

## Aware beside an unconscious patient, not the inverse! On the necessity of knowing how anesthesia modulates consciousness

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**Summary :** One of the magic's of general anesthesia is the reversible modulation of consciousness. The past 20 years have seen important progress in the understanding of consciousness physiology, and its alteration by hypnotic anesthetic agents. However, this knowledge is sparsely spread among anesthesiology practitioners. One of the reasons is that the new concepts underlying brain functioning are far from their usual basic science background, and are not necessarily easy to catch. In this narrative review, the aim is to make these current concepts within reach, including brain connectivity, network laws, and theories on consciousness. The hypotheses on how anesthetic agents interfere with brain function are also described, from their initial biochemical targets to interactions with sleep/wake regulating systems and consciousness networks. The importance of the topic to anesthesiologists is underlined, and the questions that still remain to be solved are listed..

**Keywords :** General anesthesia ; mechanisms ; consciousness ; brain networks.

### INTRODUCTION

Anesthesiologists, by providing sedation or general anesthesia to patients, have the unique power of reversibly modifying consciousness in several ways, and to varying degrees, both in terms of depth and qualitative aspects. Aside from anti-nociception and immobility, this is done to avoid patients experiencing unpleasant and sometimes traumatizing events during surgery, such as perceiving pain, or being conscious of the surrounding sounds and images of the environment, and possibly having explicit recall thereafter. Anesthesia is not simply diving people into a state of complete unconsciousness, with abolition of any perception of the environment and the self by anesthetic drugs. It is popularly assimilated to sleep, because grossly sharing some characteristic features such as a breakdown of the sensations brought by the environment, and of the responses to different stimuli, as well as a decreased muscle tone

(1-3). But anesthesia is not sleep. It should rather be considered as a fine tuning of brain function, inducing a series of possible particular brain states, where the subject is ultimately and at the highest doses, unable to generate a mental content and develop thoughts.

According to Sanders et al. (3), different con-consciousness states can occur during general anesthesia. Disconnected unconsciousness is probably the most common, with no mental content and no perception of the environment at all. But disconnected consciousness can also be seen, when the patient dreams while being disconnected from the environment. Finally, a state of connected consciousness may be encountered, and such a state may not necessarily be easy to detect, particularly in a patient that has received muscle relaxants. Episodes of connected consciousness are more frequent immediately after intense noxious stimulation such as laryngoscopy. Their incidence is estimated to be around 5% in the general population during surgical procedures of moderate severity, and is higher in younger patients. They are rarely if not never followed by explicit recall (4).

Despite recent progress in the understanding of the mechanisms sustaining consciousness and those involved in the alteration of consciousness by anesthetic agents, one has to admit that this knowledge is still sparsely spread among the anesthesiology community. Anesthesiologists frequently stand by their anesthetized patient,

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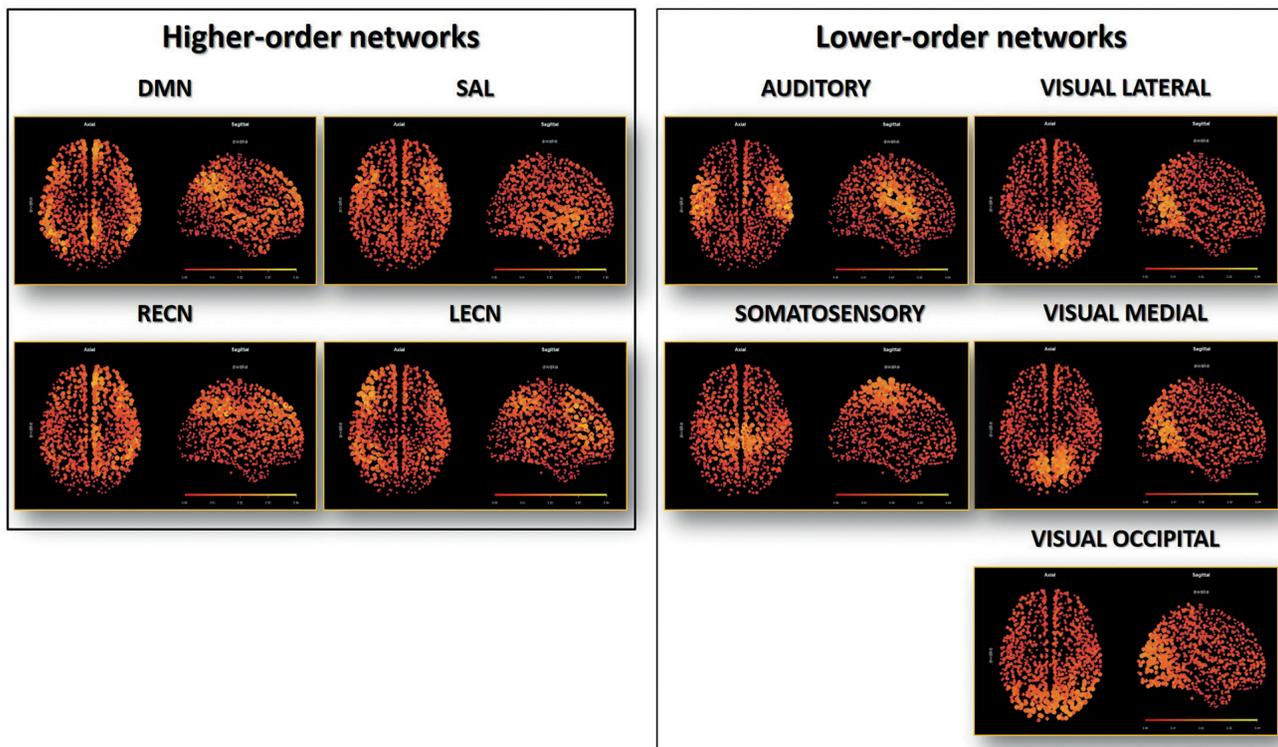


Figure 1. — Examples of brain networks. For a network, each identified node is shown (orange), and its size is proportional to the number of connections to other nodes (number of edges). Displayed networks are separated into higher-order networks (left; DMN = Default-Mode Network, LECN and RECN= left and right Executive Control Network, SAL = Salience network), and lower-order networks (right; Auditory, Sensorimotor, Visual lateral, Visual medial, and Visual occipital network).

without being aware of what really happens in their brain. This narrative review aims at making this knowledge within reach of anesthesiology practitioners, including the current approach to the analysis of the phenomenon of consciousness, and the way brain function is modulated by anesthetic agents. The importance of the topic to the anesthesiologist is threefold: first to better understand what she/he's doing on a daily basis, second to be able to design preventive strategies to avoid undesired events, and third to participate as a key stakeholder to the scientific progress aiming at understanding consciousness itself. In such a way, anesthesiologists will be aware when at the bedside of their unconscious patient, and not the inverse.

#### HOW DOES CONSCIOUSNESS EMERGE THROUGH BRAIN ACTIVITY?

Every day, hypotheses on how brain activity is organized towards generating consciousness receive support from new scientific evidence. Current concepts about consciousness physiology see the brain as a large workspace, where different more or less distant regions get down to work around the same task by interacting with each other. Consciousness would emanate from complex

functional interactions between them, both evolving spatially and temporally (5). This organization is defined as a brain network organization. The activity of networks and their mutual interactions would allow generating and integrating information (6,7).

Among brain networks, several can be evidenced in wake subjects in a resting state, that is lying down, eyes closed, and giving free rein to their thoughts. Those networks are called Resting State networks (RSN). The identification and description of RSNs may vary in the literature, but the most consistently reported ones are the following (Figure 1). One of them is the Default-Mode Network (DMN), which is involved in self-awareness (8), autobiographical memory, mind wandering, and unconstrained cognition (9). It is in a way the observer of our "house" (10). The regions composing the DMN are located in the posterior cingulate cortex/precuneus, the medial prefrontal cortex, the left and right lateral parietal cortex, the left and right inferior temporal cortex, the left and right cerebellum, the thalamus, and the brainstem (11). The left and right dorso-lateral fronto-parietal Executive Control Networks (ECNs) open to the integration of our environment (12), through perceptual and somesthetic processing, giving

the ability to respond to an external event, and to have conscious reportable perception (13,14). ECN regions encompass the left and right dorsolateral prefrontal cortex, the left and right inferior parietal lobule, the left and right premotor cortex, the midcingulate cortex, the left and right angular gyrus, the left and right precuneus, the brainstem, the cerebellum, and the thalamus (11). DMN and ECN activities fluctuate over time in an anti-correlated manner (12,15), meaning that when one is active, the other is silent, and vice-versa. This permanent switch between self-awareness and awareness of the environment is controlled by the Salience (SAL) network (16). SAL is involved in judgment of an event salience, conflict monitoring, information integration, response selection, interoceptive processes, and the emotional counterpart of pain (17,18). Its most frequently reported composing regions are the left and right orbital frontoinsula, the left and right temporal pole, the paracingulate cortex, the left and right dorsal anterior cingulate cortex, the left and right superior temporal gyrus, the left and right parietal operculum, the ventrolateral prefrontal cortex, the left and right dorsolateral prefrontal cortex, the left and right thalamus, the left and right hypothalamus, the periaqueductal gray, and the left and right ventral tegmental area. Beside the DMN, ECNs, and SAL, which are considered higher-order consciousness networks, auditory, visual, and sensorimotor networks are also frequently described. Other networks support different aspects of our perception such as associative learning (19), emotions (20), or pain and its emotional aspects (21).

#### WITNESSES OF INTERACTIONS BETWEEN BRAIN REGIONS

Interactions between brain regions suppose communication between them. One may expect that communication occurs when two regions display a synchronous fluctuation in activity, or when the activity of one region allows predicting the activity of another one. The first scenario is functional connectivity, which corresponds to a statistically significant correlation between the activity of brain regions (22-24). The second scenario is effective connectivity, where there is statistical interference between region activities in time, or time series. In that case, the recorded signal corresponding to activity in region A can be shown to statistically predict the fate of activity in region B (23,25-28).

Different types of signals that correspond to regional activity can be recorded. The blood-oxygen level dependent (BOLD) signal of

functional magnetic resonance imaging (fMRI) is one of them. It is based on the regional afflux of oxygenated blood that occurs when a region activates. This afflux is in excess of the needs. This ends up with a temporary increase in local oxygenated hemoglobin concentration, and changes in local magnetic properties that can be detected by fMRI. The fluctuations of the BOLD signal in time can constitute a time series. Other witnesses of regional brain activity can be the electrical signal of electroencephalography (EEG), the regional concentration of a labelled marker in positron emission tomography (PET), or others.

Linking those signals and their fluctuation to information generation, transfer, and handling by the brain is empirical (24,29,30), but characteristic disturbances of functional and effective connectivity in the brain have been observed in several altered consciousness states, and several species, including humans (31).

#### NETWORK PROPERTIES

Communication between brain regions gives rise to and defines brain networks. They are composed of neuronal assemblies that receive, generate and handle information. Within- and between-network interactions, also obeying to a hierarchical distribution (e.g. lower-order and higher-order networks, see Figure 1) and varying with time, treat the information and allows it to come into the consciousness field (31). Networks are governed by a set of fundamental laws and organizational principles that sustain their plasticity, and their role in handling information and generating consciousness (for an excellent review on the topic, see the paper by Lee and Mashour<sup>31</sup>).

From a theoretical point of view, networks can be considered as assemblies of nodes that are linked by edges (32) into a specific topology or architecture. The interactions between these nodes can be directed or reciprocal. The topology of a network can be described by a set of parameters, hereafter appearing in *italic* (see Table 1). They include the node degree, path length, efficiency, clustering coefficient, small-worldness, modularity, centrality, and criticality. The *node degree* is the number of edges for a given node. The *clustering coefficient* estimates how a group of nodes is isolated from other nodes. It is a kind of grouping index within a network. Networks with high *clustering coefficients* are isolated from the others, and hence have a high degree of functional specialization. The *characteristic path length* represents the

Table 1  
Network components and properties

Component/property	Description
Node	Brain region which is a junction of information transit
Edge	Connection between two nodes
Node degree	Number of edges for a node
Clustering coefficient	Index of node grouping within a network (high clustering coefficient = functional specialization)
Path length	Minimum number of edges needed to link two nodes
Efficiency	Reflects the integration capacity, and is proportional to path length (the shortest the path length, the more efficient integration)
Small-worldness	Best compromise between functional specialization (high clustering coefficient) and efficiency (short path length)
Major hubs	Most influential nodes (high number of edges, must-go-through relays, high degree of centrality)
Centrality	Index of the central character of a node
Module/modularity	Module = group of nodes separated by a hub Modularity = estimates the separation of a network into modules
Criticality	A state between order and disorder, allowing the maximum number of possible configurations

Footnote : the concepts described in the table are extracted from (31).

average of the minimum number of edges needed to link two nodes together and indexes the network integration ability or *efficiency*. Indeed, the shortest the path length, the more rapid and efficient integration, because information travels quickly across the network. In healthy brain networks, the characteristic path length is generally short and the *clustering coefficient* is high, hence favoring the best compromise between functional specialization and *efficiency* of integration. This compromise between *clustering coefficient* and *characteristic path length* defines the *small-worldness* of a network.

Other key elements of brain networks are hubs (33), of which some are essential or major hubs. They are the most influential nodes, as defined by their number of edges and their *centrality*, meaning that they are must-go-through relays for the transfer of information. Those major hubs would occupy only 10% of networks but would facilitate 70% of within- and between-network communication (34). They regulate the traffic of information, by ensuring its transmission over long distances to other regions or other networks, and thus ensuring effective communication. They also separate networks into modules. Measures of *modularity* exist, accounting

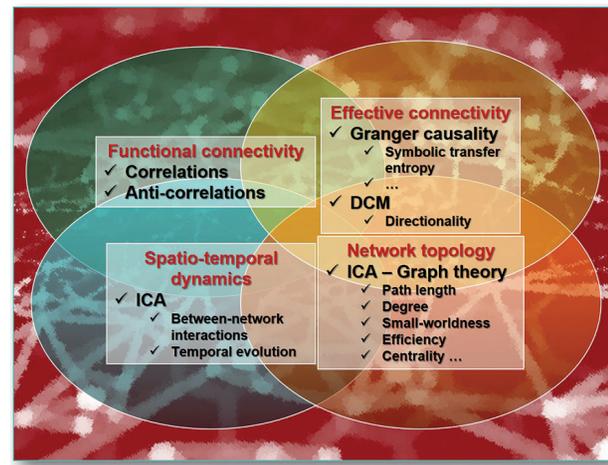


Figure 2. — Summary of the analysis techniques allowing the exploration of brain function and networks. Short explanation on each technique can be found in the text. DCM = Dynamic Causal modeling; ICA = Independent Component Analysis.

for the division of a network into modules (35). Several major hubs are essential to consciousness, including the precuneus, the superior frontal cortex, the superior parietal cortex, the hippocampus, the thalamus, and the putamen. Less major hubs, with less edges, have an important structural role in the network.

Finally, networks are not static. Links between nodes constantly change over time and space, leading to a dynamic evolution of brain configuration, and a rich repertoire of brain states at the origin of a tremendous amount of information. It is postulated that the brain dynamics constantly evolve at the border between order and disorder, a phenomenon known as *criticality*. Simply said, *criticality* is a state that allows the maximum number of different configurations (36).

#### ANALYSIS TECHNIQUES TO EXPLORE THE EFFECTS OF ANESTHESIA ON BRAIN FUNCTION AND NETWORKS

On the above-mentioned possible recorded witnesses of cerebral activity, namely the BOLD signal of fMRI, the EEG, and others, several types of analyses can be performed to study brain function and its changes during anesthesia. These analyses do not look at the same things, and it is important to know exactly what they study, in order to adequately interpret the results. They are summarized in Figure 2, and can be classified into 4 main categories, with some overlap.

The first category concerns functional connectivity, that corresponds to statistical correlations or anti-correlations between the activity of distinct brain regions (37). Two types of analyses can be performed to evidence connectivity, either through

a seed-based approach, where all brain regions connecting to a specifically defined circumscribed brain area are sought at (11), or through Independent Component Analysis (ICA) (38), where connectivity links are identified globally. Effective connectivity studies, the second category, look at causal relationships between the activity of a region and the one of another region, as well as to the directionality of this influence. They use statistical models called Granger causality (39) or dynamic causal modelling (DCM) (40-42), whose description is beyond the scope of this paper. Other techniques explore the topology of consciousness networks, including node degree, path length, efficiency, small-worldness, modularity, clustering, and criticality (43). The fourth category englobes those techniques investigating the spatio-temporal dynamics of the interactions between brain regions (44). They are also based on ICA.

#### EFFECTS OF ANESTHETIC AGENTS ON BRAIN FUNCTION AND NETWORKS

Several ancient concepts about the effects of anesthetic agents on the brain have now lived: there seems to be no unitary mechanism of consciousness alteration during anesthesia, anesthesia is not sleep, and anesthesia does not simply switch off the brain globally. The use of the above-described functional brain imaging analysis techniques, as well as laboratory experiments in animals and in vitro, have permitted to develop these concepts about anesthesia.

#### *No common pathway explaining anesthesia-induced alteration of consciousness*

The non-unitary mechanism of anesthesia is sustained by the fact that anesthetic agents with hypnotic properties (i.e. with an ability to alter consciousness) have distinct biochemical targets, largely distributed within the brain. Lugli and coworkers distinguish two main categories of biochemical targets (45). Binding to the first ones results in the potentiation of inhibitory neurotransmission. Propofol, barbiturates, etomidate, benzodiazepines and halogenated agents mainly act through this mechanism. Binding to the second category of targets leads to an inhibition of excitatory neurotransmission, and this is done by ketamine, for example. Among the inhibitory targets, the  $\gamma$ -amino-butyric acid receptor type A (GABA<sub>A</sub> receptor) and its glycine site are the most frequently cited, as well as the two-pore

potassium channels. The inhibitory capacities of GABA<sub>A</sub> receptors are promoted by propofol, halogenated vapors, etomidate, benzodiazepines and barbiturates. Potassium channels are activated by volatile halogenated anesthetics, nitrous oxide, ketamine, xenon, and propofol, leading to membrane hyperpolarization and neuronal inhibition. The excitatory effect of central nicotinic cholinergic neurotransmission is altered by propofol, barbiturates, volatile halogenated anesthetics, xenon, nitrous oxide, and ketamine. The N-methyl-D-aspartate glutamate receptor (NMDA) is inhibited by volatile halogenated anesthetic agents, nitrous oxide, xenon and ketamine (46). Alpha-2 agonist receptors have a pharmacological behavior that distinguishes them from other hypnotic drugs. They induce a hyperpolarization of locus coeruleus neurons resulting in a reduction of norepinephrine release and, ultimately, an increase in the inhibitory efferences to major excitation centers (47-48). Other possible biochemical sites of action for anesthetic agents have been identified in laboratory models, including intracellular signaling systems, and glial or mitochondrial proteins, but their involvement in the alteration of brain function seems much less obvious (1,49-50).

#### *Anesthesia is not physiological sleep*

Despite some similarities, anesthesia is not the same as physiological sleep, both behaviorally (1) electrophysiologically. Sleep occurs through the regulation of cortical arousal by brainstem sleep/wake cycle regulatory systems. Although anesthetic agents may have effect on those systems (51-54), most of them also have direct cortical action. This diversity of effects is responsible for an EEG fingerprint that is specific to each hypnotic anesthetic agent, and different from sleep EEG. Anesthetic agents that enhance GABAergic neurotransmission, such as propofol or halogenated vapors, mainly produce slow delta oscillations and coherent frontal alpha in the EEG, while slow-wave sleep is characterized by slow-delta and spindle oscillations (55). NMDA-inhibitory anesthetics such as ketamine, by inhibiting thalamic glutamatergic projections and cortical inhibitory interneurons rather produce slow-delta oscillations interspersed with gamma oscillations (55). The only exception is the  $\alpha_2$ -adrenergic agonist dexmedetomidine, whose effect on the noradrenergic system produces an EEG pattern very similar to sleep, with slow-delta and spindles.

*Anesthesia does not switch off the brain globally*

It is true that most hypnotic agents depress cerebral electrical activity and metabolism globally (56-59), but this effect is dose-dependent and targeted towards specific brain regions (60). Consciousness alteration by anesthesia is therefore not just a matter of simple decreased electrical and metabolic activity (37,50). Studies on cerebral connectivity and network properties have brought a number of brain function alterations out, that are common to all hypnotics. Regarding functional and effective connectivity, hypnotic anesthetic agents break higher-order networks down, and particularly the fronto-parietal connectivity within those networks (11,37,61). Long-distance communication is also impeded (41). Contrarily, lower-order sensory and sensorimotor networks are preserved (31). The spatio-temporal dynamics of communication within the brain are altered, with a limitation of the repertoire of possible connectivity configurations resulting in a decreased spatio-temporal complexity (62). In terms of network topology and architecture, networks see their structure reconfigured, and their global efficiency reduced. This is associated to increased clustering and segregation, as well as a disruption of the parietal major hub (31,43). The net result of all those changes is a reduction in information generation and integration by the brain (63).

## CONCLUSIONS : THE UNRESOLVED QUESTIONS

As one can see, the theories proposed to model consciousness and consciousness alteration by anesthesia are progressing fast. Based on the findings of functional brain imaging, and on the features that are common to all anesthetic agents, some have proposed unified theories of consciousness alteration during anesthesia. For example, the cognitive unbinding theory postulates that anesthetic agents isolate rather than inhibit neuronal activity, and hinder important functional structures to synthesize information (64). Another theory postulates a breakdown of information generation and integration through a reduction of possible brain repertoires and of cortical communication (65). In both cases, the net result is a loss of information integration.

Everything fits well in the proposed models, but several questions remain unresolved.

First, scientists only begin to catch a glimpse of the exact link between the known biochemical targets of anesthetic agents, their targets within the

sleep/wake regulation systems, within the cortex, and the observed functional effects (55).

Second, the sophisticated analysis methods make assumptions based on observations made in normal wake subjects and in subjects with an anesthesia-induced alteration of consciousness, but the direct proof that the observed changes are related to a physiological reality is still missing. We still lack a unified model, integrating all observations made with the different analysis techniques.

Third, although some of the observed functional changes are similar between different anesthetics, it does not mean that they all work the same way. Indeed, they have different biochemical targets, and there exist some phenomenological differences in the alteration of consciousness they produce. For example, hypnotic agents that promote GABAergic inhibition (propofol, benzodiazepines, barbiturates, etomidate, and halogenated compounds) suppress consciousness of the environment, self-awareness, and decrease muscle tone and movements. Sedation by those agents may however occasionally be accompanied by dreams, and hence disconnected consciousness (66). Dissociative anesthetics such as ketamine blunt interaction with the environment and response to stimuli, while keeping signs of wakefulness such as eye opening and reptilian movements. They produce vivid dreaming and altered self-awareness (67). Alpha-2 adrenergic agonists produce a sleep-like state, with preservation of muscle tone, dreaming, and easy reversibility by external stimulation (68,69). Studies begin to demonstrate clear functional differences between agents. For example, preservation of thalamic connectivity with key nodes of arousal and saliency detection networks clearly differentiates propofol sedation, dexmedetomidine sedation, and normal sleep (70). This probably accounts for behavioral and biochemical targets differences between agents. Noteworthy, very few data on between-agent pharmacodynamic interactions, when different agents are used together, exist in the domain of brain function.

Fourth, some clinical situations correspond to very special states of consciousness, and we have no clue of brain state at that time. This is the case for episodes of connected consciousness during anesthesia, evidenced using the isolated forearm technique (4). Such episodes can even occur in patients displaying coherent frontal alpha on the EEG, a marker of GABAergic agents' anesthesia (71). These situations may serve as models for identifying the functional mechanisms of distinct components of consciousness, and the effects of

anesthetic agents on them, including memories (72, 73).

Some solutions exist to further progress in our understanding of consciousness alteration during anesthesia. First, improved data sharing between research groups would increase the statistical power of analyses, and promote statistical comparisons between different anesthetic agents. Second, promoting and refining the in vivo exploration of neurotransmission, using, for example, positron emission tomography and specifically designed ligands would certainly help in making the link between biochemical targets, sleep/wake regulation targets, and networks. Third, studies should be designed to target a specific single component of consciousness, and not consciousness at large. Finally, we should apply the different analysis techniques to consciousness alterations of different origins, make comparisons, and hence better define their functional meaning.

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