequently, stimulation of subcortical structures in the brain, such as the thalamus, has been shown to reverse unconsciousness in both seizures and anaesthesia.[16,34] Modulation of thalamic activity decreases arousal and may contribute to the mechanisms underlying the changes in consciousness seen under general anaesthesia and seizures, and in other states including sleep and coma.[98–100]

It has been shown that many anaesthetics, including propofol, dexmedetomidine, halothane, and isoflurane, target subcortical structures such as the thalamus.[7,48,60] A subsequent theory of the thalamic switch of consciousness was developed, which proposes that the thalamocortical neurones become hyperpolarised and therefore interrupt the normal function of the thalamocortical circuits required for consciousness.[7,33,101] During anaesthesia, microfusion of nicotine and infusion of antibodies into the central medial thalamus have been shown to reverse the effects of sevoflurane and desflurane anaesthesia, even when the anaesthetics are continually administered.[43,102–105]

It is not clear if the thalamus itself constitutes the primary focus of anaesthetic modulation, or if changes that appear within it are secondary effects from other brain regions.[33] Anaesthetic-induced regulation of cortical activity may precede suppression in the thalamus, which would imply a secondary or consequential effect in the subcortical region.[26,56] But the close relationship between the thalamus and the cortex suggests that it may not be possible to separate thalamic activity entirely.[33]

In a rat model of focal onset seizures, population firing of neurones in arousal nuclei of the thalamus, such as the central

lateral nuclei, has been shown to decrease during seizures while the cortex exhibited slow waves (Fig 1).[67] There is evidence that stimulating certain subcortical areas in the brain with cholinergic agents during focal seizures and under general anaesthesia leads to arousal.[34,102,103] Gummadavelli and colleagues[34] showed that stimulating the central lateral nucleus of the thalamus under deep anaesthesia and during electrically-induced focal onset seizures led to reduced cortical slow-wave activity and increased arousal. A follow-up study by Kundishora and colleagues[66] showed that simultaneous stimulation of the central lateral nucleus of the intralaminar thalamus and the pontine nucleus oralis restored awake-like cortical activity, reversing the decreased arousal associated with focal onset seizures.

Most functional MRI studies describe increases in the thalamus during absence seizures and generalised tonic-clonic seizures.[91,92] Several studies suggest that the thalamus plays a critical role inpropagating absence seizures.[93,106] As during focal seizures,[107] stimulation to the thalamus reticular nucleus appears to suppress absence seizure activity.[108] While the exact mechanism is unclear, it is possible that abnormal activation of subcortical structures, such as the thalamus, during generalised tonic-clonic seizures plays an important role in the disruption of ascending arousal regions.[95,109]

In both anaesthesia and seizures, areas of the brainstem are likely involved with the disruption of thalamocortical function, causing unconsciousness through direct engagement with the cerebral cortex or via the thalamus and basal forebrain.[110] The nuclei that primarily affect cerebral activity are located in the upper pons and in the midbrain, with some possible influence from lower brainstem structures, and rely on a network of nuclei families, rather than a single nucleus or family.[110,111]

The mesopontine has been identified as an activator for the cortex for shifting between sleep and wakeful states through a network described as the reticular activating system.[112] It was subsequently suggested that many anaesthetics, specifically those that target gamma aminobutyric acid (GABA) type A receptors, work by suppressing the activation system in the mesopontine.[111,113,114] Recent studies have shown that microinjections of pentobarbital into the mesopontine tegmentum in a rat model induce an anaesthesia-like state.[115,116] However, because this region does not induce a coma, it has been suggested that it may act as a 'gatekeeper' to switch between states of awareness.[115] An alternative theory suggests that anaesthetics target the mesopontine primarily, with cortical inhibition as a secondary effect.[116] Regions of the upper brainstem have been shown to be responsible for emergence from general anaesthesia. In the ventral tegmental area, dopaminergic neurones induce arousal under propofol and isoflurane.[117–119]

Areas of the brainstem have also been associated with focal and generalised convulsive seizures. One theory proposes that generalised tonic-clonic seizures and focal seizures result from primary or secondary disruption of the reticular activating system.[120,121] Anticonvulsant therapy has been shown to reverse the effects of reticular neurones in animal models of brainstem-triggered generalised tonic-clonic seizures.[122,123] During in vivo focal seizures, cholinergic neurones in the pedunculopontine tegmental nucleus have been observed with decreased neuronal activity.[124,125] Moreover, stimulation of the pons and central thalamus simultaneously during focal seizures led to a return of baseline cortical electrophysiology and behaviour, although stimulation of each area separately was not sufficient to produce this same effect.[66] Similarly, stimulation of the pontine reticular nucleus increased connectivity preferentially in the basal forebrain-paralimbic networks, likely reflecting a disruption in awareness.[126]

The basal ganglia, hypothalamus, and cerebellum are other subcortical structures that may be involved in loss of consciousness in seizure and under anaesthesia,[127–130] though some of these theories are controversial.[29,131,132] The basal ganglia may be involved in modulation of neocortical generalised absence seizures and other types of generalised seizures.[133–135] Stimulation of the internal globus pallidus region of the basal ganglia has induced wakeful unawareness under propofol.[128] The claustrum may have a role in arousal as well.[136] One study suggests an association between unresponsiveness produced by propofol and disruption of functionality in the putamen (a subcortical structure in the basal ganglia) more than in the thalamus,[129] putting into question the wide acceptance of the thalamus' importance in consciousness.[137] Animal studies, for example, show some limited behavioural functions that are present even with thalamic ablation.[138]

Functional connectivity and network systems

The importance of thalamocortical interactions in mediating consciousness has been well-established. One theory suggests that conscious function relies on the complex interactions within neuronal networks that integrate information.[22–25] Specifically, changes in consciousness may occur as a result of disruption in or unbinding of these networks.[26–28,33]

In anaesthesia, two popular models define our understanding of how anaesthetics interfere with the level and content of consciousness through network changes: a 'bottom-up' and a 'top-down' approach.[31,139–141] The bottom-up approach explains the disruption that anaesthetics cause to nuclei and neuronal circuits in the brainstem and thalamus that lead to changes in the primary sensory and ultimately higher-order association cortices.[141] The second, top-down approach describes the function of anaesthetics in interrupting information flow from higher-order association to early sensory cortices.[31] The bottom-up approach may be correlated with level of consciousness, and the top-down approach with content.[31] Successful anaesthetic-induced unconsciousness likely works by targeting both the level and the content of consciousness through a combination of top-down and bottom-up approaches.[142]

Seizures with associated loss of consciousness also affect content and level of consciousness.[16,143,144] The Ictal Consciousness Inventory,[143] the Consciousness Seizure Scale,[35] the Seizure Perception Survey,[145] and the Responsiveness in Epilepsy Scale[146–148] are posited techniques to measure level and content during episodes of impaired consciousness during seizure to understand more fully the mechanisms of awareness and arousal.[149] Although the mechanisms of seizure-induced unconsciousness have not been described using top-down and bottom-up approaches specifically, it is likely that a combined approach may also be applied to understand the mechanisms of ictal loss of consciousness.

The puzzling impairment in consciousness seen during focal temporal lobe seizures, which originate in an area of the brain not typically associated with consciousness, may be explained by the network inhibition hypothesis.[16] The network inhibition hypothesis proposes that focal seizures

that initiate in areas of the brain not part of the consciousness system, such as the temporal lobe, lead to unconsciousness that is secondary to seizure spread through activation of inhibitory subcortical structures.[29] These subcortical structures deactivate frontal and parietal association cortical regions required to maintain normal consciousness.[29]

Cortical sensory processing

There are limited cortical processes that still function during loss of consciousness in both seizure and anaesthesia.[16,92,150] Neuronal responses to sound in the primary sensory areas appear to be unaffected under light anaesthesia,[51,151–154] while higher-order cortical areas reveal impaired responses.[40,153,155–157] Thus, network activity in higher-order cortical regions could be primarily affected by anaesthesia and seizure.

Cerebral blood flow and metabolic activity

Changes in unconsciousness are accompanied by fluctuations in cerebral blood flow (CBF) and metabolic activity. Anaesthesia is a hypometabolic state, producing large-scale, global reductions in those two processes.[3,33,48,49,61,158–160] CBF during anaesthesia is mediated through the cortex, and the largest reductions in CBF by propofol can be seen in the cuneus, precuneus, and posterior cingulate and retrosplenial cortex regions, and in the frontal cortex.[61,161] High concentrations of sevoflurane also produce a reduction in frontal CBF, at 1.0–2.0 MAC.[50,162]

During seizures, it is generally understood that there is an increase in CBF and metabolic demand ictally.[163,164] However, as noted above, differences in neuronal activity are observed between types of seizures and regionally within a single type. During focal seizures that impair consciousness, there is evidence that CBF and metabolic activity are increased in the area of origin, but reduced regionally in areas such as the frontoparietal cortex.[77,165] Moreover, regions in the brain during absence seizures show decreases in CBF and metabolism.[166]

It is unclear if the anaesthetic reductions in CBF and metabolic activity cause unconsciousness or if they are a result of alterations in network interactions.[33] Patients recovering from a vegetative state who regained consciousness, for example, continued to show substantially decreased global cerebral metabolism.[167,168] There is great variation in cerebral metabolic rate among individuals even at baseline,[48] which disputes the idea of a consistent correlation between metabolic activity and consciousness.[33]

Associated consequences

Many of the consequences associated with loss of consciousness are shared between certain seizures and anaesthetics. For example, changes of consciousness during seizure and anaesthesia are transient. Patients also experience a recovery period of variable duration postictally or postoperatively, with delirium, generally defined as a disturbance of consciousness, a common side-effect of both conditions.[169–172] Older adults are especially prone to delirium after anaesthesia and after seizures.[173,174]

Limitations

There are several limitations to this comparative methodology between seizures and anaesthesia-induced unconsciousness. Despite disruptions in similar anatomical structures, types of anaesthetics or seizures may act by different mechanisms.[16,17,175] At first glance, ketamine appears to be an exception to the comparison between changes of consciousness under anaesthesia and seizure because of its unique mechanisms. Ketamine, unlike most anaesthetic agents, is an antagonist of the N-methyl-D-aspartate subtype of glutamate receptors (similar to nitrous oxide and xenon).[33] It has previously been described that cats administered ketamine anaesthesia produced bursts of hypersynchronous slow waves on EEG.[176] These slow waves were rhythmic, synchronous, and frequently accompanied by spikes, forming a spike-and-wave complex.[176–179] Moreover, in many neurones, neuronal activity was modified during the slow wave bursts that mimic patterns observed during experimental seizures.[176,177] It has thus been suggested that the functional state of the brain produced by ketamine resembles absence epilepsy, because of similar EEG spike-and-wave complexes and non-convulsive loss of consciousness.[176,180] This is supported by the fact that the absence seizure therapy trimethadione also suppresses ketamine-induced seizure-like EEG activity.[180] While there is evidence of both convulsant and anticonvulsant properties of ketamine,[181–183] the exact relationship between ketamine and seizures is still unclear.

While advances in techniques that record brain activity in human patients and animal models have provided important insights into the mechanisms of unconsciousness, the difficulty of understanding these mechanisms rests in the complexity of consciousness and its effects. When we study consciousness, we are limited to studying conditions such as anaesthesia and seizure that have changes in consciousness as a secondary effect. All of these states have effects on cognition, blood flow, and metabolism, making it difficult to define loss of consciousness exclusively. Once we establish the exact interplay of regions of the brain involved in these conditions and mechanisms of network changes, it will be easier to identify and clarify consciousness. Until then, direct comparisons between changes in neuronal activity in the anaesthetic- and seizure-induced states of unconsciousness are an ideal strategy for the advancement of consciousness research.

Conclusions

The past decade has explored new frontiers of research into the effects of anaesthesia. At this point, however, it is only possible to study the downstream effects of anaesthesia, as we do not yet understand the fundamentals of the complicated unconscious state that anaesthesia induces. To clarify these effects, the unconscious state under anaesthesia should be compared with other states associated with unconsciousness. Both seizures and anaesthetics cause disruption in similar anatomical structures that lead to impaired consciousness. Although they differ in behaviour and mechanism, both of these conditions disrupt the functionality of subcortical structures that mediate normal activity in the frontoparietal cortex, which represent the consciousness system.[16,33,42] Understanding which brain networks are shared between these conditions will provide new insights into the mechanisms of alterations in consciousness seen in seizures and anaesthesia,

and can lead to novel therapies and anaesthetics targeting these networks.

Author's Contributions

BFG is the sole author of this paper, accountable for its accuracy and integrity.

Declarations of interest

The author declares that they have no conflict of interest.

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