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Consciousness, Anesthesia and Brain Resting State Networks

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Consciousness is a great mystery to science. Despite several attempts, none of the current theories have managed to explain how and why it exists. Theories struggle with fundamental philosophical questions, such as the hard problem, that contests how something mental, like consciousness, can be explained by physical phenomena such as neural activity. Modern neuroscientific study of consciousness puts aside this and a few other yet unreachable questions. It focuses on finding the neural correlates of consciousness (NCC) comprising the physical phenomena, which correlate with certain aspects of consciousness. In the NCC studies, consciousness is usually taken to have two aspects: the states of consciousness, encompassing awake, dreaming, and unconscious states, and contents of consciousness, such as an experienced perceptual stimulus.

Experimental anesthesia and functional brain imaging are essential tools for the search of the NCC. Anesthesia offers a reliable and reversible method to alter the subject's state of consciousness. The brain function during these altered states of consciousness can be measured with functional imaging methods, such as functional magnetic resonance imaging (fMRI). It measures neuronal activity via a blood oxygen level dependent (BOLD) signal. Functional connectivity analysis of the BOLD-signal can be used to explore the organization of spatially distinct brain areas into functional networks, which are associated with specific cognitive functions such as attention control and emotional regulation. Recently, several studies have shown that changes in functional connectivity between and within these networks are also associated with altered states of consciousness induced by anesthetic drugs. This review will cover the essential questions and methodology of current exploration of neural correlates of states of consciousness, focusing on the resting state networks and the use of fMRI and experimental anesthesia as research tools. Effects of different anesthetics on these networks are also compared.

Different anesthetics used in experimental anesthesia have quite distinct pharmacological mechanisms of action, even though the induced brain functional connectivity patterns resemble each other. Propofol-induced unconsciousness is mediated either from corticocortical or thalamocortical disconnection. The nonspecific thalamic nodes, related to arousal and distribution of information, may have an important role in propofol-induced unconsciousness. Dexmedetomidine has similar patterns in connectivity changes as propofol, but the connectivity between deeper brain regions and thalamus remains less affected, possibly explaining the easier arousal from dexmedetomidine-induced unconsciousness. Ketamine increases the overall functional connectivity but disrupts the connectivity in the higher-order networks of the brain inducing “dissociative anesthesia”. The role of thalamic functional connectivity during ketamine anesthesia has not been studied and would be an interesting subject for future studies.

Asiasanat: tietoisuus, anestesia, lepotilaverkostot

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1 INTRODUCTION

Consciousness as a state we experience constantly when awake and while dreaming, is still a great mystery to science. There is no acknowledged explanation for how and why it exists even though numerous theories of consciousness have been proposed. Most of them struggle with a few fundamental questions. The hard problem is probably the most famous, contesting how something mental, like our thoughts or consciousness, can be derived from a physical object such as the brain.

Neuroscientific study of consciousness has put these complicated questions aside for now to focus on a scientifically more straightforward task of finding the neural correlates of consciousness (NCC). They are the minimal neuronal mechanisms that jointly enable conscious experience (Koch *et al.*, 2016). NCC, as well as the whole concept of consciousness is divided into contents and states of consciousness. Contents of consciousness are the different components that we experience in our consciousness, such as experienced visual or auditory stimuli. Visual processing has especially been studied to understand the neural correlates of the contents of consciousness. The state of consciousness refers to being awake, dreaming, or being unconscious and it has been studied by measuring the effects of experimental anesthesia and natural sleep for example.

For measuring brain activity during altered states of consciousness, three imaging modalities are commonly used in the search of NCC: functional magnetic resonance imaging (fMRI), electroencephalogram (EEG), and positron emission tomography (PET) imaging. These modalities offer a non-invasive way to trace alterations in brain activity. Areas of the brain that have temporally correlated activity are considered to be functionally connected. With further analysis, functionally connected networks can be revealed. These networks are called resting state networks as they can be studied also when the subject is at rest without any specific task. They have different functions, for example in cognitive processing and in regulating attention. Recent studies also link functional connectivity between and within the networks to altered states of consciousness induced by anesthetic drugs. Resting state networks come across as promising targets for finding the NCC, and the answer to understanding how brain function relates to consciousness might be in understanding the function and relation

of these networks. This review will cover the essential questions and methodology of current exploration of the neural correlates of the state of consciousness focusing on the resting state networks and the use of fMRI and anesthesia as research tools.

2 FROM CONSCIOUSNESS TO ITS NEURAL CORRELATES

Consciousness is the function of the mind which allows us to experience the world from a subjective point of view. Such experiences include the redness of an apple and understanding the phrases we hear. It also allows us to wonder about the concept of consciousness and speculate the nature of the whole concept of consciousness. Countless philosophers and scientists have formed and tested numerous theories of consciousness, but none of them has been acknowledged as an all-encompassing theory that explains its fundamental nature. The main problem with explaining consciousness is how to link and explain the interaction of mental experiences and their physical substance. *Hard problem*, coined by Chalmers (1996), questions how anything physical, such as neuronal activity in the brain, can give rise to a totally distinct phenomenon of subjective experience like the redness of an apple. *Explanatory gap*, coined by Levine (1983), associates the hard problem. It underlines the gap between neuronal activity and subjective experiences by asking if we can ever determine what happens in between. Some have declared these questions unsolvable. (Revonsuo, 2010; Långsjö, Revonsuo and Scheinin, 2014)

2.1 Philosophical theories

Monistic philosophical theories argue that the universe is made of one substance: physical (materialism), mental (idealism), or neither of these (neutral monism). Theories concerning consciousness are *eliminative materialism* that tries to eliminate the whole uniqueness and mental side of conscious experiences to some unsurprising mechanical brain functions. *Reductive materialism* accepts consciousness as a mental phenomenon but argues that it can still be reduced to a physical process in the brain. *Microphysicalism* claims that everything in the world can be reduced into so small basic blocks that will themselves explain both the laws of physics and the mental world. (Revonsuo, 2010)

Emergent materialism is the opposite of reductive materialism. The main statement can be compared to organisms that create a whole that is more than the sum of the different cells themselves. Also, consciousness could somehow emerge from the brain's single neurons working together. Emergent materialism has two components: *weak emergence* that hopes we can one day figure the brain function so precisely that the mystery of emerging consciousness vanishes. *Strong emergence* argues that the relationship between neurons and consciousness is inexplicable. Emergent materialism is in principle a viable theory but may not be more than wishful thinking for future neuroscience. (Revonsuo, 2010; Långsjö, Revonsuo and Scheinin, 2014)

Functionalism is a neutral monistic theory that treats consciousness as complex causal relations between given entities or simplified as the software of the brain. This way there is no need to determine physical or mental origin for consciousness. It is just a state of function in an information-processing system. Global workspace theory is an example of functionalist theory where subjective information processed in the brain creates the stream of consciousness. (Revonsuo, 2010; Långsjö, Revonsuo and Scheinin, 2014)

Panpsychism is another neutral monistic theory consisting of a view that every single atom in the world contains something mental. This way consciousness is created from the amount of material and everything from a rock to a single cell would have some level of consciousness. (Revonsuo, 2010)

Currently one of the most promising theories of consciousness associates functionalism and panpsychism in *integrated information theory* (IIT) created by Giulio Tononi *et al.* (2016). It claims that consciousness consists of the complexity of integrated information and in the human brain, with extremely high levels of complexity, consciousness also becomes highly developed. This theory, however, has its weaknesses: how can unconsciousness exist when there is always some information and complexity in the brain. The explanatory gap between mind and matter remains and the theory also allows sophisticated machines to gain consciousness to some extent. (Revonsuo, 2010; Långsjö, Revonsuo and Scheinin, 2014)

2.2 Neural correlates of consciousness

With the difficulties of answering the hard problem and the explanatory gap, scientists turned the study to focus on more empirical and experimental ways. After the first case reports in the 1960s about surgical and brain-damaged patients with some associations to consciousness, the relationship between mind and brain started to gain interest. In the 1990s neuroscientists started first proper empirical and experimental studies to find the neural correlates of consciousness (NCC), referring to minimal neural mechanisms that are jointly sufficient for a specific conscious experience. (Långsjö, Revonsuo and Scheinin, 2014; Koch *et al.*, 2016; Seth, 2018)

At first, the study focused mainly on the contents of consciousness and visual consciousness was the most studied subject; what happens and in what order in the visual cortex, when for example a flash of light or an image is brought into our consciousness. The focus was mainly on the cortex of the brain. (Långsjö, Revonsuo and Scheinin, 2014). A separate strand started focusing the study on the state of consciousness by examining the transition of different states utilizing sleep, brain-damaged patients, and anesthesia. The goal was to find the core neural network that enables the state of consciousness per se. (Långsjö, Revonsuo and Scheinin, 2014; Seth, 2018)

2.3 Definition of consciousness

Concept of consciousness includes more than the state of being awake as it generally may be understood. According to Hudetz (2008), consciousness is a subjective experience of internal or external stimuli and one's own existence in time and space. Among researchers, the current concept of consciousness is even wider, a vague superordinate heading covering contents of consciousness and different and altered states and types of consciousness (Långsjö, Revonsuo and Scheinin, 2014).

A generally used division of the whole concept of consciousness is the distinction between *states* of consciousness and *contents* of consciousness. The state of consciousness refers to the background state of the brain that allows us to have any subjective experiences i.e.contents of consciousness. Different states of consciousness are for example being awake, dreaming or unconsciousness. The contents of consciousness refer to the specific qualitative and subjective experiences

perceived in the conscious state, such as a seen image and a heard tune. (Långsjö *et al.*, 2012; Långsjö, Revonsuo and Scheinin, 2014)

The state and contents can also be divided further. Nowadays commonly used division of the state of consciousness includes connected and disconnected consciousness and unconsciousness (Figure 1). *Connected consciousness* allows conscious perception of external stimuli (visual, auditory, etc.) and internal awareness (inner speech, mind-wandering, and autobiographical memories). Explicit and implicit memories are possible. When anesthesia deepens and the subject falls asleep, there may follow a state of *disconnected consciousness*, e.g. dreaming. This includes conscious experiences without perception of the environment. In a disconnected conscious state, the subject has internal awareness, but no awareness of the external world. Conscious sensory processing can happen (seeing colors and smelling something for example), but it is not related to the external world. Memories are also possible in this state. The most commonly expected anesthetic state is *unconsciousness*, defined as inability to achieve any subjective experiences. All responses in this state are non-voluntary and imply no conscious connection to the environment. Sensory processing is possible, but it is not accessible by consciousness. (Bonhomme *et al.*, 2019)

		Disconnectedness	
	Connected consciousness	Disconnected consciousness	Unconsciousness
Awareness to external stimuli	Yes	No	No
Behavioral responsiveness	Yes	No	No
Subjective experiences	Yes	Yes	No

Figure 1. | Different states of consciousness (Scheinin *et al.*, 2021).

A clinically straightforward way used to divide consciousness is *awareness* and *arousal*. Awareness refers to all the contents of consciousness creating a conscious experience. It can be divided into self- and external awareness, and it is dependent on a sufficient level of arousal, i.e. level of consciousness. Clinically awareness is measured as the ability to communicate, follow orders, or localize pain to show that

the subject is connected to the environment. Arousal, on the other hand, refers to the base level of consciousness that exists, if the subject for example opens eyes for a loud noise or painful stimulus. (Boly *et al.*, 2008; Hudetz, 2008; Heine, Soddu, Gomez, *et al.*, 2012; Långsjö, Revonsuo and Scheinin, 2014). Awareness and arousal are usually positively correlated, such as falling asleep, when arousal starts to decrease so does awareness. However, REM sleep is an exception when there is high awareness but low arousal. (Boly *et al.*, 2008; Heine, Soddu, Gomez, *et al.*, 2012)

3 USING ANESTHESIA AS A TOOL TO STUDY THE NEURAL CORRELATES OF CONSCIOUSNESS

Modern general anesthesia is based on the synergy of different pharmacological substances. The idea of this balanced general anesthesia was introduced by John Lundy in 1929 and it consisted of narcosis, amnesia, analgesia, and immobility that can be achieved without deep levels of the central nervous system (CNS) depression. (Bailey, 2001). Anesthetic drugs induce unconsciousness and amnesia. Some of them are mildly analgetic but in balanced general anesthesia, opioids are commonly used to prevent painful stimuli. Immobility is created with a muscle relaxant to ensure desirable working conditions for the surgeon. (Olkkola *et al.*, 2020)

The narcotic features of anesthetic drugs can also be used in experimental anesthesia to alter the state of consciousness reversibly and reliably. They offer an ideal way to study the neural correlates of the states of consciousness and they are a necessary addition to the methods of natural sleep and disorders of consciousness. With the use of experimental anesthesia, the brain’s neural activations and deactivations can be studied reliably and repeatedly during the loss (LOC) and the return of consciousness (ROC). (Långsjö, Revonsuo and Scheinin, 2014; Bonhomme *et al.*, 2019)

3.1 Unconsciousness during anesthesia

Concerning the concept of studying consciousness as a state, especially with anesthetic drugs, there is a fundamental challenge of how to precisely define the subject's state of consciousness. Consciousness itself can not directly be measured

and thus the subject's state of consciousness has commonly been tested by measuring the loss of responsiveness: the consciousness is regarded as lost when the motor responses to commands end. However, this requires motivation and co-operation. Memory trace is another way to verify that the patient was properly sedated during anesthesia. However, this method also has its limitations as the anesthetics cause amnesia even with sedative doses and intraoperative awareness might happen even though there is no explicit memory from it. (Hudetz, 2008; Långsjö, Revonsuo and Scheinin, 2014)

When responsiveness is used as a measurement for consciousness, a sedated subject might not be motivated enough to answer the question even though the level of consciousness is sufficient. Also, the voluntary motor process responsible for answering might be more affected by the anesthetic than the sensory-perceptual process responsible for awareness leading to clinically noted unconsciousness. This is because the exact mechanism of anesthetic actions on different neuronal areas is not known. Also, patients with akinetic mutism or locked-in syndrome can be fully conscious without the ability to express it. (Hudetz, 2008)

Means to measure consciousness without the need for co-operation have been developed. EEG applications, such as BIS, PSA, Narcotrend, and Entropy are widely used in normal surgical anesthesia. These methods have been proven with large patient populations but still, fail to provide an explicit and instant assessment of consciousness. They mostly rely on the dominance of high versus low-frequency content in EEG. (Hudetz, 2008). Also, fMRI has been used to determine consciousness: In a case report by Owen *et al.* (2006) a subject in clinically vegetative state activated the same brain regions as the reference group when they heard stories. Also, corresponding willful activations were observed when asked to for example imagine playing tennis, suggesting that the patient was conscious. Qiu *et al.* (2017) studied the patterns of resting state networks to predict patients' arousal from comatose state and found common factors for predicting consciousness to return.

The last interesting factor to consider is the relation of consciousness to memory. According to Hudetz (2008), there might be a chance that unconsciousness under moderate levels of anesthesia might be only because of amnesia from anesthetics. Consciousness itself might be present, but all the conscious experiences are just

forgotten as they emerge as if they were never even recorded. Sanders *et al.* (2012) researched the subject with isolated forearm technique (IFT), where a cuff is used to prevent muscle relaxant from paralyzing the patient's arm and provide a way for communication during anesthesia. They executed a Medline search, leading to the discovery that in up to 37% of the cases there was a positive response in IFT during anesthesia. The incidence of anesthesia awareness with explicit recall of the surgery is only 0,2% (Sandin *et al.*, 2000), suggesting that connected consciousness during anesthesia, measured with IFT, is more common than expected.

3.2 Different anesthetic drugs

Anesthetic drugs have developed far from the first public demonstration of ether-anesthesia in 1846 and nowadays there are many options to choose the best suitable for the subject. All anesthetics have their characteristic effects on how they affect consciousness and brain function. Their mechanisms of action, however, are not quite completely understood. The general theory of an anesthetic to induce LOC is that the molecules bind with certain proteins, receptors, and ion channels in neuronal synapses. The effects they have on these targets vary significantly but the neuronal activation/deactivation patterns are quite similar. (Franks, 2008)

All anesthetics affect generally the whole brain's neurons. There is no consensus of a common pharmacological mechanism or a specific location for anesthetic drugs to induce unconsciousness. However, some important areas that anesthetics have an effect on are the thalamus and functional networks of the forebrain in the parietal-cingulate-precuneus region. On the network level the effect that anesthetics have on functional connectivity differs depending on the agent, dose and network studied. The anesthesia-induced LOC is generally considered to be a disruption of higher-order cortical information integration. (Franks, 2008; Hudetz, 2012). In this article three intravenous anesthetics, propofol, dexmedetomidine, and ketamine are reviewed in detail.

3.2.1 GABAa receptor:

The most common anesthetic method to induce loss of consciousness is by potentiating the activity of inhibitory gamma-amino-butyric acid (GABA) in pentametric

GABAa receptors, found throughout the CNS. It is considered to be the main mechanism of action with propofol, thiopental, etomidate, and volatile anesthetic agents (e.g. sevoflurane, isoflurane, and desflurane). They potent the GABA-induced Cl- currents and with higher concentrations may also activate the receptors directly. Of all anesthetics, only ketamine, xenon, and cyclopropane have little or no direct effect on GABAa-receptors. (Franks, 2008; Långsjö *et al.*, 2012; Olkkola *et al.*, 2020)

Propofol:

Propofol is a commonly used intravenous anesthetic. Its pharmacological mechanism of action is considered mainly to be mediated through GABAa-receptor complex activation that prolongs inhibitory postsynaptic currents and increases inhibitory synaptic transmission. (Franks, 2008)

It is non-soluble to water and must therefore be used as an emulsion. It is widely distributed and has fast clearance, so a continuous infusion or repeated boluses are needed to keep the subject sedated. The induction dose of healthy adults is 2-2,5mg/kg causing LOC in about 30 seconds. The recovery of consciousness happens also fast in 5-10 minutes when the concentration in blood is around 1-2µg/ml. In clinical practice, anesthesia may be maintained with a target-controlled infusion (TCI) pump. It calculates the desired cerebral concentration, which can be individually titrated with computer models. (Olkkola *et al.*, 2020)

Propofol causes apnea by reducing the hypoxic and hypercarbic breathing reflexes. It also reduces blood pressure and cerebral perfusion depending on the dose by vasodilatation and direct cardiac effect. Pressure is also decreased in the eye and the skull which is useful in certain situations. Propofol's analgesic EC50 is weak, with concentration up to 16µg/ml. It causes amnesia with sub-anesthetic doses and less postoperative nausea than other anesthetics. Propofol is metabolized mainly in the liver to inactive glucuronides and sulphate conjugates that are excreted into urine. (Olkkola *et al.*, 2020)

3.2.2 NMDA receptor:

Another target to pharmacologically induce unconsciousness is to inhibit the action of glutamate. Glutamate is an excitatory neurotransmitter, that has many receptors in the CNS but for anesthetic effect, the N-methyl-D-aspartate (NMDA) receptors are considered most important. These receptors also mediate spinal cord synaptic transmission and provide neuroprotection. (Franks, 2008; Långsjö, Revonsuo and Scheinin, 2014)

Ketamine:

Ketamine is an NMDA receptor antagonist, and its main pharmacological mechanism is blocking the excitatory NMDA-receptors non-competitively. It might also have effects on opioid or opioid-like receptors especially with higher concentrations, but it does not seem to have a direct effect on the GABAa receptor-complex. (Franks, 2008)

Ketamine is an interesting anesthetic drug as the effects it has on the brain are almost inverse compared with other anesthetics. Ketamine raises the brain's metabolism and perfusion, especially with sedative subanesthetic levels. It is the only anesthetic that does not cause global depression in the cerebral blood flow (CBF), and it is also hemodynamically neutral, analgesic, and generally does not cause apnea. (Olkkola *et al.*, 2020)

Ketamine induces loss of responsiveness with a bolus of 0,5-1,0mg/kg in 30-60 seconds. For maintenance, the dose is about half of the induction dose every 10-15min or a continuous infusion of 0,5-3,0 mg/kg/h. The return of connected consciousness happens in 5-15min and is due to redistribution. It is a racemic compound, and its S-enantiomer binds NMDA-receptor 4-5 times more eagerly than R-enantiomer and delivers the anesthetic and analgesic effects. (Olkkola *et al.*, 2020)

To cause unconsciousness, ketamine is suggested to create a sensory block to the brain's association tracts so that the subject goes into dissociative anesthesia and sometimes to a cataleptic state when the eyes are open and breathing and reflexes remain normal. Similar behavioral abnormalities have been reported with other NMDA receptor antagonists. (Långsjö *et al.*, 2005; Franks, 2008; Olkkola *et al.*, 2020)

3.2.3 Alpha-2 adrenoceptor:

Alpha-2-agonists are sedative compounds that can also be used as anesthetics. They are sympatholytic, anxiolytic, and analgesic. They are also used to prevent the rise of blood pressure during intubation for example. Their effects can be blocked by alpha-2- antagonists. (Olkkola *et al.*, 2020)

Dexmedetomidine:

Dexmedetomidine is a specific and selective alpha-2 adrenoceptor agonist. It can be used in short sedation, but it is not recommended to use in the induction or maintenance of anesthesia. For sedation, the dose is 1μ/kg in 10-20min and after that continued according to the response (0,2-0,7μg/kg/h). The distributive half-life is around 6 minutes, and the half-life of the elimination phase is two hours. Dexmedetomidine is metabolized in the liver. (Olkkola *et al.*, 2020)

Dexmedetomidine induces anesthesia similarly to normal sleep by mainly activating the alpha-a2-receptors in locus coeruleus (LC) that inhibit the sympathetic nervous system's noradrenaline release in ventrolateral preoptic nucleus (VLPO). This activates inhibitory GABA and galantamine mediated tracks leading to the loss of consciousness. Also, hypothalamic sleep pathways are suggested as the mechanism of action. Dexmedetomidine has a unique feature that the subject can be woken up from pharmacologically deep sedation with a loud noise for example. (Franks, 2008; Olkkola *et al.*, 2020)

4 FUNCTIONAL MAGNETIC RESONANCE IMAGING AND BRAIN RESTING STATE NETWORKS

To find the NCC, a method to measure brain activity is essential. None of the current modalities can measure neuronal activity directly, but it can be seen via a secondary phenomenon, such as electric current, metabolic activity, or changes in blood flow. Electroencephalogram (EEG) uses electrodes on the skull to measure electrical

changes caused by neuronal firing. Positron emission tomography (PET) is an imaging method that utilizes radioactive tracers such as fluorodeoxyglucose (FDG) that accumulates to the areas in the brain where metabolism is high. Functional magnetic resonance imaging (fMRI) is an application for magnetic resonance imaging (MRI) that measures neuronal activation via altering blood flow and oxygen-levels of hemoglobin.

4.1 Basics of MRI and fMRI

Magnetic resonance imaging is generally the best modality for anatomic brain imaging. It has excellent tissue contrast which allows it to precisely define brain structures and anatomical connections (Valanne and Soinila, 2015). Its spatial resolution is in the millimeter level (Boly *et al.*, 2008). With some modifications, it can also measure the functional signal, with temporal resolution of around a second, or with echo-planar up to 20-100ms (Poustchi-Amin *et al.*, 2001).

The image acquisition is based on the features of an atom nucleus in a magnetic field when excited with a resonating radiofrequency pulse, hence the original name of nuclear resonance imaging. The most commonly used atom is hydrogen (H) and the image contrast on some occasions is created from the different concentrations of hydrogen atoms in the tissue. (Lipton, 2014)

4.2 BOLD-contrast

In fMRI, the functional component comes from blood oxygen level dependent (BOLD) signal. Hemoglobin molecule has different magnetic properties when it has oxygen in it (diamagnetic oxyhemoglobin) versus when it has released the oxygen to tissue (paramagnetic deoxyhemoglobin). A clear dip in the BOLD signal can therefore be seen when the oxygen is consumed. After the initial dip, there is a compensatory peak in the signal when fresh blood and oxyhemoglobin are carried in place after 4-6 seconds. With this known behavior of the signal, it is possible to determine where the neurons consume oxygen and are active. (Lindquist and Wager, no date; Buxton *et al.*, 2004; Liu, 2013) Similar regional brain activation to similar tasks are seen both in BOLD-signal and EEG, confirming the neural origin of the BOLD-signal (Tagliazucchi *et al.*, 2012).

4.3 Weaknesses of fMRI

Like all current functional brain imaging modalities, also fMRI has its weaknesses. Two main problems are the signal-to-noise ratio and relatively slow speed of image acquisition, both resulting from the core mechanism of MRI. The signal-to-noise ratio of fMRI is relative to the temporal resolution and normally when acquiring anatomical images many repetitions of the same slice are made to better average the significant signal from noise, making the scans last even hours. Tracing a fluctuating brain activation with BOLD signal, however, needs fast enough image acquisition, around twice as fast as the fluctuations, for a satisfactory estimate. This means that the fast imaging techniques cannot use repetitions of a slice and the signal-to-noise ratio of the BOLD signal remains weak. Repetitions can be however made with the study design such as the subject repeats the task multiple times during imaging protocol to get a good average and contrast. Also, group analysis is a viable option to enhance the result. In group analysis, standardized subjects are scanned in a similar setting, and with normalization enhanced BOLD data can be received. (Lindquist and Wager, no date). Noble *et al.* (2017) showed that group analysis made with data from multiple sites and with different scanners is reliable enough for the current studies.

The slow speed in image acquisition creates noise to the signal from subjects' involuntary movements. To counter this, all imaging acquisitions need to be preprocessed. Motion correction is used to get rid of the small involuntary movements as well as cardiac pulsation and respiratory cycles. Different tissue types like white matter and cerebrospinal fluid (CSF) might create noise and need to be preprocessed. Also, variances in hypercapnia or oxemia create noise to the signal and can be compensated with artery spin labeling (ASL) for example. (Lindquist and Wager, no date; Liu, 2013; Jann *et al.*, 2016). The scanner itself creates a considerable amount of noise in the result, but by trying to remove it totally, also some significant signal might be lost. (Lindquist and Wager, no date; Långsjö *et al.*, 2012; Liu, 2013; Jann *et al.*, 2016). Also, the scanner background noise (SNB) affects the subjects: Benjamin *et al.* (2010) noticed that areas in the dorsal medial prefrontal cortex were more activated when subjects were told to either focus or ignore the SNB compared to when instructed just to lay in the scanner.

In conclusion, some of the flaws in fMRI can be overcome with good study designs, sufficient preprocessing, and group analysis, but in the end, fMRI is compromising with sufficient fast acquisitions versus signal-to-noise ratio. (Långsjö *et al.*, 2012)

4.4 Functional connectivity

The idea of functional connectivity was developed in the ’80s by observations in EEG when coherencies were found between hemispheres and across cortical regions. (Rosazza and Minati, 2011). Functional connectivity is defined as temporal correlations or synchronization in neural activity between spatially remote neurophysiological events (Friston, 1994; Rosazza and Minati, 2011). Generally, it has been used to describe the organization, interrelationship, and integrated performance of different regions of the brain (Rogers *et al.*, 2007). It can be studied with different modalities. In fMRI, the functional connectivity is measured from low frequency (<0,1Hz) BOLD-signal fluctuations observed throughout the brain (Rosazza and Minati, 2011). Functional connectivity does not explain the direction or influence of the connections, but with additional models, effective connectivity can be derived from the same data. (Friston, 1994; Bonhomme *et al.*, 2019)

The simplest method to study functional connectivity is called a seed-voxel-based approach. It uses a selected region of interest (ROI) and compares its activation over time to the whole brain’s activations. Functional connectivity can be analyzed from the temporal correlation of the activity in the ROI and other areas of the brain. A separate analysis of frequency and phase of these correlating activations can be made to specify the activations functional connectivity strength for example. (Biswal, 2012; Heine, Soddu, Gómez, *et al.*, 2012). A weakness of seed-voxel-based approaches is that the ROI and threshold must be determined before the analysis, and they have significant effects on the result. ROI selection is especially important in group analysis where a wrongly determined ROI can alter the detected functional connectivity remarkably (Sohn *et al.*, 2015).

Independent component analysis (ICA) is a more sophisticated data-driven method that can analyze the whole brain at once and find functionally connected areas without pre-determined ROIs. It divides the dataset from the brain scan into maximally statistically independent components, separates the different sources from the signal,

and creates a visualization of these components and their sources. Therefore, cardiac noise or involuntary movement, for example, can easily be discarded. However, the results from data-driven methods are more difficult to interpret because it does not offer any classification or ordering of the components. Usually, the easiest way to interpret ICA results is by a visual inspection, but this is dependent on the researcher and the reproducibility might be inaccurate. Also determining the number of significant components may create errors; If the number of components is too high, the functionally connected networks may be divided and on the other hand, these areas can merge into each other if the amount of components is too low. (Biswal, 2012; Heine, Soddu, Gomez, *et al.*, 2012). Solutions for these practical problems have been proposed in a form of probabilistic ICA (Boly *et al.*, 2008). Intrinsic connectivity distribution (ICD) is a promising data-driven method that does not rely on pre-defined seed regions or connectivity thresholds (Qiu *et al.*, 2017).

In comparison, the seed-voxel-based methods and ICA create similar results. The better suitable of these is generally determined by the purpose of the study: Seed-voxel-based analyses are good at testing hypotheses such as what areas activate with a certain region of interest when waking up from anesthesia. ICA is good at mapping and visualizing functionally connected areas in certain states of consciousness for example. (Rosazza and Minati, 2011). If effective connectivity needs to be measured, Granger causality (GC) or dynamic causal model (DMC) can be used. (Bonhomme *et al.*, 2019).

4.5 Brain resting state networks

The first ideas of the brain being constantly active come from the 1920's EEG-studies. In the '50s researchers noticed that solving a complex arithmetic problem did not increase the global cerebral metabolic rate significantly. Later it was measured that task-evoked regional signals increase the brain metabolism by only around 5% compared to the resting state. The interest in studying the brain at rest grew on the basis that there must be something significant happening with the intrinsic activity because it takes the majority of the energy that the brain spends. (Boly *et al.*, 2008)

The discovery of brain resting state networks happened accidentally. In the early fMRI studies when the researchers were trying to get rid of some of the background noise of the MRI scanner, a coincidental discovery of slow (<0,1Hz) coherent spontaneous

fluctuations originating from remotely located brain areas was made. When analyzed, these slow spontaneous BOLD fluctuations formed functionally connected networks. (Långsjö, Revonsuo and Scheinin, 2014) The coherent fluctuations in the fMRI BOLD signal correlate with areas that have known functional similarities and it was understood that the brain's neural populations that share a functional structural purpose, defined as nodes, form a functionally connected network when they share a common purpose with other nodes. (Sohn *et al.*, 2015)

Later, the globally strongest hubs of functional connectivity in resting state fMRI were found in the areas of default mode network (DMN) and the sensory cortices (visual cortex and posterior cingulate/precuneus). Other commonly studied networks are the executive control network and salience network (Figure 2). (Tomasi and Volkow, 2011; Heine, Soddu, Gómez, *et al.*, 2012; Långsjö, Revonsuo and Scheinin, 2014)

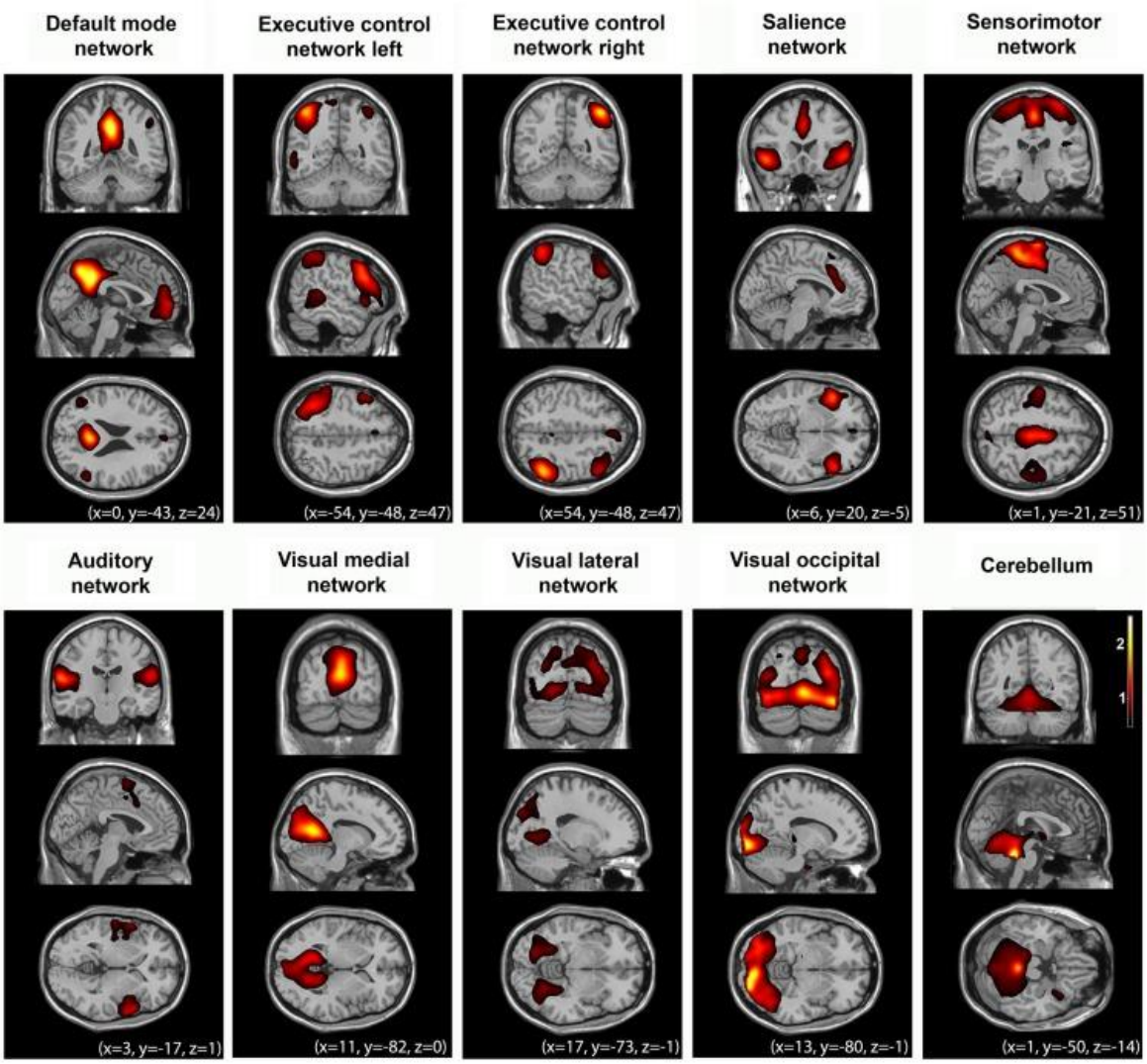

Figure 2. | Functional magnetic images of resting state networks. Image: (Heine, Soddu, Gomez, *et al.*, 2012)

4.5.1 Default mode network:

The first hints of default mode network (DMN) come from PET studies when researchers discovered unexplained deactivation in certain brain areas during active tasks compared to passive tasks like mind-wandering/eye fixation. Later the network was identified with fMRI. Its functions and more precise activations were understood better than just being “task-negative”. It is activated by default, without any specific task, hence the name default mode network. It is the most studied of the resting state networks, perhaps because it does not require much for the subject. (Rosazza and Minati, 2011; Heine, Soddu, Gómez, *et al.*, 2012; Långsjö *et al.*, 2012) DMN’s features are coherent activity that emerges principally under resting conditions. It has been observed across different states of consciousness in humans and other primates and is influenced by the characteristics of the task performed just before the scan. (Rosazza and Minati, 2011; Heine, Soddu, Gomez, *et al.*, 2012).

DMN consists of areas involving the precuneus/posterior cingulate cortex (PCC), mediofrontal/anterior cingulate cortex (ACC), and temporoparietal junction areas. The areas forming the DMN have the highest structural and functional connectivity suggesting that It uses the most direct structural connections of all the networks (Horn *et al.*, 2014). DMN can be mapped using the PCC as ROI. PCC is the most interconnected node and thus considered especially important for the network. (Heine, Soddu, Gomez, *et al.*, 2012)

DMN generally is suggested to be involved in self-referential processing including inner speech, mind wandering, stimulus-independent thoughts, social cognition, introspection, and integrating cognitive processes (Långsjö *et al.*, 2012). PCC is involved in autobiographical memory while anterior parts of the network associate more with the inner self (Heine, Soddu, Gómez, *et al.*, 2012). DMN is observed more active during passive cognitive state and it relatively de-activates during tasks requiring focused attention for example (Rosazza and Minati, 2011). The network can be divided into smaller components, suggested responsible for the different tasks of DMN, by measuring anticorrelations within the DMN (Uddin *et al.*, 2009). The connectivity of DMN is also noticed to predict recovery of consciousness from altered states of consciousness (Qin *et al.*, 2015).

4.5.2 Executive control network

Executive control network (ECN), sometimes referred to as frontoparietal network (FPN), is a task-positive network that activates during goal-oriented cognitive tasks and goal-directed behavior. Its main functions are sustaining attention, performing complex and rule-based problem solving with work memory. The executive control network is involved with the salience network, in externally directed attentional demands and tasks requiring cognitive control. It has a strong anticorrelation with DMN, suggesting the division of labor between different functions of internal and external awareness. (Uddin *et al.*, 2009; Heine, Soddu, Gomez, *et al.*, 2012; Bär *et al.*, 2016)

ECN encompasses areas of the bilateral middle, inferior, and superior frontal cortices, bilateral inferior parietal lobes, ACC/supplementary motor area (SMA), and bilateral insular cortices. The left side is considered to involve more language and cognitive processing and the right side perceptual somesthetic and nociceptive processing. Both sides are deactivated during sleep and anesthesia, but light sedation does not affect them significantly. (Heine, Soddu, Gomez, *et al.*, 2012)

4.5.3 Salience network

Salience network (SN) is activated during salience emotional processing, conflict monitoring, information integration, and response selection. Also, pain-related processes and imagination or anticipating painful stimuli have been linked to salience network activation. It is considered to be an important mediator or switch between frontoparietal and default mode networks. (Heine, Soddu, Gómez, *et al.*, 2012)

SN consists of areas in the anterior insula (AI) and anterior cingulate cortex (ACC). It has connections to subcortical and limbic structures. SN with DMN and ECN is suggested to form a triple network where SN controls the orientation of consciousness to internal (DMN) and external (ECN) directions (Figure 3). (Heine, Soddu, Gomez, *et al.*, 2012)

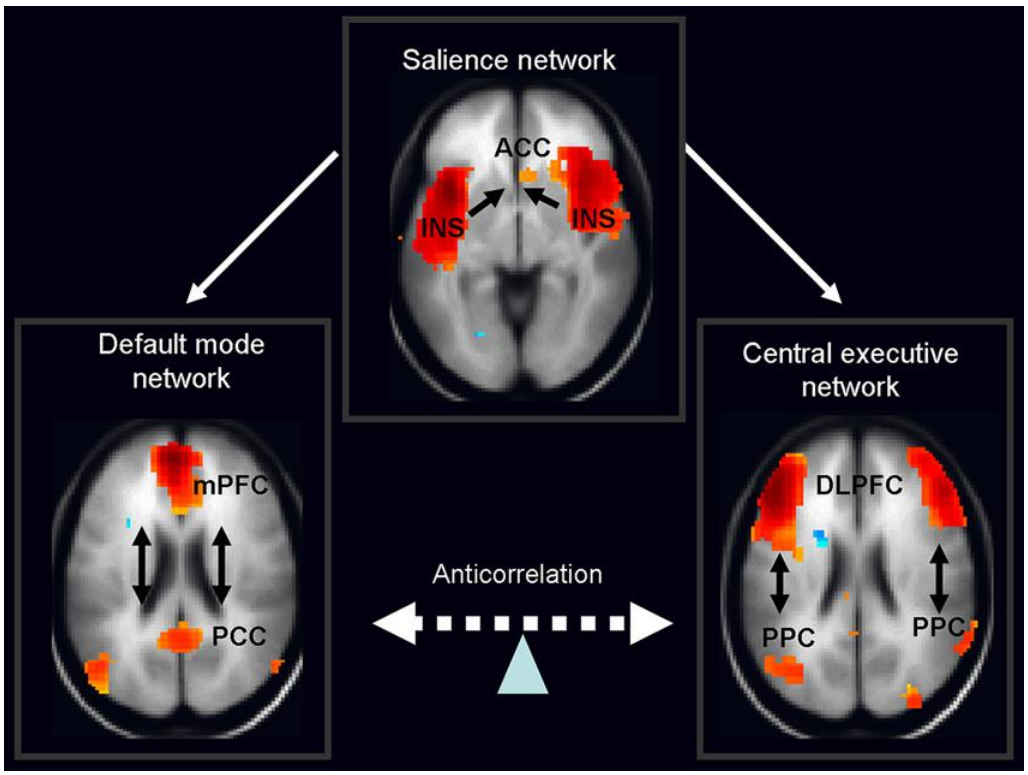

Figure 3. | SN, controlling DMN and ECN (here central executive network) and directing the orientation of consciousness. Image: (Nekovarova *et al.*, 2014)

4.5.4 Sensorimotor, visual, and auditory networks

Sensorimotor network activations relate to motor tasks and the areas it consists of are supplementary motor area/midcingulate cortex, bilateral primary motor cortex, and bilateral middle frontal gyri. Sensorimotor areas have not been studied relating to the search of NCC. (Heine, Soddu, Gómez, *et al.*, 2012)

Visual network consists of three independent components: lateral visual network consisting of the middle temporal visual association area at the temporo-occipital junction. This part is associated with complex visual rendering such as emotional stimuli. The second component is the medial visual network responsible for simple visual stimuli. Occipital visual network corresponds with higher-order stimuli, for example, orthography. (Heine, Soddu, Gómez, *et al.*, 2012) The visual network has been widely studied for the neural correlates of the components of consciousness, but not with the states of consciousness.

Auditory network is located in primary and secondary auditory cortices. Also, Heschl's gyrus, bilateral superior temporal gyri, and posterior insular cortex are associated with

auditory stimuli. The network is responsible for auditory processing, for example, pitch/tone and speech recognition. Concerning both visual and auditory networks, there are no reported significant changes in the connectivity between different states of consciousness. (Heine, Soddu, Gómez, *et al.*, 2012)

5 ANESTHETIC-INDUCED CHANGES IN FUNCTIONAL CONNECTIVITY AND BRAIN RESTING STATE NETWORKS

Anesthetic drugs, such as the aforementioned propofol, dexmedetomidine, and ketamine, create the unconscious state by pharmacological mechanisms that are not yet entirely understood. Their suggested micro-level mechanisms vary, even though they have common features on a macro level, seen with fMRI for example. Also understanding the macro-level mechanisms induced by anesthesia should help explain the mechanisms of consciousness. (Långsjö, Revonsuo and Scheinin, 2014; Bonhomme *et al.*, 2019)

5.1 Propofol

In fMRI studies, propofol-induced anesthesia provokes a large drop in overall connectivity but also creates hypersynchronous cortical states that are seen in EEG as well. (Barttfeld *et al.*, 2015; Song and Yu, 2015) The decreased connectivity localizes to cortico-cortical (DMN and SN) and higher-order thalamocortical connections. The most dominant changes in connectivity scaled with the extent of altered consciousness are in the frontal lobes (Barttfeld *et al.*, 2015; Liu *et al.*, 2017). Propofol-induced loss of consciousness (PI-LOC) can be seen by tracking the coactivation patterns of PCC (Amico *et al.*, 2014). The decrease in connectivity is shown to be independent of changes in reduced CBF (Qiu *et al.*, 2017). Propofol-induced anesthesia increases the connectivity between the thalamus and primary sensory areas, and the negative correlation between DMN and ECN disappears. (Hudetz, 2012; Jordan *et al.*, 2013). In propofol-induced unconsciousness, the regional cerebral blood flow (rCBF) seen in PET studies suffers a sharp decrease in all brain regions and especially in the thalamocortical and frontoparietal networks (Song and Yu, 2015) and there is also a decrease in the cerebral metabolic rate (CMR) (Alkire, 2008).

The main unsolved question of PI-LOC is the significance of the decrease in thalamocortical and cortico-cortical connections. Barttfeld *et al.* (2015) argue that the PI-LOC is directly mediated by the decrease of thalamocortical connectivity rather than corticocortical connectivity, similar to falling asleep. Alkire and Miller (2005) propose that it could be because of a neuronal hyperpolarization block at the thalamic level. Also, during ROC, brain activity returns in the thalamus and lower-order brain regions, not in the cortex, suggesting consciousness being a bottom-up process. (Långsjö *et al.*, 2012). A recent paper by Scheinin *et al.* (2021) suggests that cortical suppression may not be sufficient for unconsciousness, and might represent unspecific effects of the administered anesthetic agent. Instead, their results suggest that the loss and return of the connected state of consciousness associates with concomitant reciprocal changes in neural activity in a network of brain structures encompassing the thalamus, cingulate cortices, and bilateral angular gyri. Another observation by Mhuircheartaigh *et al.* (2010), also suggesting a deeper origin of PI-LOC, is that there is a reduction in functional connectivity between the putamen and other brain regions during progressive failure to perceive or respond to different stimuli. This reduction happens even before the thalamocortical connectivity decreases.

On the contrary, Monti *et al.* (2013) argue that PI-LOC originates from a decrease in cortico-cortical connectivity, without a thalamocortical component. Boveroux *et al.* (2010), Boly *et al.* (2012), Guldenmund *et al.* (2013), Jordan *et al.* (2013), Monti *et al.* (2013) and Warnaby *et al.* (2016) also report that there is preserved thalamic connectivity to the cortex during PI-LOC. Studies also suggest that propofol disrupts the top-down processing by decoupling DMN's higher-order processes from posterior sensory processes and suppresses the frontal feedback connectivity (Boveroux *et al.*, 2010; Jordan *et al.*, 2013). Similar results were also found with EEG studies as there was no thalamic component in LOC, but a decrease of backward corticocortical connectivity from frontal to the parietal cortex (Boly *et al.*, 2012). The thalamocortical disconnection might then be secondary for this cortical connectivity breakdown (Hudetz, 2012).

However, there are interesting observations in the studies of Hudetz (2012), Liu *et al.* (2013, 2017) and Song and Yu (2015), supporting a role for thalamus in PI-LOC. Thalamus can be divided into specific and non-specific (intralaminar) nuclei. The specific system transforms sensory and motor information as the non-specific controls

the cortical arousal and distribution of information across cortical areas. When the disconnection of thalamus is more precisely measured, the specific thalamic nuclei were only moderately affected as the non-specific nuclei were severely suppressed. This suggests that both results from previously mentioned studies concerning thalamic origin of PI-LOC may be true if the thalamic connectivity had two components with different behavior in the loss of consciousness.

5.2 Ketamine

Ketamine, as mentioned earlier, is a unique anesthetic that has many features and clinical applications in addition to inducing anesthesia. Ketamine increases functional connections globally but disrupts especially higher-order network connectivity. With smaller doses, ketamine first disconnects DMN from areas involved in depression and with increasing doses disrupts the connectivity between pain-related and sensory areas to produce analgesia. (Bonhomme *et al.*, 2016, 2019)

With doses large enough to induce unresponsiveness, especially the connectivity from anterior to posterior parts of the brain is disrupted and the anticorrelation between DMN and other networks decreases. During deep unconsciousness, ketamine breaks down connectivity inside the DMN, particularly separating the medial prefrontal cortex from other areas of DMN. The anticorrelation activity is broken down and the connectivity of SN decreases. Minimal effects however are seen in ECN, auditory, visual, and sensorimotor networks. Also, thalamocortical connectivity is seen to remain relatively well and even increase with deep levels of unconsciousness. These findings suggest that the mechanism of action is the breakdown of connectivity in the frontoparietal DMN, sharing similar features with propofol-induced unconsciousness. The role of remaining thalamocortical connectivity has not been analyzed further and remains unclear. (Bonhomme *et al.*, 2016, 2019)

5.3 Dexmedetomidine

Dexmedetomidine-induced unconsciousness has also similar features with propofol. Dexmedetomidine reduces connectivity within higher-order networks and between them and the thalamus. As with propofol, during dexmedetomidine-induced unconsciousness, the thalamic connectivity to lower-order (auditory, sensorimotor, and visual) networks remains. (Guldenmund *et al.*, 2017; Bonhomme *et al.*, 2019)

However, the connectivity between the key nodes of a core network responsible for arousal, involving subcortical and limbic regions (brain stem, thalamus, hypothalamus, ACC, and salience network) remains relatively intact with dexmedetomidine when compared to N3 sleep and propofol. This might explain the unique feature of dexmedetomidine that unconsciousness caused by dexmedetomidine can be reversed with mild physical stimulation or loud voices without altering the concentration of the anesthetic. These areas also resemble the areas that first activate after propofol sedation. (Långsjö, Revonsuo and Scheinin, 2014; Guldenmund *et al.*, 2017; Bonhomme *et al.*, 2019). During the arousal from dexmedetomidine unconsciousness, the induced activations are mostly localized in the deep, phylogenetically old brain structures, rather than the neocortex. (Långsjö *et al.*, 2012)

A fMRI/PET study by Akeju *et al.* (2014) reports intact cortico-cortical functional connectivity with dexmedetomidine induced unconsciousness, while the thalamocortical connectivity is disrupted. It suggests a thalamic origin for dexmedetomidine-induced unconsciousness. The mechanism of a rapid return of consciousness can also be explained by returning thalamic connectivity while the cortex remains ready to be awake. The differences between sleep or dexmedetomidine unconsciousness versus deep anesthesia or a comatose state could also be explained by the disruption of only thalamocortical connectivity with intact cortical connectivity and disruption of the cortical networks.

6 DISCUSSION

Comparing the effects that the anesthetic drugs have on brain resting state networks, common factors among anesthetics and interesting areas for future research were found. Starting with propofol, the altered states of consciousness are strongly correlated with the depression of cortico-cortical connectivity and disruption of connectivity between non-specific thalamic nodes and the cortex. There is no consensus about the origin of these observed decreases in connectivity. It remains unsolved which of the observed changes is causally related to the observed change in the state of consciousness. The functional connectivity of lower-order networks with the thalamus remains intact or even increases during anesthesia. This backs up the

theory that propofol-induced unconsciousness would originate from the disruption of the higher-order networks on the cortex, while information still flows from the thalamus. However, there is also a significant decrease in thalamic connectivity to the higher-order networks especially from the non-specific nuclei, suggesting that the disrupted cortical activity connectivity would be due to thalamic disconnection.

Ketamine has some similarities in the effects it induces on the resting state networks as propofol. It induces unconsciousness by breaking down the functional connectivity in higher-order networks, but quite surprisingly the connectivity of ECN remains. Similarly, as in PI-LOC, the DMN anticorrelation is disrupted while the sensory and sensorimotor functional connectivity is preserved. With ketamine-induced unconsciousness the thalamocortical functional connectivity remains or even increases, suggesting that the anesthetic state induced by ketamine is caused by disrupted connectivity in the cortex. However, there has not been further analysis of these findings and the case might be similar to propofol, where there may also be decreases in some thalamocortical connections causing unconsciousness.

In dexmedetomidine-induced altered states of consciousness, there are also similarities to propofol in the effect on resting state networks. The decreased connectivity in higher-order networks is the main mediator of unconsciousness and connectivity in lower-order networks remains. Dexmedetomidine anesthesia has a unique attribute that the subject can quickly regain consciousness when stimulated with a loud voice for example. The explanation for this is proposed to be in the relatively preserved connectivity between the thalamus and deeper brain areas. An interesting discovery is also the remaining cortical connectivity in dexmedetomidine unconsciousness that might also explain the rapid recovery from dexmedetomidine anesthesia and normal sleep. The cortex would remain functionally connected and ready for a powerful enough stimulus to wake up the subject. This unique attribute of dexmedetomidine also enables new kinds of study designs as it does not need alterations in the CNS concentration.

The role of thalamus as a mediator of consciousness is an unanswered question that appears in many studies with different anesthetics. Some role for the thalamus seems certain, as in the mammalian brain every cortical region has connections to and from the thalamus and its different nuclei, and the brain has therefore been called a

thalamocortical system (Jones, 2001). Thalamus has also been noted as important for normal consciousness (Kirsch *et al.*, 2017) and for a mediator of the cortico-cortical connections (Murray Sherman and Guillery, 2013). The ultimate role of the thalamus as the primary mediator of altered states of consciousness, mainly in propofol studies, remains debatable. Ward (2011) argues that the thalamus might just be a read-out of cortical information. Velly *et al.* (2007) and Alkire (2008) also claim that thalamic depression may come after cortical depression. On the other hand, the theory of a thalamic switch-off argues that the thalamus might serve as a switch for controlling consciousness. (Barttfeld *et al.*, 2015).

Interesting areas for future research remain firstly the role of the thalamus and its different nuclei. Does thalamus have a primary or secondary role in the altered states of consciousness, or is the origin of consciousness in the deeper areas of the brain or in the cortex? How should the effect of ketamine on thalamic functional connectivity be interpreted; does the increased thalamic connectivity indicate a primary role for the cortex or is it similar to the increased connectivity seen with propofol between thalamus and lower order networks? Dexmedetomidine with its unique features might help to resolve some fundamental issues in study designs by providing a tool to study different states of consciousness while keeping the level of drug exposure constant.

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