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THE BLACKED OUT BRAIN

Neural Mechanisms of Unconsciousness in General Anesthesia and Disorders of Consciousness

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Abstract

Finding the neural mechanisms of unconsciousness is a pursuit with significance to both the scientific study of consciousness as well as for the improvement of clinical diagnosis of patients with severe structural brain damage that has resulted in disorders of consciousness (DOC), such as coma or vegetative state . This literature review gives an account for what consciousness studies have contributed to the understanding of the neural mechanisms of unconsciousness, focusing on experiments using anesthetic agents to investigate the loss and return of consciousness. Mechanisms that frequently correlate with the loss of consciousness are modulation of the brainstem, the thalamus, and the cortex, but different anesthetic drugs act on different areas. According to a bottom-up approach unconsciousness can be induced by sleep-circuits in the brainstem, and according to a top-down approach unconsciousness can be induced by cortical and thalamocortical disruption. But the mechanisms involved during loss of consciousness are not the same as for return of consciousness, and this paper includes evidence for the mechanisms involved during the return being closer to what research should be further investigating. The mechanisms involved in return from anesthesia-induced unconsciousness resemble those mechanisms involved in recovery from DOC. Studying mechanisms of unconsciousness can further our understanding of consciousness, as well as improve the diagnosis and treatment of patients with DOC.

Keywords: neural mechanisms of unconsciousness, general anesthesia, disorders of consciousness, recovery of consciousness

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Introduction

During every single day of our entire lives - consciousness is right there. We see and we feel, we think and we experience everything in a subjective first-person perspective. What enables all of the really amazing, horrific, utterly boring and occasionally funny experiences that we have is the lump of fat and tissue that is our brain. Somehow, something the brain is doing ends up creating our entire world and for the past decades, this something has gotten under the eye of scientific query. But despite theoretical progress and advanced technological possibilities the questions of why we are conscious and how consciousness arises from neural activity remain mysteries.

A current neuroscientific framework with the aim of unraveling the mysteries of consciousness was suggested by Francis Crick and Christoff Koch at the beginning of the 1990´s. This framework is focusing on finding the areas in the brain which correlate with conscious experience, referred to as the Neural Correlates of Consciousness (NCC). Finding the NCC would mean that we can compare areas and processes in the brain that are associated with consciousness to brain processes that are not, and hopefully yield clues on how consciousness arises by comparing what differs between these areas (Crick & Koch, 2003).

This paper, however, is not a review on consciousness. Rather, it describes what happens in the brain when consciousness is not there anymore; it is a literature review on the neural mechanisms of *unconsciousness*. Unconsciousness is a state of having no experiences what so ever, there is no feeling of eternal void or darkness, it is just absolutely nothing (Revonsuo, 2010). This state can occur due to a broad range of reasons; e.g. physiological, pharmaceutical, or pathological (Mashour & Hudetz, 2018). The most common of these is the physiologically induced unconsciousness which happens when we fall asleep and have time periods without any kind of dreaming, i.e. no subjective experiences. There is nothing it is like to be someone who is asleep without dreams (Revonsuo, 2010). Another state of unconsciousness that is more commonly seen in hospitals is the pathological cause of unconsciousness, for example patients who after severe traumatic brain injuries are unconscious, such as during a coma.

This literature review will focus on pharmaceutically caused unconsciousness, i.e. general anesthesia. Anesthetic agents such as propofol, sevoflurane, and dexmedetomidine are pharmaceutics that can cause unconsciousness in a way that can be experimentally controlled. They can turn consciousness 'on and off'. Switching consciousness "on and off"while measuring brain

activity can yield clues on the neural correlates and mechanism of unconsciousness (Långsjö, Revonsuo, & Scheinin, 2014)

The modulation of three areas frequently appear to be associated with anesthesia-induced unconsciousness; various cortical areas, the thalamus and the brainstem (Brown, Lydic, & Schiff, 2010). Anesthesia-induced unconsciousness can be caused by activation of sleep generating nuclei in the brainstem, known as a "bottom-up approach", but also from the disruption of cortical and thalamocortical networks, known as a "top-down approach" (Mashour & Hudetz, 2017). How these different mechanisms can cause unconsciousness is not only relevant in the pursuit of unraveling scientific mysteries, but it also holds profound value to the diagnosis and treatment of those patients suffering from pathological unconsciousness, known as Disorders of Consciousness (DOC).

The aim of this literature review is to give an account for what the neural mechanisms of unconsciousness are. The main focus will be on reviewing the mechanisms found from experimental studies conducted with general anesthesia imaging brain activity during the loss and return of consciousness. Because of the body's resistance to transition between such behavioral states, a phenomenon known as 'neural inertia', I will then argue that studying recovery from anesthesia provides better correlates of unconsciousness compared to studying the mechanisms during the induction. Also, the mechanisms involved in the recovery from anesthesia-induced unconsciousness resemble those involved in the recovery from DOC, so a second focus will be on explaining these disorders and the recovery from them. Further understanding the recovery process from unconsciousness can hence provide us with the minimal neural activity needed for consciousness to occur, as well as improved diagnosis and treatment of DOC.

There are two major obstacles within general anesthesia that will be addressed in this paper; the first being that loss of consciousness cannot be measured so loss of responsiveness is used as a surrogate in all studies included in this paper, but loss of response does not necessarily mean loss of subjective experience (Noreika et al., 2011; Radek et al., 2018). The other challenge is that anesthetic agents do not target brain mechanisms exclusively related to the onset of unconsciousness but rather acts 'all over the place', which leads to it being hard to distinguish what mechanisms actually are related to unconsciousness (Långsjö et al., 2014). Studies included in the present paper were evaluated based on how well the study design investigated consciousness and how well the changes in consciousness was separated from unrelated effects of the anesthetic agent.

General Anesthesia

This section will start with a general background on what general anesthesia is and what it can be used for, followed by a description of typical responses when someone gets anesthetized. Following that are some clarifications of the terminology used within anesthesia studies, i.e. what Levels and Contents of consciousness are, to provide a sufficient background for the subsequent discussion about the neural mechanisms of anesthesia-induced unconsciousness.

General anesthesia is most commonly used in surgical settings to pharmacologically induce a temporary loss of consciousness along with an inability to create memories (amnesia), feel pain (analgesia) or move ones body (immobility), in order to perform surgery without the patients having experiences of the procedure (Brown et al., 2010). General anesthesia can also be used within the field of consciousness studies to experimentally switch consciousness 'on and off' while measuring brain activity while its 'on' and comparing them to when its 'off' in order to find what areas and processes are associated with (un)consciousness (Långsjö et al., 2014). Study designs that can find these areas are the ones that record brain activity during normal waking state when the participant is aware and conscious, followed by a recording during the anesthesia-induced loss of consciousness when the participant is lying completely still and oblivious about their environment and then during the recovery of consciousness when they open their eyes and interact with the environment again (Långsjö et al., 2014).

Switching consciousness "on and off" with general anesthesia refers to the binary State of consciousness. Someone who is in a state of consciousness have subjective experience(s) of some kind while someone who is in a state of unconsciousness has got no subjective experiences what so ever, i.e. there is nothing it is like to be a person in unconsciousness - it is just nothingness, like dreamless sleep (Revonsuo, 2010). Unconsciousness as a state is not objectively detectable with current technological equipment, so researchers as well as clinicians have to rely on unresponsiveness as an index of unconsciousness (Långsjö et al., 2014). To put unresponsiveness in context follows a description of someone losing consciousness due to anesthesia.

Loss and Return of Responsiveness

Brown et al. (2010) describe typical reactions during induction, maintenance, and recovery of anesthesia, of which here follows a comprised summary. They write that a small induction of the anesthetic agent Propofol sedates the person and typically makes them close their eyes and appear calm. Further increasing the dose after this can cause a so called paradoxical excitation, a state characterized by purposeless or defensive movements during an exhibition of euphoric or dysphoric

feelings (Brown et al., 2010). Because of this movement it can serve problematic to image brain activity with technologies requiring the participant to be still (Palanca et al., 2015), something that will be further discussed in limitations. After this phase of movement due to paradoxical excitation, the person will begin to breathe irregularly if the dose is increased and they will have occasional stops of breathing so they need bag-mask ventilation to not suffocate. At this point they lose the capacity to focus their eyes or track moving objects, such as the researcher's moving finger in front of their eyes, as reflexes in the eyes are lost. Heart rate increases and blood pressure either increase or decrease. By now, the person is considered unconscious. (Brown et al., 2010).

Within surgical settings the patients need to be anesthetized until the point where they are so unresponsive that they do not react to pain (Mashour, 2014), or loud noises and shakes (MacDonald, Naci, MacDonald, & Owen, 2015), which is a state so deeply anesthetized that it is functionally equivalent to brain death or coma; the patient cannot breathe on their own, does not react to painful stimuli, lacks brainstem reflexes and is therefore considered unconscious (Brown et al., 2010). But this profound depth of anesthesia is not necessary when conducting experiments (Mashour, 2014), where the participants are regarded unconscious when they no longer respond to verbal commands (MacDonald et al., 2015) such as "squeeze my hand" or "open your eyes", which is a depth of anesthesia shallow enough for the participant to regain their senses if pain is caused to their bodies (Mashour, 2014).

Brown et al. (2010) describe the behavioral hallmarks during recovery from anesthesia-induced unconsciousness as follows; when the procedure is finished the drugs are cut off and after that follows a passive process where the time of waking up depends on the person and the specific characteristics of the drug. A first clinical sign that the person is about to wake up is the return of spontaneous breathing, followed by increased heart rate and blood pressure, salivation and tearing eyes, and then the capacity to respond to painful stimuli but residual inability to localize the pain. As the anesthetized person continues to recover they begin to move facial muscles and limbs again; swallowing, coughing and making defensive movements. By now the person typically breathes on their own but has yet to follow verbal commands and open their eyes (Brown et al., 2010).

Unresponsiveness as an index of unconsciousness. In theory, subjective experiences and hence consciousness could persist in the anesthetized person throughout the entirety of the above described loss of behavioral indications of consciousness. Empirical evidence for this being the case has been suggested by for example Radek et al. (2018) who found that almost 86% of anesthetized

healthy participants reported having had internally generated subjective experiences (dreaming) during periods of loss of responsiveness. Both researchers and physicians generally agree that unresponsiveness as an index of unconsciousness is inadequate.

Critique of the unresponsiveness definition of unconsciousness is boiled down to its core best explained as the two things not being the same since there is a dissociation between these two concepts, which means that consciousness can occur despite a lack of responsiveness (Sanders, Tononi, Laureys, & Sleigh, 2012). The most common of situations would probably be when we fail to follow verbal commands because we are asleep but we none the less have inner conscious experiences from dreaming (Sanders et al., 2012). Another example is anesthesia awareness, which is an excruciating form of consciousness during unresponsiveness, where the person has full awareness of the environment and what is going on around them but lack the capacity to indicate this awareness due to the total immobility caused by anesthetic agents (Sanders et al., 2012). A less dramatic yet equally important example is the possibility that the participant during anesthesia is fully capable of hearing the verbal command to open their eyes or squeeze someone's hand, even fully capable of following it, but completely lack the motivation to do so as in the case with patients having akinetic mutism (Långsjö et al., 2014). What these examples show is that consciousness and responsiveness are dissociable.

So why do researchers and clinicians continue to use unresponsiveness as an index of unconsciousness? The short answer is that until a better index of unconsciousness is found, unresponsiveness 'will have to do'. The long answer is that unresponsiveness has historically been the only possible way to estimate someone's conscious state and in the clinical diagnosis of for example disorders of consciousness there has been no other method to rely on up until recently (Owen et al., 2006). But even with contemporary technological advancement consciousness defined as subjective experience necessarily defies all attempts to be measured since science can only measure things of objective nature. But there are ways around this problem that the study of anesthesia-induced unconsciousness uses in order to still study unconsciousness.

Levels and Contents of Consciousness

A common simplification that makes consciousness possible to approach scientifically is to divide it into Contents of consciousness and Levels of consciousness (Långsjö et al., 2014). These are distinguished both conceptually since they refer to different phenomena but also empirically since for example Mashour and Hudetz (2017) points out that Level and Contents have two distinct

neural pathways, where Level is suppressed by subcortical areas and Contents are suppressed by thalamocortical and corticocortical decrease (Mashour & Hudetz, 2017).

Contents of consciousness are the specific subjective experiences that constitute our worlds at any given moment; it is the specific smell of coffee or the sound of a bird (Mashour & Hudetz, 2017). Research that investigates contents of consciousness typically gather data about the presence or absence of contents through verbal reports about sensory stimuli from the participants, e.g. by asking them to say 'yes, I see a face' when they do or alternatively press a button indicating perceiving the face or not (Koch, Massimini, Boly, & Tononi, 2016). According to Koch et al. (2016), the content-specific NCC are the neurons which only fires to specific things such as seeing a face, and in all other circumstances do not fire. To detect the content specific NCC, neural activity is imaged when specific content is present, during the 'yes, I see a face'-period, and then compared to when the same content is absent while all else is kept constant (Koch et al., 2016). There is convincing evidence that the cortex has a causal role in the generation of contents of consciousness (Långsjö et al., 2014) because neurons in the cortex can be artificially activated or suppressed through for example Transcranial Magnetic Stimulation (TMS), making contents appear or disappear (Koch et al., 2016).

Levels of consciousness refer to the degree to which someone is conscious which serves as a prerequisite for contents to exist (Långsjö et al., 2014). Someone in a low level of consciousness would be drowsy and not very responsive while at a high level they would be awake and alert, and respond sufficiently (Mashour & Hudetz, 2017). Research that investigates levels of consciousness typically does so by assessing purposeful response to verbal command (Mashour & Hudetz, 2017) such as "squeeze my hand" or "open your eyes". Level of consciousness is what is manipulated with anesthetic agents, because anesthetic agents can decrease the level of consciousness on a dose-dependent continuum, meaning that the level of consciousness correlates with the dose of the anesthetic agent in a linear manner - the higher the dose the lower the level of consciousness (MacDonald et al., 2015). In experimental settings the participant is getting the dose until they reach loss of responsiveness (MacDonald et al., 2015).

For the purpose of this paper it is necessary to distinguish level of consciousness from the closely related words wakefulness and arousal, as well as distinguishing contents of consciousness from awareness. Arousal and awareness are concepts that sometimes are used in a synonymous manner, but are more commonly used within the medical practice when explaining disorders of

consciousness, which is why a further distinction will be made when the subject of disorders of consciousness is touched within this essay. The following studies investigate the level of consciousness, indexed by the loss and the return of responsiveness.

Neural Mechanisms of General Anesthesia

This section will start with presenting a general background on anesthetic drugs and which ones will be included in this paper, followed by a presentation of the two dominant frameworks within anesthesia studies that explain the neural mechanisms of unconsciousness; the top-down mechanisms and the bottom-up mechanisms. Following that, are arguments that studying return of consciousness will provide better neural correlates than studying loss of consciousness, followed by what studies doing so have suggested on the subject.

For as long as anesthetics have been around the question of how they make consciousness disappear has too. The first public display of pharmacologically induced unconsciousness was carried out in 1846 by the dentist William Thomas Green Morton, who used inhalational ether to anesthetize his patient (Långsjö et al., 2014). Ether is nowadays only one among a wide repertoire of agents that can induce unconsciousness, and three of the more commonly used ones are included in this paper; propofol, sevoflurane, and dexmedetomidine. A common feature of these three agents is that they all cause unconsciousness by suppressing neural activity (Akeju et al., 2014; MacDonald et al., 2015) but it is worth mentioning that not all anesthetic agents do. For example ketamine rather increases activity but as it is debated whether ketamine really induces a state of unconsciousness and not just severe dissociation (Hudetz, 2012) it will be excluded from the present paper.

The three anesthetic agents that are included in this paper; propofol, sevoflurane and dexmedetomidine, are diverse in how and where they work (Mashour, 2014). Propofol is an anesthetic agent that decreases the activity in frontoparietal networks in correlation with decreased consciousness (Boveroux et al., 2010) while sevoflurane impairs connectivity in anterior areas associated with higher order processing (Ranft et al., 2016; Sleigh, 2016) and dexmedetomidine acts on sleep-wake nuclei in the brainstem (Akeju et al., 2014). Despite these differences in targets, the functional result is the same for virtually all of them; unconsciousness, and hence, one main problem when looking for the neural mechanisms of anesthesia-induced unconsciousness is to find what the common property of these diverse agents may be (Mashour, 2014).

According to Hudetz (2012), one theory that would explain how this rich diversity of anesthetic targets could induce one single common outcome is the 'wet-blanket theory' which states that these agents all suspend functions evenly across the brain much like a wet blanket would suppress everything in a nonspecific manner (Hudetz, 2012). But the mystery remains since some specific regions have shown to be more important than others (Mashour & Hudetz, 2017). The thalamus is a prime candidate that was early on detected to play an important part for both levels and contents of consciousness since it is a site for virtually all incoming sensory information (contents) as well as part of the ascending arousal pathway (levels) (Mashour & Hudetz, 2017). This lead to a theory of the thalamus serving as a 'switch', i.e. that it singlehandedly activated and deactivated consciousness (Alkire, Haier, & Fallon, 2000). But the study by Alkire et al. (2000) only investigated two anesthetics; halothane and isoflurane, which does not appear to primarily act on cortical networks as for example propofol does (Boveroux et al., 2010). It appears that consciousness can be subsequently suppressed by modulation of activity in either cortical or subcortical areas, or both (Mashour & Hudetz, 2017)

The studies included in this section were all investigating the neural mechanisms of either loss of consciousness or return of consciousness, or both. The studies were all experimental (not clinical) and carried out on healthy human adults. The researchers induced unconsciousness by either propofol, sevoflurane or dexmedetomidine, and measured the effects with electroencephalography (EEG), functional magnetic resonance imaging (fMRI), or positron emission tomography (PET). The present paper has a focus on presenting studies using the latter two methods, i.e. fMRI and PET. Loss of consciousness was in all of the included studies indicated by loss of response to verbal command.

The Bottom-Up Mechanisms

Anesthesia-induced unconsciousness can be caused by modulation of so called bottom-up mechanisms in the brain. Bottom-up mechanisms are various brainstem areas associated with natural sleep generation, e.g. the modulation of arousal-promoting nuclei. Certain brainstem nuclei are commonly agreed upon to be important in sleep generation, and these same regions are modulated in a similar manner by certain anesthetic agents (Mashour & Hudetz, 2017).

The brainstem plays a key role in the regulation of wakefulness. Specifically the pons is of importance since it consists of the reticular formation and the locus coeruleus (LC). The reticular formation is involved in the regulation of sleep-wake cycles and the LC is involved in the degree of

arousal due to being the main site of production of the excitatory neurotransmitter norepinephrine (Gazzaniga, Mangun, & Ivry, 2013). If the pons is damaged it can result in deep states of unconsciousness, such as coma or vegetative state (Gazzaniga et al., 2013). Sleep is a state that is actively generated in the brainstem, hypothalamus and basal forebrain (Brown, Purdon, & Van Dort, 2011). In order for us to be awake, a specific part of the hypothalamus that is called the ventrolateral preoptic nucleus (VLPO) needs to be inhibited from inhibiting the ascending arousal system. When the VLPO is not inhibited, it will release the inhibitory neurotransmitters gelanin and GABA which in turn inhibits the ascending arousal system, and wakefulness decreases (Brown et al., 2011). LC neurons fire regularly during wakefulness, less during sleep, and spikes in activity just before waking up from sleep (Zhang et al., 2015)

A typical example of how consciousness can be suppressed by anesthetic agents through bottom-up mechanisms is how Dexmedetomidine works. Dexmedetomidine activates neurons that are associated with the generation of sleep, e.g. neurons in the VLPO (Moore et al., 2012) which induce a sleep-like state with lowered body temperature and slow-wave cortical activity, closely resembling non-rapid-eye-movement sleep (Zhang et al., 2015). Dexmedetomidine makes LC neurons hyperpolarize, which in turn inhibit the pre-optic area in the hypothalamus and decrease noradrenergic signaling in the thalamus and cortex (Brown et al., 2011).

One study that used dexmedetomidine to induce unconsciousness was conducted by Akeju et al. (2014). They measured brain activity and connectivity with PET and fMRI on 10 healthy participants undergoing dexmedetomidine-induced unconsciousness. Unconsciousness in their study was defined as lack of response to the verbal command ”open your eyes”. This study is a good example of how bottom-up mechanisms can cause unconsciousness since they found that activity in the thalamus was reduced and its connectivities with the default mode network (DMN) was disrupted when the participants ceased to respond to the verbal command, but noteworthy is that corticocortical connectivity was spared during unconsciousness. The authors suggest in their discussion that different depths of unconsciousness could be associated with different brain mechanisms, e.g light anesthesia and sleep could be generated by disruption of connectivity between the thalamus and the cortex, while a deeper anesthetic states or coma could possibly be generated as the corticocortical connectivities are lost (Akeju et al., 2014).

Song et al. (2017) used data from the study by Akeju et al. (2014), and reanalyzed it with the hypothesis that functional connectivity from LC neurons to brain regions that regulate arousal

would be inhibited by dexmedetomidine. They found that functional connectivity from LC neurons to the PCC, thalamus and basal ganglia covaried with the level of arousal. The PCC was the only cortical area that varied in activity as the level of arousal varied (Song et al., 2017).

Studies on unconsciousness have historically had a tendency to translate consciousness into wakefulness, and wakefulness can indeed be understood by for example describing the ascending arousal pathway and the activity of LC neurons (Mashour, 2014). Evidence for the role of the brainstem in wakefulness can, as previously mentioned, also be found in patients with severe brain damage since lesions to the brainstem will cause a person to enter a coma which is a state of no wakefulness and no responsiveness (Koch et al., 2016). But on the other hand, if the brainstem with its functions is spared but widespread damage to the cortex is the case, then the person will still be rendered unconsciousness and diagnosed to be in a so called vegetative state which is also known as unresponsive wakefulness syndrome since these patients are, indeed, fully awake but yet fail to respond to the environment in any purposeful manner and hence, brainstem functions are not sufficient for consciousness (Koch et al., 2016).

Akeju et al. (2014) and Song et al. (2017) provide good evidence that wakefulness can be lost by modulation of bottom-up mechanisms only, and that loss of response follows suit after wakefulness disappears, while cortical regions are spared. But wakefulness is not consciousness, and these can be dissociated. The most common dissociation between wakefulness and consciousness is the one we experience while we are asleep and dreaming; we are not awake and do not respond to verbal commands but we have vivid subjective experiences. Bottom-up processes are of importance for the degree of wakefulness but wakefulness is not necessary for subjective experiences. Subjective experience rather relies on top-down mechanisms (Mashour & Hudetz, 2017).

The Top-Down Mechanisms

Anesthesia-induced unconsciousness can be caused by modulation of so called top-down mechanisms in the brain. Top-down mechanisms are the activity of various cortical and thalamocortical networks that are associated with various subjective experiences, such as having thoughts or seeing a color (Mashour & Hudetz, 2017). This approach is associated with the suggestion that consciousness could arise from the connectivity of large-scale functional networks (Crick & Koch, 2003), where anesthesia-induced unconsciousness is a result of the connectivity of these networks being reduced (Deshpande, Kerssens, Sebel, & Hu, 2010). Top-down modulation is

most prominent in thalamocortical and frontoparietal networks (Mashour & Hudetz, 2017) but which of these networks are the primary reason for loss of consciousness could still be considered a discussion (Barttfeld et al., 2015), if they are even to be considered mutually exclusive (Mashour & Hudetz, 2017).

The thalamocortical pathways begin in the thalamus which, as previously noted, plays an important role for both contents and levels of consciousness, and various connections then ascend to areas across the entire cortex. For example the activity in the connections that the thalamus has with the posterior parietal cortex has shown to decrease in a linear dose-dependent manner with the anesthetic agent propofol (Stamatakis, Adapa, Absalom, & Menon, 2010). The frontoparietal networks, on the other hand, are large-scale functional brain networks that stretch from the frontal part of the brain, e.g. anterior cingulate cortex, through medial areas and back to parietal areas, e.g. the precuneus. These frontoparietal connections include networks such as the Default Mode Network (DMN) and the Executive-Control Network (ECN), that respectively are associated with awareness of oneself and awareness of the environment (Boveroux et al., 2010). In this way, loss of consciousness as result of modulated top-down mechanisms means that consciousness is suppressed as awareness of the self and the environment decreases, such as after suppression of the DMN and the ECN (Mashour & Hudetz, 2017).

Propofol and sevoflurane are two anesthetic agents that appear to primarily act on top-down mechanisms where they cause unconsciousness by disrupting functional connectivity in thalamocortical and frontoparietal networks (Mashour & Hudetz, 2017). Functional connectivity is the connectivity across various brain regions that at any given moment share functional properties, e.g a certain behavior (Mashour & Hudetz, 2018).

Boveroux et al. (2010) conducted a study where they investigated how the anesthetic agent propofol changed resting-state functional connectivity networks, such as DMN and ECN. They hypothesized that loss of consciousness would be associated with decreased connectivity in DMN and ECN. Loss of consciousness in their study was defined as loss of responsiveness, evaluated with the so called Ramsay Scale. The Ramsay Scale ranges from 1-6 where the higher the number the lower degree of responsiveness. Responsiveness in this study was assessed as the ability to follow the verbal command "squeeze my hand" for two consecutive times. The participant was considered fully awake or to have recovered consciousness if the response to the verbal command ("squeeze my hand") was clear and strong (Ramsay 2), the participant was deemed to be in mild

sedation if the response to verbal command was clear but slow (Ramsay 3), and in deep sedation if there was no response to verbal command (Ramsay 5–6). The results showed that propofol-induced decrease in consciousness correlates with decreased corticocortical and thalamocortical functional connectivity in frontoparietal networks (*e.g.* DMN and ECN) (Boveroux et al., 2010).

Sevoflurane appears to have a similar effect. For example, Palanca et al. (2015) recorded resting state fMRI in 10 healthy participants during the induction of sevoflurane. But instead of imaging brain activity at fixed behavioral states, they imaged at fixed doses of sevoflurane. The baseline state was imaged during 0% sevoflurane, which was then slowly increased from 0% up to 1.2% and continuously imaged. This study had the problem of participants moving in the MRI (further discussed in limitations) so only baseline and 1.2% could be reported. Palanca et al. (2015) also used the Ramsay Scale along with the modified Observer's Assessment of Alertness/Sedation Scale (OAA/S) to asses responsiveness. The participants were deemed unconscious at a 6 on the Ramsay Scale, which was unresponsiveness to the researchers tapping on the participant's forehead along with loud auditory stimulus, in combination with a 0 on the OAA/S Scale, i.e. unresponsiveness to painful stimuli. The results showed that during 1.2% sevoflurane, when the participant was unconscious, thalamocortical and corticocortical functional connectivity was significantly reduced in the DMN and the ventral attentional networks (Palanca et al., 2015).

Using fMRI as these two studies have done results in a very good spatial resolution, i.e the images can give quite detailed information on where in the brain activity is modulated (Gazzaniga et al., 2013). But a major obstacle when measuring functional connectivity with fMRI is that the images have a very poor temporal resolution, i.e it is hard to tell at what point in time the decreased or increased activity occurred. EEG on the other hand, has a poor spatial resolution but a good temporal resolution (Gazzaniga et al., 2013).

According to Crick and Koch (2003), a lot of what the brain is processing does not reach conscious awareness, but rather stays non-conscious and results in rapid and stereotyped actions which could be referred to the brains 'zombie mode'. This zombie mode is thought to rely on feedforward connectivity between neurons (Crick & Koch, 2003). For something to reach awareness and hence become subjective experiences, neurons need to fire in a feedback manner (Crick & Koch, 2003). Lee et al. (2009) hypothesized that this feedback connectivity would be reduced during general anesthesia. They measured EEG during baseline, unconsciousness, and recovery. They found that feedback connectivity was reduced during unconsciousness and returned

during recovery (Lee et al., 2009). A limitation with this study is that they did not titrate the propofol in a slow manner which is needed for detection of the precise mechanisms of unconsciousness (Långsjö et al., 2014) but rather as a bolus for 20 seconds (Lee et al., 2009) which could have lead to missing certain aspects of the mechanisms of unconsciousness (Långsjö et al., 2014).

Ranft et al. (2016) simultaneously recorded resting state fMRI and EEG in 16 healthy participants during the slow induction of sevoflurane, leading to both temporally and spatially detailed results. The baseline state was recorded with eyes closed lying down in the MRI while controlled for the participant naturally falling asleep. The anesthetized state was induced in a slow manner, starting with a five minute induction of 0.4% sevoflurane, followed by an increase by 0.2% every three minutes until the participant reached unconsciousness which in this study was indexed by a loss of response to the verbal command "squeeze my hand" for two consecutive times. EEG and fMRI were recorded when the dose reached 2% at which point artificial ventilation was required, and at 3% as a fixed group comparison. The dose was then increased until the EEG showed 'burst suppression' which is EEG oscillations characterized by spontaneous bursts of activity for about a second followed by a few seconds of suppressed activity, commonly seen in patients in a coma and during deep anesthetic states (Ching, Purdon, Vijayan, Kopell, & Brown, 2012). Burst suppression occurred at about 4.4% sevoflurane (Ranft et al., 2016). The results showed that the most significant decreases of activity were in the thalamic network, the left and right anterior frontoparietal network, and the dorsolateral prefrontal network (Ranft et al., 2016). This study shows that sevoflurane disrupts connectivity in anterior areas to a greater extent than posterior areas, which can continue firing despite unconsciousness having occurred (Sleigh, 2016).

Loss of consciousness is continuously associated with modulation of top-down mechanisms but it appears that if looking for the minimal set of neuronal activity, i.e. what is the least sufficient activity for consciousness to occur, then the loss of consciousness is not what to measure since these networks are still 'shut down' upon recovery from unconsciousness (Långsjö et al., 2014). What this means is that when the participants emerge from unconsciousness and are able to respond to verbal commands again, they are able to do so before thalamocortical and frontoparietal networks are active at the level of baseline (Långsjö et al., 2014).

Recovery from Anesthesia

Intuitively, one could assume that consciousness is lost as activity in some specific areas or networks, e.g DMN, is modulated and when those are passively restored to what they were before then consciousness is regained - i.e. that loss and return of consciousness are mirror phenomena. But this is not the case. Accumulating evidence indicates that the neural mechanisms involved in the loss of consciousness are not the same as the ones involved during the recovery of consciousness (Kelz, García, Mashour, & Solt, 2019). According to Kelz et al. (2019), there are two categories of studies in support of questioning this mirror phenomena-assumption, the first being that specific sleep-wake nuclei that are involved in loss of consciousness through bottom-up mechanisms are not involved in the recovery of consciousness. The second reason is that the neural mechanisms of recovering from anesthesia are lagging behind the behavioral indications of recovery, which means that the anesthetic dose during loss of consciousness is higher than during recovery (Kelz et al., 2019).

Hysteresis is the Greek word for 'lagging behind' or 'deficiency'. According to Tarnal, Vlisides and Mashour (2016) there are two components of hysteresis. The first component is the 'lagging' which in the case of anesthesia-induced unconsciousness means that changes occurring during the withdrawing of anesthetics are behind in time compared to changes occurring during the induction of anesthetics. The second component is 'rate independence' which in this case means that the relationship between inducing and withdrawing anesthetics depends on the dose during induction rather than the speed at which it is induced (Tarnal et al., 2016). Neural inertia could be the explanation of hysteresis. It is a term coined by Dr. Max Kelz which refers to the central nervous system's tendency to resist behavioral transition between different states, e.g. resisting the transition between consciousness and unconsciousness. An example of what could be a deficit neural inertia is patients with narcolepsy, who rapidly transition between awake and asleep (Tarnal et al., 2016).

There are several examples of how the neural mechanisms of induction and recovery of anesthesia-induced unconsciousness are not mirror phenomena. For example feedback connectivity during propofol peaks at different values during loss and return of consciousness (Lee et al., 2009). In dexmedetomidine-induced unconsciousness, both thalamocortical and corticocortical connectivity is lost as consciousness is lost, but when the participants recover from unconsciousness only thalamocortical activity is needed for the participants to be responsive again (Akeju et al., 2014), and it appears that specifically the thalamic connections with the PCC can be associated with recovered consciousness (Song et al., 2017). Worth mentioning is that other studies, using propofol,

failed to find a significant difference in BOLD patterns between mild sedation before the loss of consciousness and during the emergence from unconsciousness (Boveroux et al., 2010).

None the less, is it better to look for the correlates of losing or regaining consciousness? Långsjö et al. (2014) argue that the correlates of recovery better represent the minimal set of neural correlates necessary for consciousness. This is because the normal wakefulness prior to anesthesia and the primitive conscious state after anesthesia are vastly different states, and because of neural inertia the moment of recovering from anesthesia has got less neural activity than during loss of consciousness. Hence, the minimal set of neural correlates supporting level of consciousness should be studied during the recovery from anesthesia (Långsjö et al., 2014).

Långsjö et al. (2012) recorded PET during the emergence from unconsciousness in 10 participants having gotten dexmedetomidine and 10 participants having gotten propofol. The reason for using two different agents (dexmedetomidine and propofol) was to control for the confounder of different drugs acting on different mechanisms, this way the study design enabled the possibility to compare what regions were the same for both drugs. Långsjö et al. (2012) also dissociated the changes in consciousness from the global effects of the drug by combining neuroimaging with pattern analysis. Each participant had an individualized dose at which point they reached unresponsiveness that was set prior to the study. Hence, the levels of the independent variable were not the dose as in some prior studies mentioned in this paper but instead, the level of the independent variable was the degree of consciousness during; baseline, sedation, loss of response, return of response (Långsjö et al., 2012). Unresponsiveness was indexed by loss of response to the verbal command "open your eyes". The group receiving dexmedetomidine was not returning from unconsciousness due to the drug being cut off, but rather the dexmedetomidine was kept at a constant level while the participants were stirred into wakefulness (until they opened their eyes on command). The results show, contrary to studies investigating loss of consciousness, that the minimal set of neurons required to support consciousness is associated with activation of the brainstem and the thalamus, and these arousal structures subsequently functionally couples with frontal and parietal cortices (Långsjö et al., 2012). These same mechanisms are also suggested to improve arousal following chronic brain injury (Schiff et al., 2007).

Disorders of Consciousness

This section will start with clarifications of terminology, e.g what the concepts of arousal and awareness refer to, in order to provide a sufficient background for the four different diagnoses

included in this paper. Subsequently, there is a discussion on what the neural mechanisms of recovery from these disorders of consciousnes are suggested to be. Studies included in this section was unsystematically picked from highly cited reviews.

Disorders of Consciousness (DOC) is an umbrella term for various deficits in consciousness due to severe structural brain damage. Severe structural brain damage can come from either traumatic brain injuries such as after a heavy blow to the head, or non-traumatic brain injuries such as after a stroke (Laureys, Owen, & Schiff, 2004). Some patients with DOC are completely unconscious all the time while others are occasionally conscious, and some are impossible to accurately diagnose which can lead to excruciating situations for families and loved ones.

How to properly diagnose and subsequently treat DOC is poorly understood within clinical neuroscience (Di Perri, Stender, Laureys, & Gosseries, 2014) but investigations from anesthesia-induced unconsciousness could serve helpful in better diagnosing and treating patients with DOC as these two deeply unresponsive states in resemble each other both when measured with EEG (Di Perri et al., 2014) and as some mechanisms of recovery from unconsciousness in both cases are the same (Schiff et al., 2007). A foundational question in both cases of unconsciousness is the same: are these persons not experiencing anything, i.e is there nothing it is like to be these people, or do they have some kind of subjective experience? (Sanders et al., 2012). It is ethically critical to be able to answer this question (Boly et al., 2012). But the main problem in doing so remains, as the standard for diagnosing these patients is based on behavioral criteria (Boly et al., 2012) as follows in the following section of the present paper.

Arousal and Awareness

Before describing the four diagnoses included in this paper, it is important to address the subject of levels and contents of consciousness again. Because when medical doctors and clinical neuroscientists describe patients with DOC they usually do not refer to impairments in levels or contents of consciousness. Within clinical practice and studies, medical doctors and researchers have a history of rather using the words awareness and arousal, because that is what has been investigated in clinical circumstances (Laureys, 2005). Arousal conceptually resembles levels in that it is associated with brainstem functions, can occur in degrees, and serves as a prerequisite for contents or awareness. Except, arousal can be completely dissociated from consciousness in a way that levels cannot (Långsjö et al., 2014). Medical doctors do at times deal with patients that are fully aroused yet completely unconscious (Långsjö et al., 2014), which is why the word arousal, as

opposed to level, will be used in this section. Awareness reminds of contents in that it is the subjective experiences that constitute our consciousness which are associated with neocortical activity (Långsjö et al., 2014). But contents can be just about anything - sounds, smells, sights - while awareness within clinical practice rather specifically refers to internal (the self) and external (the environment) awareness, associated with frontoparietal networks such as DMN and ECN.

No arousal, no awareness: coma. The most profoundly unresponsive state within DOC is coma. Brown et al. (2010) describe patients in a coma as lying flat down with their eyes closed while appearing oblivious about the environment. They are in a deeply unresponsive state and do not exhibit responsiveness to anything, not even to vigorous stimuli such as violent shaking of their bodies. Some comatose patients may occasionally move their facial muscles or limbs, and sometimes they do react to painful stimuli with withdrawal but they exhibit no defensive mechanisms or capacity to understand where the pain is coming from (Brown et al., 2010). Coma is caused by a damaged brainstem which leads to a malfunctioning arousal system (Koch et al., 2016), but to distinguish it from temporary loss of consciousness such as during concussions where people typically exhibit similar behavior, a coma is only diagnosed after an hour of no arousal and no awareness (Laureys et al., 2004).

Present arousal, no awareness: vegetative state. There are patients who remain behaviorally unaware of themselves and their environment, just as comatose patients, but they do suddenly regain wakefulness. This diagnosis was previously known as vegetative state but recently also gets referred to as unresponsive wakefulness syndrome (VS(UWS). Laureys (2005) describes that VS/UWS is a diagnosis that often succeeds a coma, being diagnosed when the patient opens their eyes and becomes awake, starting to move their limbs and occasionally make incoherent noises but despite the seemingly conscious state the patient, per definition, is still unaware of both themselves and their environment (Laureys, 2005).

VS/URWS is caused by a (regained) functioning brainstem but damaged cortex (Koch et al., 2016). Some comatose patients gradually regain brainstem functions after 2-4 weeks which is when the diagnosis of VS/UWS can be set (Laureys et al., 2004). It is important to stress that these patients are the reasons for the dissociation between wakefulness and arousal since they are just as unaware as comatose patients but exhibit wakefulness with for example sleep-wake cycles and open eyes. After that being diagnosed with VS/UWS, the patient will subsequently be diagnosed with either Persistent or Permanent VS/UWS (Laureys et al., 2004). Persistent VS/UWS means that the

patient has been unresponsive for a month but still does have a chance of regaining awareness, so it does not imply irreversibility. If the state is deemed irreversible, the patient will be diagnosed with what is called Permanent VS/UWS. Irreversibility and hence Permanent VS/UWS is diagnosed depending on what caused the brain injury. If it was caused by a traumatic brain injury, i.e. a blow to the head, then the state will be deemed permanent after about a year. If the state on the other hand was caused by a non-traumatic brain injury, e.g. after a stroke, then the state is deemed permanent after three months (Laureys et al., 2004). During VS/UWS global metabolism is typically decreased with about 50% (Laureys, 2005) especially in medial prefrontal and inferior parietal cortices (Dehaene & Changeux, 2011)

Present arousal, fluctuating awareness: minimally conscious state. Some patients further recover from VS/UWS and enter a state of being minimally conscious. If the patient enters a state in which they are capable of behaviorally indicating, in any kind of way, that they to some degree are aware of themselves or their environment, then they are diagnosed to be in a Minimally Conscious State (MCS) (Laureys et al., 2004). Patients in a MCS can fluctuate between consciousness and unconsciousness but they have to be able to reliably showcase at least one of the following four criteria; 1) following simple commands, such as blinking their eyes twice on command, 2) in any kind of way indicating a yes or no responses, which is regarded to be successful independently of whether the response is accurate or not, 3) produce meaningful words or sentences that is not incoherent noise or 4) produce meaningful behavior that is not a reflex, for example using an object such as a comb in a meaningful way (Laureys et al., 2004). Patients who reach a MCS within the first three months post brain damage typically continue to recover into a point past MCS and even full recovery within a year from brain injury (Schiff, 2010), but some patients do remain minimally conscious for decades which motivates efforts to further investigate to what degree these patients are conscious and what treatment could be used to improve their state (Voss et al., 2006) which is what the rest of this paper will focus on. But before that, a fourth and final diagnosis should be explained.

Present awareness, but fully paralyzed: locked-in-syndrome. Locked-in Syndrome is not an impairment in consciousness but rather an impairment in motor functions. Someone in a locked-in state has got full capacity of awareness of both themselves and their environment, but they lack the motor functions to produce meaningful behavior to indicate this state of awareness. So, they have normal consciousness but they exhibit behavior which is per definition the diagnosis of being in a coma or VS/UWS (Schiff, 2010). Which is why this paper will now present how studies of

DOC have investigated consciousness in non-responsive patients, to give a background for the complexity of investigating recovery from unconsciousness in unresponsive patients.

Detecting Consciousness in Unresponsive Patients

Modern neurology has yet to better study, understand and treat disorders of consciousness. Fundamental understanding of these disorders remains unknown due to the difficulty of interpreting and distinguishing a patient's potentially conscious from non-conscious behavior, such as occasional movement of their limbs or faces (Boly et al., 2012). Misdiagnosis in this group has been estimated to be about 40% when based on behavioral assessments, with a clear tendency to underestimate the degree of consciousness and for example rate minimally conscious patients as unconscious (Schnakers et al., 2009). Modern research within this field hence aims at finding tools for assessing consciousness that are not dependent on behavior, such as brain activity that correlates with consciousness in order to better diagnose and treat these patients (Boly et al., 2012).

There are according to Boly et al. (2012) two types of paradigms to investigate consciousness during unresponsiveness in patients with DOC; active paradigms where researchers aim at finding brain activity in response to verbal commands despite a lack of behavioral response, and passive paradigms where researchers aim at finding brain activity that is automatic processing in these patients when they do not perform any tasks. Examples of both of these paradigms are two studies carried out by Owen et al. (2006) who investigated a non-communicative 23-year old woman diagnosed to be in VS/UWS for the past 5 months after a traffic accident. Their first study used a passive paradigm where they investigated the patient's automatic brain activity in correspondence to spoken sentences, and found that areas associated with semantic understanding were active as she heard the words, indicating awareness of what was being said to her (Owen et al., 2006). After establishing this possibility, Owen et al. (2006) conducted a study that was an active paradigm where they used fMRI and asked her to actively mentally imagine two different tasks when they asked her to. She was asked to either imagine playing tennis or imagine walking around in her house, two tasks that are associated with activity in different areas of the brain. She successfully followed the researcher's commands to do the mental imagery tasks and hence could be rediagnosed as conscious despite lacking the ability to behaviorally indicate it (Owen et al., 2006). Noteworthy, is that Monti et al. (2010) later found 5 more patients being able to do this out of 54 patients investigated, and were able to communicate yes-no questions with these patients where yes was one mental imagery and no was another (Monti et al., 2010).

Does this mean that the problem of who's conscious and who's not is solved? Unfortunately, no. Out of the 54 patients that Monti et al. (2010) investigated more than 5 could possibly have conscious experiences but might have been too drowsy on the day of investigation to manage to produce a response, or possibly lack the motivation to communicate with the researchers, or maybe some were conscious but unable to hear the commands spoken to them due to their brain damages. A negative outcome cannot serve as evidence of no consciousness (Owen et al., 2006). In conclusion, the challenge of knowing who's conscious and who's not remains but studies like the ones by Owen et al. (2006) and Monti et al. (2010) can help some patients in getting the accurate diagnosis.

Recovery from Disorders of Consciousness

Spontaneous recovery of consciousness in patients with DOC appears to occur slowly over long time periods, sometimes taking months or even years, with a few examples of spontaneous recovery after decades (Schiff, 2010). Recovery from VS/UWS is, just as recovery from anesthesia, associated with reactivated frontoparietal networks and these networks' connections with the thalamus (Dehaene & Changeux, 2011). Recovery from VS/UWS can happen due to structural improvement such as regrowth of white matter, but also due to therapeutic interventions such as stimulating arousal or, paradoxically, giving patients sleeping pills.

Voss et al. (2006) investigated structural regrowth of white matter in two patients that were improving from unresponsive wakefulness syndrome (VS/UWS) into minimally conscious state (MCS). The first patient had severe brain damage following a motor vehicle accident that took place in 1984. He was initially diagnosed to be in a coma but soon transitioned into VS/UWS followed by consistent improvement over the years, and he was finally diagnosed to be in MCS due to his ability to grunt and nod, which improved over the years until he could finally say the word "mom" followed by producing increasingly coherent sentences. At the time of the study, this first patient had been in MCS for 19 years and had made his first sentences eight months prior to the study (Voss et al., 2006). The second patient also suffered severe brain damage following a motor vehicle accident 6 years prior to the study and had been in MCS for about 5 years, estimated to have fluctuating consciousness due to his ability to at times have meaningful movement of one eye and one hand (grasping and letting go of objects) and follow verbal commands (Voss et al., 2006). Voss et al. (2006) used DTI to investigate white matter in these two patients and found that it

significantly increased as the patients transitioned closer and closer to normal consciousness diagnosed with behavioral criteria.

White matter mainly consists of axons which makes up tracts that are the structures mediating communication between neurons. This communication is assumed to be necessary for the production of meaningful behavior, i.e. goal-directed and communicative behavior, and is often lost in patients with DOC (Schiff, 2010). But both structural and functional cortical connectivity is typically seen to remain intact in minimally conscious patients but their condition is none the less characterized by intermittent evidence of meaningful behavior and awareness (Schiff, 2010). Schiff et al. (2007) hypothesized based on this that minimally conscious patients possibly could become more aware of themselves and their environment if these residual cortical networks got aroused from thalamic stimulation. So they implanted deep brain stimulation (DBS) in the central thalamus of a patient who had been in MCS for 6 years and found that the patient improved both cognitive abilities and functional ability to move and control limbs during DBS. The authors interpreted the results as DBS reactivating the frontal lobe's control over arousal regulation (Schiff et al., 2007), which by others has been interpreted as the thalamus having a causal role in arousal (Mashour & Alkire, 2013).

As previously mentioned, global metabolism is decreased with about 50% in VS/UWS patients (Laureys, 2005) especially in mesial prefrontal and inferior parietal cortices (Dehaene & Changeux, 2011). Something that has occasionally shown to paradoxically improve this low metabolism is the sedative drug Zolpidem, going under brand names such as Ambien and Stilnoct (Schnakers & Monti, 2017). Zolpidem is a drug usually prescribed for patients with sleep impairments such as insomnia, and it is thought to sedate the person by decreasing the inhibitory output from globus pallidus to the central thalamus and has been found to paradoxically cause patients in MCS to "wake up" (Schnakers & Monti, 2017).

Patients in MCS that successfully improve their state of consciousness or even wake up completely remain a minority among all patients tested with zolpidem, with success rates ranging from about 5-7%, and among these few patients a change in diagnosis is not always observed (Chatelle et al., 2014). But among this rare minority of patients, Chatelle et al. (2014) investigated what brain changes were associated with zolpidem-improvement in three minimally conscious patients. Chatelle et al. (2014) administered zolpidem or placebo (water) in a randomized double-blind study design. 30 minutes after the dose was given, behavioral assessment of level of

consciousness was conducted with a standardized coma scale, and after 90 minutes cerebral metabolism was investigated with PET. The researchers found that as a group, these three patients had a significant increase in glucose metabolism in bilateral superior frontal gyri and right medial frontal cortex upon zolpidem-improved behavioral response. At non-significant levels, other areas showed increased metabolism as well, such as left inferior frontal and parietal areas, and mesiofrontal cortices.

Discussion

The neural mechanisms of both pharmaceutical (anesthesia) and pathological (DOC) unconsciousness involve changes in the brainstem, the thalamus and the cortex due to either functional or structural modulation. Investigating the neural mechanisms of anesthesia-induced unconsciousness can serve helpful for the diagnosis and treatment of the poorly understood group of patients with DOC. Also, better understanding the biology of unconsciousness can help medical doctors determine whether a patient is conscious or not with the help of criteria that are not behavioral, which are inadequate.

Depending on whether level/arousal or contents/awareness is assessed, during loss or return of consciousness, different areas are more or less relevant. Although, it appears that the minimal set of neuronal activity necessary for level of consciousness to occur is primarily associated with thalamic and thalamocortical activity, as investigated in both anesthetized participants (Långsjö et al., 2012; Mashour & Hudetz, 2017) and patients with DOC (Voss et al., 2006; Schiff et al., 2007). Loss of consciousness due to DOC and anesthesia are behaviorally resembling each other, where especially people in coma and in deep states of anesthesia-induced unconsciousness are equally unresponsive. On the other hand, at a first glance they are neurobiologically divergent since anesthesia-induced unconsciousness happens due to temporary functional disruptions which can be reversed by the anesthesiologists at practically any point in time, while disorders of consciousness happens due to structural damage, meaning parts of the brain are damaged or even missing, which is not reversible in that sense.

But the neurobiological foundation needed for return of consciousness appears similar in these two groups, and according to studies included in this paper it could be associated with thalamic reconnection with various cortical areas, especially frontal regions but also the PCC. This is why anesthesia research can help in diagnosing and treating these patients. Recovery from DOC can be improved by for example structural regrowth and stimulation of central thalamus.

As cognitive neuroscience has progressed, so has the probability of patients with DOC to be accurately diagnosed (Owen et al., 2006) and treated (Schnakers & Monti, 2017). Consciousness studies using anesthesia to switch consciousness 'on and off' continue to culminate the scientific knowledge about the brain before, during, and after unconsciousness, possibly closing in on finding the neural correlates of consciousness (NCC). But one major obstacle that at the time of writing still remains is that consciousness has been and still is impossible to directly measure with scientific methods and hence; the main limitation of any study of consciousness as a state is that consciousness defined as subjective experience has to be substituted with consciousness defined as responsiveness, or other inadequate behavioral indications.

Limitations

This limitation section will present limitations of two categories, the first category is the major challenges of studies on anesthesia-induced unconsciousness, along with suggested focus for further research. The second category is the limitations of the present paper.

The major challenge when studying unconsciousness is that unresponsiveness not necessarily implies unconsciousness. This is a limitation that has not only been dedicated its own heading in this thesis but is also something that has permeated the entire paper and hence may not need to be dedicated further emphasis. Another limitation is that of study designs choosing the wrong this to measure. For example, a common occurrence in experiments investigating the neural mechanisms of anesthesia-induced unconsciousness is that the decrease of neural activity is measured during a fixed dose, e.g. at 0% and at 1.2% sevoflurane as in the study by Palanca et al. (2015). This results in the confounder of different participants being in different states of consciousness at the time of measurement due to individual reaction differences to the chosen anesthetic agent. This leads to consciousness not only being substituted with responsiveness, but also to not being what is actually measured at all (Långsjö et al., 2012). Further research needs to compare the different participants' neural mechanisms at the same behavioral state. A technical challenge for studies using methods that need the participant to be still, e.g. fMRI, is to keep participants from moving when they are anesthetized. For example functional connectivity within the default mode network (DMN) is often reduced with propofol while this is not the case with sevoflurane which, of course, could be the result of different target mechanisms of propofol and sevoflurane but it could also be because of motion artifacts (Palanca et al., 2015). Further research needs to control for eventual movement of the participants.

Due to hysteresis, further research also needs to focus on the recovery from anesthesia-induced unconsciousness more than the loss of consciousness when looking for the neural correlates of (un)consciousness. More research is needed on the minimal neural correlates of consciousness, especially on more types of anesthetic agents, as well as being conducted with multimodal approaches, e.g. both fMRI and EEG, in order to provide both spatially and temporally high resolution.

The major limitation of the present paper is that the studies included were not by any means gathered in a systematic manner, but rather picked from highly cited reviews and chosen based on relevance of the study's hypothesis and study design along with clear results, and included based on how well they fit for the topic and stated aim of the present paper. The results from the studies included were not double checked or analyzed in any way. Because of this, the generalizability of the present paper should be regarded as nonexistent. In order to motivate generalizable neural mechanisms of unconsciousness a more empirical approach needs to be undertaken, e.g. summarizing studies in a meta-analysis.

Conclusion

What the neural mechanisms of anesthesia-unconsciousness are depend on what anesthetic agent is used and what the study design measures. Various anesthetic agents target different mechanisms in the brain. Loss of consciousness due to sevoflurane-induced anesthesia is associated with significant reduction of functional connectivity in the thalamocortical network, the ventral attentional networks, and default mode network (DMN) (Palanca et al., 2015), as well as decreased activity in the left and right anterior frontoparietal network, and the dorsolateral prefrontal network (Ranft et al., 2016). Loss of consciousness due to propofol-induced anesthesia correlates with decreased corticocortical and thalamocortical functional connectivity in frontoparietal networks (Boveroux et al., 2010). On the other hand, loss of consciousness due to dexmedetomidine-induced anesthesia is associated with modulation of sleep generating nuclei in subcortical areas (Akeju et al., 2014). But, since the brain shows a tendency to resist transition between behavioral states, a phenomenon known as neural inertia, the minimal set of neural activity needed for consciousness to exist is rather found during the return of consciousness after the anesthetic agent has been cut off (Långsjö et al., 2014). Studies investigating the mechanisms of return of consciousness has found that consciousness arises as reactivation of the brainstem and the thalamus, and these arousal structures subsequently functionally couples with frontal and parietal cortices (Långsjö et al., 2012).

These same areas are investigated to be of importance during the recovery of consciousness due to structural brain damage having lead to DOC (Schiff, 2010). Regrowth of white matter is associated with improvement of vegetative state/unresponsive wakefulness syndrome (Voss et al., 2006), stimulation of the central thalamus causes patients in minimally conscious state to improve (Schiff et al., 2007). Some minimally conscious patients paradoxically improve by receiving a dose of the sedative drug zolpidem (Schnakers & Monti, 2017; Chatelle et al., 2014)

Better understanding the neural mechanisms of recovery from anesthesia-induced unconsciousness could serve helpful in the diagnosis and treatment of patients with DOC, but further research is needed. Further research should focus on the return of consciousness due to neural inertia, while using various anesthetic agents due to them targeting different mechanisms, while recording brain activity with multimodal approaches to achieve both temporal and spatial high resolution.

Word count: 10 514

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