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Neural correlates of consciousness during general anesthesia using functional magnetic resonance imaging (fMRI)

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ABSTRACT

This paper reviews the current knowledge about the mechanisms of anesthesia-induced alteration of consciousness. It is now evident that hypnotic anesthetic agents have specific brain targets whose function is hierarchically altered in a dose-dependent manner. Higher order networks, thought to be involved in mental content generation, as well as sub-cortical networks involved in thalamic activity regulation seems to be affected first by increasing concentrations of hypnotic agents that enhance inhibitory neurotransmission. Lower order sensory networks are preserved, including thalamo-cortical connectivity into those networks, even at concentrations that suppress responsiveness, but cross-modal sensory interactions are inhibited. Thalamo-cortical connectivity into the consciousness networks decreases with increasing concentrations of those agents, and is transformed into an anti-correlated activity between the thalamus and the cortex for the deepest levels of sedation, when the subject is non responsive. Future will tell us whether these brain function alterations are also observed with hypnotic agents that mainly inhibit excitatory neurotransmission. The link between the observations made using fMRI and the identified biochemical targets of hypnotic anesthetic agents still remains to be identified.

Key words
General anesthesia • Mechanisms • Brain functional imaging

(Un)consciousness and general anesthesia: an old and long lasting (love) story

The tight relationship between the alteration of consciousness and general anesthesia has been evident since the advent of modern anesthesia in the middle of the 19th century. Both entities are non dissociable (Eger et al., 2006). Etymologically, anesthesia refers to the absence of any sensation, and aims at allowing patients tolerating painful and unpleasant interventions. However, clinical practice reveals various degrees in depth and qualitative aspects of conscious perception alteration during general anesthesia, either of the external environment or of the inner self, depending on the doses and properties of the agents used. In addition, alteration of conscious perception must be integrated into the interrelated other pharmacodynamic effects of anesthesia, such as anti-nociception, anxiolysis, amnesia, and immobility. Studying the mechanisms of anesthesia-induced alteration of consciousness is therefore not an easy

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task, although one may benefit from specific reversible effects of selected agents on one component of consciousness or the other to separate the global mystery into more specific questions to be solved. For example, α_2-adrenergic agonists are known to induce a clinical state of sedation (subject lying down, immobile, and eyes closed) while preserving some of the brain cognitive functions (Bonhomme et al., 2008), a state clinically and electrophysiologically close to stage II slow wave sleep. Hence those agents allow separating wakefulness from awareness, and may help dissecting the complex entity of consciousness. Studying anesthesia-induced alteration of consciousness is therefore useful for anesthesiologists, who want to understand what they are doing everyday, and for neurophysiologists, who want to understand how consciousness emerges from brain activity.

From the early theories to the present time

Conceptions have evolved since the early hypotheses made on the mechanisms of anesthesia-induced alteration of consciousness (Franks, 2006). In that domain, two mechanistic levels must be distinguished: the molecular targets of anesthetic agents and their effect on the neural correlates of consciousness themselves. At both levels, as we shall see, ideas have progressed from a holistic view towards more targeted specific effects. It is now well accepted that the biochemical target of anesthetic agents is not directly the lipid bilayer of neuronal membranes, but rather hydrophobic gaps or pockets into neural proteins (Kopp et al., 2009). Those targets can be classified into two main categories encompassing those related to the potentiation of inhibitory neurotransmission, on one hand, and the inhibition of excitatory neurotransmission, on the other hand (Kopp et al., 2009). $GABA_A$ receptor and its glycine site, as well as potassium channels are among the most accurately identified inhibitory targets, while glutamatergic ion channels, nicotinic acetylcholine receptors, and serotonine receptors belong to the excitatory category. Several other possible sites of action have also been proposed, including intracellular signaling systems, and mitochondrial or glial proteins, but their relevance to the hypnotic effect of anesthetic agents is less evident. According to the classification of biochemical targets, hypnotic anesthetic agents can be split into those with a main effect on inhibitory neurotransmission such as barbiturates, propofol, etomidate, benzodiazepines and halogenated compounds, those with a main effect on excitatory neurotransmission such as ketamine, and those with a mixed effect such as xenon and nitrous oxide (Solt et al., 2007). Having circumscribed the most probable cellular effect sites, the question then arises on how the functional alteration of the abovementioned largely distributed biochemical systems can modify brain function to end with an alteration of consciousness.

Tweezers rather than hammers

The precise link between biochemistry and anesthesia-induced alteration of brain function is still missing. A global depression of brain function was initially thought to be the final common mechanism of anesthesia-induced loss of consciousness, based on the observations of reduced cerebral metabolism by most hypnotic anesthetic agents (Pierce et al., 1962; Forster et al., 1982; Newberg et al., 1983; Cold et al., 1985; Alkire et al., 1995; 1997), and on their depressing effect on the electroencephalogram (EEG) (Alkire, 1998). However, it has long been known, and confirmed on several occasions, that an increase in brain metabolism can be observed after the administration of some hypnotic agents, such as ketamine (Langsjo et al., 2005), with a concomitant increase in EEG activity (Hirota, 2006), and that the depressing effect on EEG, when present, is not uniform. For increasing doses, most hypnotic agents acting on inhibitory neurotransmission exhibit a first EEG activation (called β activation) followed by EEG suppression (Bennett et al., 2009). In addition, the effect of anesthetic agents on the EEG is not uniform over the cortical surface (Rampil, 1997). The advent of techniques allowing the observation of the functioning brain, positron emission tomography (PET) first and functional magnetic resonance imaging (fMRI) thereafter, changed conceptions. Following the pioneer work of Fiset and coworkers, as well as Alkire and coworkers, it has been acknowledged that hypnotic anesthetic agents are rather tweezers than hammers. Depending on the

administered dose, they exert their effect on specific brain regions. Propofol dose-dependently and bilaterally reduces the activity in the thalamus, midbrain reticular formation, cuneus-precuneus, posterior cingulate, as well as prefrontal cortices, and parietal associative cortices (Fiset et al., 1999; Kaisti et al., 2003). Despite subtle differences, halogenated compounds (Kaisti et al., 2003), barbiturates (Veselis et al., 2004), benzodiazepines (Veselis et al., 1997) and α_2-adrenergic agonists (Bonhomme et al., 2008) share similar brain regions with propofol, where activity is reduced in a dose-dependent manner. Similarities are also evident with regional brain activity modifications observed during other altered states of consciousness, namely slow wave sleep, generalized seizure, coma and vegetative state (or Unresponsive Wakefulness Syndrome – Laureys et al., 2010; Boveroux et al., 2008). These observations allow highlighting denominators that are common to all the above-mentioned altered states of consciousness: brainstem structures, and particularly the thalamus, cuneus-precuneus and posterior cingulate cortex, and the fronto-parietal association cortices.

Where is the switch?

The identification of targets shared by a series of hypnotic agents has led to hypotheses regarding an eventual consciousness switch. The first candidate was the thalamus, or more precisely thalamocortical connectivity. Making a parallel with sleep physiology (Steriade et al., 1993), which share in part behavioral and electrophysiological characteristics with general anesthesia (Murphy et al., 2011), Alkire and co-workers proposed that the final common mechanism of the alteration of consciousness during anesthesia could be a thalamocortical hyperpolarization resulting from a direct hyperpolarizing effect, a GABA neurotransmission enhancement, as well as a glutamate and cholinergic neurotransmission inhibition at the level of thalamocortical, corticothalamic, and reticulothalamic loops (Alkire et al., 2000). The precuneus, known to play an essential role in conscious processes, has also been in line (Cavanna, 2007). However, not all hypnotic anesthetic agents produce the same brain activation/deactivation pattern. For example, ketamine provokes an increase in regional brain activity, mainly in the anterior cingulate, the thalamus, the putamen, and the frontal cortex (Langsjo et al., 2003). In addition, increasing concentrations of propofol or sevoflurane first affect electrocortical activity, before affecting subcortical electrical activity (Velly et al., 2007). Midbrain reticular formation and thalamus appears to request higher doses to suppress their activity than cortical regions involved in higher order cognitive processing (Heinke et al., 2005). Tactile and pain stimulation-elicited cortical activations are attenuated by lower doses of anesthetic agents than thalamic activations (Antognini et al., 1997; Bonhomme et al., 2001). Finally, a dose-dependent decrease in thalamic activity can be observed with partially preserved cognitive functions when sedation is induced by α_2-adrenergic agonists (Bonhomme et al., 2008). Hence, the hypothesis of a single and circumscribed consciousness switch has not outlived the accumulation of experimental data.

Placing anesthesia in the context of consciousness theories

Going a step further in understanding anesthesia-induced alteration of consciousness necessitates integration with the current concepts of consciousness physiology. In Baar's global workspace theory (Baars et al., 2003), mental content would emerge from a pooling of perceptual and mnemonic information generated by specialized functional brain networks into a global workspace. Regulating systems would then allow one cognitive element or the other to come in front of the conscious scene. The specialized networks would be made of hierarchically organized interconnected brain regions that would synchronize their activity to generate information. Connectivity into those networks would dynamically change as a function of circumstances. An alternative theory supported by current empirical evidence is the information integration theory of consciousness (Tononi, 2008). This theory predicts that anesthesia-induced unconsciousness should be related to a breakdown of large-scale cerebral connectivity (loss of integration), and/or a stereotypical pattern of brain responses (loss of information) (Alkire et al., 2008b). Among the brain networks suggested to be involved in consciousness, some of

them elicit resting state activity, that is functional connectivity when the subject is conscious, lying down, eyes closed, and doing nothing else but thinking. The most reproducible resting state networks include the medial frontoparietal default mode network (DMN), involved in the awareness of self (Mason et al., 2007), the dorsolateral frontoparietal executive control network (ECN), involved in the awareness of the environment (Boly et al., 2008), and the auditory and visual networks (Damoiseaux et al., 2006). The activity in the DMN and in the ECN fluctuates with time in an anti-correlated manner (Fox et al., 2005; Boly et al., 2008). When DMN is active, ECN is silent, and vice versa. Perception of external stimuli would only be possible when ECN is active. Other networks sustain different aspects of consciousness such as associative learning (Sperling et al., 2002), emotions (Paulus et al., 2005), or pain and its emotional components (Coghill et al., 1994). Hence, the preponderant effect of hypnotic anesthetic agents on cortical activity could account for a dose-dependent effect on those networks, with subsequent repercussions on cortico-sub-cortical interactions and sub-cortical structures activity. The disruption of network functionalities could in turn be responsible for the different pharmacodynamic effects of hypnotic agents. Several arguments sustain this hypothesis.

Connectivity changes during anesthesia-induced alteration of consciousness

The first elements in favor of networks dysfunction during anesthesia came from task-induced visual (Heinke et al., 2001), auditory (Heinke et al., 2004; Kerssens et al., 2005; Plourde et al., 2006), verbal (Fu et al., 2005), emotion (Paulus et al., 2005), anticipation to pain (Wise et al., 2007) and memory (Sperling et al., 2002; Honey et al., 2005; Alkire et al., 2008a) activation studies, and from the observation of a greater sensitivity of higher order association areas than lower order processing regions to anesthesia (Dueck et al., 2005; Heinke et al., 2005; Ramani et al., 2007). Direct evidence of connectivity alterations came from EEG recordings combined with transcranial magnetic stimulation (TMS) and from recordings of synchronized low-frequency blood oxygen level-dependent oscillations (BOLD) signals using fMRI (Peltier et al., 2005). Depending on the technique used, the seed regions observed, and on doses attained, several connectivity modifications have been identified. Combined TMS-EEG studies revealed shorter duration and altered propagation of TMS-elicited responses within the cortex during midazolam sedation as opposed to wakefulness (Ferrarelli et al., 2010). Functional MRI studies showed that connectivity into the DMN persists, although reduced at low doses of sevoflurane (Deshpande et al., 2010; Martuzzi et al., 2010), and propofol (Stamatakis et al., 2010). The situation is similar at low doses of benzodiazepines, while connectivity increases in networks not related to consciousness, such as in the sensory and motor networks (Greicius et al., 2008). When propofol is targeted to the point of loss of responsiveness, connectivity in the DMN and ECN is dose-dependently reduced, the anti-correlation between those two networks disappears, and their activity becomes anti-correlated with thalamic activity (Boveroux et al., 2010). In that situation, connectivity in lower order visual and auditory networks is preserved, including thalamo-cortical connectivity, while cross modal interactions between those two networks is altered. Regarding the perception of external stimuli such as auditory or painful stimuli, and despite preserved thalamo-cortical connectivity in sensory networks under propofol sedation, sub-cortical thalamo-regulatory systems involving the putamen show impaired functionality that could be responsible for a defect in the cortical integration of information (Mhuircheartaigh et al., 2010).

Interestingly, anesthesia-induced connectivity modifications show similarities with observations made during other altered consciousness states. For example, connectivity into the DMN is normal in fully conscious or locked-in syndrome patients, moderately altered in minimally conscious patients, and severely altered in unresponsive wakefulness patients (Vanhaudenhuyse et al., 2010). This is also true during deep non-rapid-eye-movement sleep (Koike et al., 2011). During a psychologically-induced hypnotic state, which is increasingly used as an alternative to general anesthesia, connectivity into the anterior part of the DMN is reduced (McGeown et al., 2009; Demertzi et al., 2011), while functional modulation into a large network

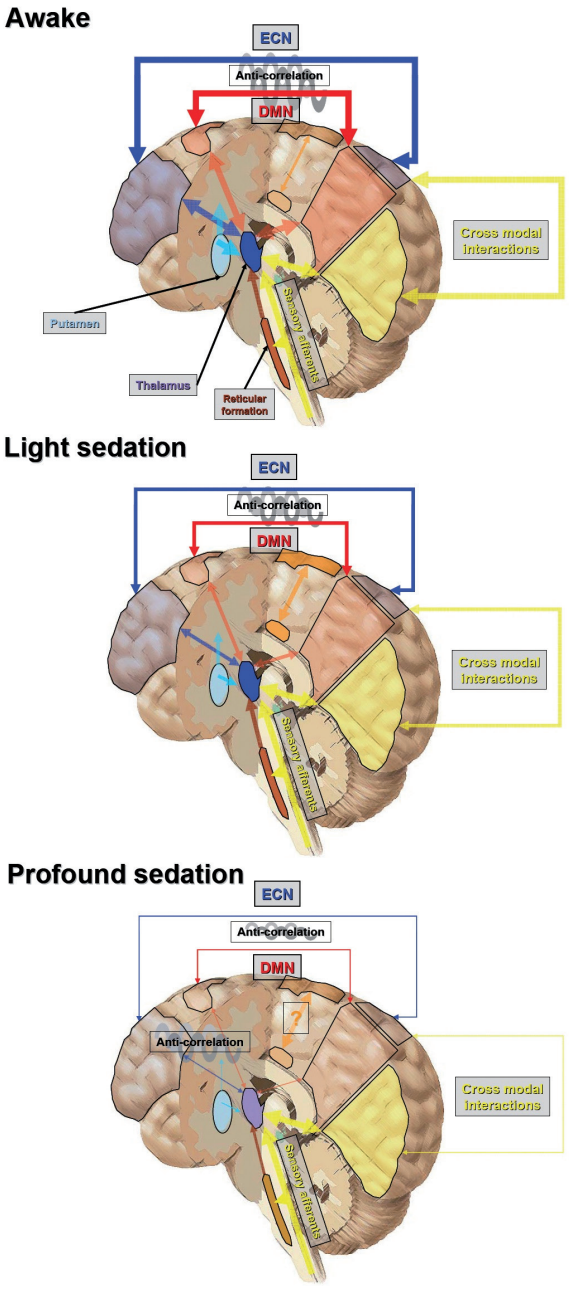

Fig. 1. - Schematic representation of brain connectivity modifications as observed during fMRI studies at different levels of sedation by hypnotic agents that promote inhibitory neurotransmission.
Awake state: consciousness is thought to be sustained by synchronized activity into the anti-correlated default mode network (DMN, red) and executive control network (ECN, blue), as well as in other higher order information processing networks (not presented). Cortical activity is sustained by the activity of the midbrain reticular formation (brown) and by cortico-thalamic interactions into those networks. Sensory information from the periphery is transferred through the thalamus (yellow) to lower order sensory networks, where there exist cross-modal interactions, before being transferred to higher order networks. Information transfer through the thalamus is regulated by sub-cortical systems involving the putamen (light blue).
Light sedation: connectivity into higher order cortical networks decreases, as anti-correlation between DMN and ECN does (thinner arrows, lighter colors). Functional connectivity is also reduced into the sub-cortical systems regulating thalamic activity (putamen, light blue). The connectivity in lower order sensory networks, including thalamo-cortical connectivity, is preserved, while connectivity into sensory-motor networks increases (orange).
Profound sedation: connectivity into DMN and ECN further decreases and anti-correlation between them disappears. Those networks present an anti-correlated activity with the thalamus. Connectivity into lower order sensory networks is still present but cross-modal interactions are altered. For those deep stages of sedation, no information is available in the literature regarding connectivity into sensory-motor networks (question mark).

involved in the emotional aspects of pain perception increases (Faymonville et al., 2003; 2006). All these elements support the pivotal role of the DMN in supporting the emergence of the conscious experience.

State of the art: trying to make the point

Merging all acquired experimental data at the present time, a schematic and still hypothetic functional mechanism of action can be drawn, at least for hypnotic agents that boost inhibitory neurotransmission (Fig. 1). Unlike sleep whose *primum movens* occurs in brainstem structures (Lydic et al., 2005), it seems that the first site of action for those hypnotic agents is cortical, at the level of higher order processing networks. At sub-hypnotic concentrations, they alter connectivity and anti-correlation of the DMN and ECN, as well as connectivity in other higher order networks, including emotional and memory networks (Alkire et al., 2008a). Lower order sensory networks display a preserved connectivity, which is even increased in sensory-motor networks. At that stage, thalamo-cortical connectivity persists, but sub-cortical systems involving the putamen and regulating thalamic activity are impaired. Midbrain reticular formation is still active, and thalamus remains activated by external stimulation. At a deeper stage, in an unresponsive individual, connectivity in higher order networks is heavily reduced, anti-correlation between DMN and ECN disappears, and the activity into those networks becomes anti-correlated with the thalamus. Even at such a deep level of sedation, connectivity in lower order sensory networks is present, but cross-modal sensory interactions are altered.

Future directions

Despite substantial progress in the understanding of anesthesia-induced alteration of consciousness, several points remain to be elucidated. The exact link between biochemical targets of hypnotic agents, electrophysiological modifications, and fMRI observations is still not known with precision. For those agents that primarily act on cortical activity, a modification of cortical GABAergic inhibitory interneuron activity could be that link (Brown et al., 2010). Although anesthesia-induced connectivity modifications are arguments in favor of a correspondence between coherent spontaneous BOLD fluctuations and consciously-directed mental activity, they do not constitute a direct proof. A supplementary argument could be the observation of similar connectivity modifications with hypnotic agents that inhibit excitatory neurotransmission, such as ketamine. If all this reveals true, anesthesia-induced alteration of consciousness could be the result of an inability of the brain to integrate internal and external information in a coherent whole, hence compromising the emergence of mental content, while external information still attains the cortex but do not go further than lower levels of cortical hierarchy. Additional elements for the understanding of anesthesia-induced alteration of consciousness, and consciousness itself, will also certainly be obtained through comparisons between anesthesia and other altered states of consciousness such as sleep, different types of coma, and hypnosis using the above-mentioned advanced brain imaging techniques but also high density EEG (Murphy et al., 2011) and combined TMS-EEG.

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