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**Towards a better understanding of anesthesia emergence mechanisms: Research and clinical implications**

Cascella M *et al*. Anesthesia emergence mechanisms

Marco Cascella, Sabrina Bimonte, Maria Rosaria Muzio

**Marco Cascella, Sabrina Bimonte,** Division of Anesthesia and Pain Management, Department of Supportive Care, Istituto Nazionale Tumori “Fondazione G. Pascale” - IRCSS, Naples 80131, Italy

**Maria Rosaria Muzio,** Division of Infantile Neuropsychiatry, UOMI-Maternal and Infant Health, ASL NA3 SUD Torre del Greco, Naples 80059, Italy.

**ORCID number:** Marco Cascella (0000-0002-5236-3132); Sabrina Bimonte (0000-0002-5408-9675); Maria Rosaria Muzio (0000-0002-8172-2325).

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**Correspondence to:** **Marco Cascella, MD, Academic Fellow, Professor,** Division of Anesthesia and Pain Management, Department of Supportive Care, Istituto Nazionale Tumori “Fondazione G. Pascale” - IRCSS, Via Mariano Semmola, Naples 80100, Italy. m.cascella@istitutotumori.na.it

**Telephone:** +39-81-5903586

**Fax:** +39-81-5903778

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**Abstract**

Emergence from anesthesia (AE) is the ending stage of anesthesia featuring the transition from unconsciousness to complete wakefulness and recovery of consciousness (RoC). A wide range of undesirable complications, including coughing, respiratory/cardiovascular events, and mental status changes such as emergence delirium, and delayed RoC may occur during this critical phase. In general anesthesia processes, induction and AE represent a neurobiological example of “hysteresis”. Indeed, AE mechanisms should not be simply considered as reverse events of those occurring in the induction phase. Anesthesia-induced loss of consciousness (LoC) and AE, until RoC are quite distinct phenomena with, in part, a distinct neurobiology. Despite anesthetics produce LoC mostly by affecting cortical connectivity, arousal processes at the end of anesthesia are triggered by structures deep in the brain, rather than being induced within the neocortex. This work is aimed to provide an overview on AE processes research, in terms of mechanisms, and EEG findings. Because most of the research in this field concerns preclinical investigations, translational suggestions, and research perspectives are also given. Furthermore, there is still little known about the relationship between AE neurobiology, and potential complications occurred during the emergence, and after the RoC. Thus, another scope of this review is to underline how a better understanding of AE mechanisms could have significant clinical implications, improving the patients’ quality of recovery, and avoiding early, and late postoperative complications.

**Key words:** Anesthesia; Delirium; Electroencephalography; Propofol; Isoflurane; Consciousness; Awareness

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**Core tip:** Emergence from general anesthesia is not simply the reverse process of induction. The exhaustive knowledge of its complex neurobiological mechanisms is mandatory for avoiding, or limiting, a large number of anesthesia complications including altered mental status, and emergency awareness. Moreover, in a fascinating translational perspective, this matter could offer new insights into the processes involved in cortical arousal, giving significant data to the research on brain arousal. On the other hand, research on the sleep-wake regulatory network, and on alterations in arousal processes could provide interesting suggestions for the general anesthesia research.

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**INTRODUCTION**

Emergence from anesthesia (AE) is the ending stage of anesthesia featuring the transition from unconsciousness to complete wakefulness and recovery of consciousness (RoC)[1]. Despite smooth and safe emergence is a primary target of anesthesia, during this critical phase a wide range of undesirable complications may occur. These AE complications include coughing - which may induce an increase in intracranial and intraocular pressures - respiratory events (*e.g.,* laryngospasm) resulting in oxygenation problems, hypertension, and tachycardia as well as mental status changes such as emergence delirium (ED)[2], and delayed RoC (*i.e*., hypoactive emergence)[3].

By addressing the matter according to a neurobiological perspective, AE and RoC processes should not be simply considered as reverse events of those occurring in the induction of anesthesia. In mathematical terms, this non-linear system between induction and AE mechanisms represents a fascinating neurobiological example of “hysteresis”; thus, anesthesia can be ideally compared to travel with a forward way (induction) which differs from that of the return (emergence). Recently, several research groups have demonstrated that the anesthetic-induced transition from wakeful state to loss of consciousness (LoC), and vice versa the RoC phase are subjected to the control of distinct neural circuits[4,5].

The aim of this work is to provide a comprehensive review of the literature, for assessing the state of the art in research on AE processes. Because most of the research in the field concerns preclinical investigations, translational suggestions, and research perspectives are also given. Furthermore, there is still little known about the relationship between AE neurobiology and AE potential complications. Thus, another scope of this review is to underline how a better understanding of AE mechanisms could have significant clinical implications, consisting in an improvement of the patients’ quality of recovery, avoiding early, and late postoperative complications.

**NEUROBIOLOGY OF EMERGENCE**

***Mechanisms of emergence***

Explanation of these mechanisms presupposes the knowledge of the operative mechanisms of anesthetics, namely the neural correlates of anesthetic-induced unconsciousness. Although it does not represent the primary goal of this work, here we will try to underline the most recent pieces of evidence on the topic (for more details, see the reviews[6-9]). This extremely complex matter can be simplified by assuming that anesthetics interfere with cortical and subcortical signals, inducing, in turn, changes in the functional/effective connectivity across brain regions. During general anesthesia, alterations in functional and effective connectivity from different brain regions (*e.g*., from frontal to parietal regions) have been widely demonstrated[9]. For instance, inhalation anesthetic agents impair frontal–posterior interactions by interfering with the gamma (20-60 Hz) oscillations which have a key role in arousal and maintenance of consciousness[10]. Studies performed by using high-density electroencephalography (hd-EEG) demonstrated that propofol-induced LoC features an increase in frontal delta power as the result of cortical propagation of processes starting from subcortical regions (*e.g.*, lateral sulci and cingulate gyrus)[11]. In turn, these slow-delta oscillations propagate asynchronously across the cortex, inducing a functional disruption of the connectivity between distinct cortical areas. Moreover, by using a combination of positron emission tomography and functional magnetic resonance imaging (PET/MRI), Akeju *et al*[12] demonstrated that the main effect of dexmedetomidine-induced LoC was the impairment of the thalamo-cortical functional connectivity.

Summarizing, connectivity changes within distinct brain regions lead to different depths of anesthesia (DoA). Thus, loss of communication between the thalamus and the cortex is responsible for the beginning of LoC. Alterations in the cortico-cortical functional connectivity, and in the functioning of several brainstem nuclei (*e.g.*, the ventrolateral preoptic nucleus) which project to the thalamus and cerebral cortex, complete the induction and maintain the surgical anesthesia status. During the AE period, mechanisms responsible for LoC and anesthesia maintenance are gradually reversed, whereas other specific awakening mechanisms are activated. These mechanisms encompass several ascending arousal brain pathways responsible for the activation and promotion of the emergence, until the RoC. Among the arousal-promoting brain regions involved in the active AE processes the thalamus has a key role[13]. Alkire *et al*[14] proved, in rat, that midline intrathalamic microinfusion of nicotine reversed sevoflurane-induced loss of righting reflex (LORR), an indicative sign of unconsciousness in rodents. Other preclinical investigations, focused on voltage-gated potassium channels, were performed to better assess the role of thalamic central medial nucleus for AE induction[15,16]. However, the thalamic systems are not the sole pathways involved in active AE. Investigations focused on the dopaminergic (DA) projections from the substantia nigra (SN) and ventral tegmental area (VTA) of the midbrain to the pedunculopontine, thalamus, dorsal raphe, locus ceruleus (LC), and laterodorsal tegmental areas, basal forebrain (BF), and lateral hypothalamus)[17,18] suggested the existence of a mesencephalic arousal pathway. On these basis, it has been showed, in animals, that the intravenous administration of methylphenidate, or dextroamphetamine - which increase the dopaminergic and adrenergic neurotransmission through the reuptake inhibition - or the use of a D1 receptor agonist (chloro-APB) restored LORR and increased theta oscillations (decreasing delta- and alfa-power) during inhaled[19,20] or endovenous anesthesia[21]. Furthermore, Taylor *et al*[22] obtained the same results through a selective stimulation of the VTA dopaminergic neurons, whereas the administration of a D1 antagonist (SCH-23390) attenuated the arousal response. Thus, they called this active transition from the anesthetized state to the awake state “reanimation from general anesthesia”[22].

The hypothalamus is another brain structure involved in the AE mechanisms. The orexinergic neurons are localized in a hypothalamic area around the fiber bundle of fornix. This orexin system (OS) plays a key role in induction of sleep-to-wake transitions, and maintenance of wakefulness[23]. A series of studies proved that it induced AE facilitating in both intravenous[24], and inhaled general anesthesia[25]. More recently, Zhang *et al*[26] demonstrated, in rats, that isoflurane depressed the excitability of orexinergic neurons. Although both orexins (*i.e*., orexin-A, OXA, and orexin-B, OXB) promoted emergence, OXA played a significant role (through orexin receptor-1).

Functionally, the OS is related to the locus coeruleus norepinephrine system (LC NE), and the posterior hypothalamic histaminergic tuberomammillary nuclei (TMN HA)[27] which are well-known wake-promoting cell groups of the sleep-wake regulatory network[28], and implicated in the operative mechanisms of inhaled anesthesia[29]. In particular, LCNE is functionally connected to the posterior cingulate cortex (PCC), thalamus, and basal ganglia forming the LCNE arousal system, which has been suggested to have an important role in the AE[30]. In addition, orexinergic projections to the hippocampus, and basal ganglia have been also demonstrated[31].

In this complex scenario, there is a functional connection between OS, BF cholinergic structures (*i.e*., medial septum, vertical limbs of the diagonal band of Broca, nucleus basalis of Meynert, and substantial innominate), and the brainstem ascending reticular arousal system (ARAS). Indeed, the BF has diffuse projections to all parts of the neocortex, basolateral amygdala, and hippocampus, whereas the ARAS has cholinergic cortical projections, but also connection with the thalamus, hypothalamus, and the BF region, which in turn modulate the OS (feedback mechanism). Summarizing, the OS contributes to arousal processing by increasing cortical activity due to excitatory projections to wake-promoting cell groups in the posterior hypothalamus, BF, and brainstem. On the other hand, orexin neurons are controlled by positive and negative feedback mechanisms mainly mediated by the hypothalamus and other areas (*e.g.*, perifornical area)[32] (for more details on orexin pathways, see the review[33]). Taken together, these data suggest that arousal processes at the end of anesthesia are triggered by structures deep in the brain, rather than being induced within the neocortex.

***Electrical activity during recovery from anesthesia***

The brain’s response to anesthetics is registered with scalp electroencephalogram (EEG) which represents the recording of cortical synaptic activity of both excitatory and inhibitory post-synaptic potentials from cortical or thalamic neurons[34]. Apart from this non-invasive EEG modality, used in human studies, other approaches such as the [electrocorticogram](http://xueshu.baidu.com/s?wd=electrocorticogram&f=12&nojc=1&tn=SE_baiduxueshu_c1gjeupa&ie=utf-8) (ECoG, EEG measured directly from the cortical surface), or other modalities, *e.g*., stereoelectroencephalography (SEEG), an EEG registered via depth probes - are used in specific clinical settings (*e.g*., SEEG in epilepsy) or for experimental investigations, in animals. Moreover, neurophysiological changes in the brain under general anesthesia are often studied through a combination of EEG approaches (including hd-EEG methods) with brain activity measures such as functional near-infrared spectroscopy (fNIRS)[35], and neuroimaging modalities, (*e.g*., functional magnetic resonance imaging, fMRI) [36], or by combining EEG with electrodiagnostic methods, including electromyography and evoked potentials (EP)[37].

Studies on EEG activity during anesthesia induced a significant impetus to research aimed at elucidating the dynamics of anesthesia. Again, technological advances, and mathematical approaches, allowed to draw several brain monitoring devices which are commonly used in clinical practice. However, explanation of features and clinical utility of DoA monitoring systems is not the scope of this review (see[38]).

Featuring of anesthesia-related electrical activity consists of a wide range of EEG patterns, mainly depending on the anesthesia phase (induction, maintenance, emergence), the DoA status, and the type of anesthetics used. Before induction, the awake subject with eyes closed shows a prominent alpha activity (10 Hz) which is maximal over parieto-occipital scalp locations. After inducing anesthesia, EEG pattern consists in an increase in beta activity (13-25 Hz), until the LoC[39], whereas during the maintenance phase different EEG patterns are observed, depending on the DoA level. Although during a light anesthesia, it is possible to register a decrease in EEG beta band (13-30 Hz) and an increase in both EEG alpha (8-12 Hz) and delta activities (0-4 Hz), as the DoA state becomes deeper, beta activity decreases, and there is an increase in delta and in alpha frequency band oscillations, this latter anteriorly located (“alpha anteriorization”)[40]. A further DoA status features an EEG pattern comprising flat periods interspersed with periods of alpha and beta activity. This very characteristic EEG pattern, is known as *burst suppression*. It can be also recognized in deeper coma status due to various conditions including cerebral anoxia, cancers, drug intoxications, encephalopathies, or hypothermia[41]. The anesthesia-induced burst suppression seems to be associated with a state of cortical hyperexcitability generated by decreased inhibition[42].

As the anesthesia state deepens, EEG shows a progressive stretching between the alpha activities. The amplitudes of the alpha and beta activities progressively decrease, and in turn, the EEG assumes isoelectric form. In this context, the deepest DoA status has been reached[43]. About correlation between EEG findings and different anesthetic agents, previous studies showed that this general scheme is particularly applicable for halogenated inhalational anesthetics, and propofol whereas, in contrast, opioids and ketamine usually induce less marked EEG changes. Furthermore, etomidate and barbiturates lead to a rapid shift toward the high voltages delta and theta frequencies[44].

Classically, during emergence it is possible to observe a loss of delta activity, combined with a progressive decrease in frontal alpha power and increased higher frequencies patterns[45]. Moreover, ECoG studies showed that specific findings (*i.e.*, slow oscillation in large-scale functional networks) are maintained during the LoC and RoC phases[46]. However, the canonical EEG sequence during AE can undergo variations. In a fascinating clinical study Chander *et al*[47] described different AE patterns. At the AE beginning they recognized a pattern characterized by high power of alpha and beta bands (95% patients) which they termed as “Slow-Wave Anesthesia” (SWA); in the minority of patients they registered an EEG with a very low spindle and delta power (called “Non Slow-Wave Anesthesia”, NSWA). Interestingly, they also found that EEG patterns between start of emergence and RoC vary by patient, and described four trajectories between the beginning of AE and the RoC. More recently, Liang *et al*[48] performed another attempt to classify emergence EEG patterns in sevoflurane anesthesia. Thanks to an integrated approach obtained by a multivariate statistical model, they identified four types of emergence EEG patterns. Interestingly, some among these emergence modalities were age-related and could be associated with postoperative mental changes. Probably, it is possible to assume that the occurrence of different EEG patterns at the emergence reflects the different degree of influence of brainstem activity on cortical re-connectivity, through the thalamus mediation[13]. This piece of evidence could prove that AE modulation can be mostly obtained by controlling brainstem activity (*e.g*., by opioids). Although we adopted a general descriptive scheme (*i.e.,* anesthesia-induced EEG changes at the emergence), it is important to underline that because of the distinct operative mechanisms of action, different anesthetics may induce different types of EEG dynamics, also in the AE phase. Recent studies are increasingly characterizing these profiles[49], especially in regard to dexmedetomidine[50].

**CLINICAL IMPLICATIONS**

A better understanding of AE mechanisms has significant clinical implications, improving the quality of recovery of patients following surgery. For instance, it has been proved that the EEG modality at the emergence affected the residual level of sedation and post-operative pain[47]. Thus, in a hypothetical scenario, it could be possible to modulate the path of emergence, choosing for the one which correlates with the desired target. The possibility to increase the predictability of the time of emergence may help prevent delayed emergence - defined as the failure to regain consciousness 30-60 min after general anesthesia[51] - and other more frequent AE complications, such as ED, and respiratory complications. This is a significant issue as delayed emergence was associated with a longer postoperative hospital stay[52], whereas ED in children may lead to physical harm to the child and distress to patients, parents and staff. Moreover, although usually self-limiting, it can last up to 48 h, and children who manifested ED are more likely to suffer from new-onset postoperative maladaptive behavioral changes[53]. Again, ED in adults can lead to serious complications, such as self-extubation, accidental removal of catheters and injury[54].

Although about 20% of accidental awareness with recall during general anesthesia (AAWR) events occur at the AE, and the 90% of these cases are potentially preventable (*e.g.*, through the use of neuromuscular monitoring)[55], in very rare AAWR cases there is no readily identifiable cause[56]. A more precise AE management can help to avoid these unexpected awakenings events, which are often associated with severe psychological consequences, such as posttraumatic stress disorder (PTSD).

**TRANSLATIONAL DATA AND RESEARCH PERSPECTIVES**

Positive results from preclinical and clinical studies on this topic should encourage additional research (Table 1). For instance, clinical investigations should translate preclinical findings to evaluate possible interventions for inducing active AE, and in turn for preventing AE complications. For this purpose, thanks to its actions consisting of arousal promotion, and breathing enhancement, the dopamine uptake inhibitor methylphenidate was the first drug to be tested in humans. Researchers from the Ohio State University assessed, in adult patients, whether methylphenidate (given orally 20 mg, 2 h before induction) decreased the emergence time from isoflurane general anesthesia, and gave rise to a fast cognitive improvement with efficient pain control and post-operative nausea and vomiting (PONV) prevention (NCT02327195). To date, the recruitment status of this prospective, randomized, double-blind, placebo-controlled trial (RCT) is indicated as completed (*n* = 54) and we are waiting for the publication of the results. Probably, this RCT will encourage further research with a multicenter involvement and a greater sampling. Another RCT in adult patients scheduled for pancreatic surgery is on-going at Massachusetts General Hospital (NCT02051452). Apart from the AE time effect, the investigators focused on safety and tolerability of methylphenidate in this clinical setting, and the impact on postoperative delirium (PD) and post-operative cognitive function (POCD). The estimated study completion date is December 2018. We hope that results from this RCT will offer clinical data to better define the correlation between AE and postoperative mental status changes. Data from preclinical research suggested that other interesting molecules should be tested for evaluating their effects on emergence features and postoperative cognitive outcomes. For instance, Zhang *et al*[57] demonstrated that amantadine, a dopamine agonist used to treat Parkinson’s disease and parkinsonism syndromes, attenuated postoperative learning and memory decline via inhibition of neuroinflammation, in rodents. Interesting, this study may suggest that interventions focused on AE modulation may interfere with microglial activation and the cascade of neuroinflammation, implicated in POD/POCD pathogenesis[58].

Clinical investigations should attempt to better clarify results, and discrepancies, of preclinical and clinical studies. Although OXA has been proved to be involved in arousal from general anesthesia, in rodents[24,26], and the Kushikata[59]’s studies showed that plasma OXA significantly increased at AE from both propofol and sevoflurane anesthesia, Wang *et al*[60] proved that higher plasma OXA concentrations were not associated with a reduction in AE time, in elderly patients. However, in these categories of patients the authors showed a higher level of plasma OXA compared to that found in young patients[60], suggesting an age-dependent difference in the orexin-induced anesthesia arousal regulation. Probably, the lower density of orexin receptors in elderly can offer a potential explanation to the evidence that elderly require a longer AE time[61] despite a higher orexinergic activation.

In addition, we believe that further preclinical research may be necessary to evaluate correlations between AE mechanisms and postoperative cognitive complications. For instance, more detailed investigations, in rodents, should investigate on the effect of AE modulation on early postoperative behavioral changes. In a translational perspective, indeed, a paramount aim should be to demonstrate whether any potential intervention on active AE processes can effectively induce an improvement in cognition, rather than just affect reducing the AE times.

Again, studies on the pathophysiology of PD, and POCD offers interesting prospects for research investigation. For instance, alterations in the prefrontal cortex, and in the dopaminergic projection to the LC are implicated in the genesis of PD and POCD. Moreover, the orexinergic system is connected - through the functional mediation of the TMN HA - to the hippocampus, neostriatum, nucleus accumbens, and amygdala, which represent key regions involved in the pathogenesis of PD, and POCD (for more details see our review on the topic[62]).

Further research is also warranted to better explain the mechanisms which induce AE activation. Certainly, many aspects of the anesthetics working are still to be elucidated. For instance, it has been demonstrated that the OS could be another possible target for isoflurane[26], whereas the role of serotonergic neurones in dorsal raphe nucleus - implicated in the mechanisms of general anesthesia[63] - on the orexinergic signal should be an interesting field of research for investigating on the linkage between AE modalities and RoC features, such as pain and mood. Effects of specific antinociceptive interventions (*e.g.*, neuraxial anesthesia) as potential mechanisms interfering with emergence processes and clinical consequences should be addressed in order to prove specific experimental findings such as the brainstem involvement in arousal dynamics. AE Translational approaches could promote a feedback between different neuroscience fields of study. Thus, general anesthesia research could offer significant information to the research on mechanisms controlling arousal processes involved in physiological and pathological phenomena, such as sleep and coma[43].

**CONCLUSION**

In neurobiological terms, the ending stage of anesthesia is not simply the reverse process of induction. Recent findings demonstrated that induction and emergence are partly subjected to the control of different neural pathways. The exhaustive knowledge of these mechanisms may help prevent a large percentage of anesthesia complications, including altered mental status, and AAWR phenomena. Consequently, a better understanding of AE neurobiology could open a new era in anesthesia aiming to design new, and safer, anesthetic strategies. Moreover, in a fascinating translational perspective, this matter could offer new insights into the complex mechanisms involved in cortical arousal, giving significant data to the research on brain arousal processes and relative alterations. On the other hand, research on the sleep-wake regulatory network, and on alteration in arousal, and cognitive processes, could provide interesting suggestions for the general anesthesia research.

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**REFERENCES**

1 **Hight DF**, Dadok VM, Szeri AJ, García PS, Voss L, Sleigh JW. Emergence from general anesthesia and the sleep-manifold. *Front Syst Neurosci* 2014; **8**: 146 [PMID: 25165436 DOI: 10.3389/fnsys.2014.00146]

2 **Munk L**, Andersen G, Møller AM. Post-anaesthetic emergence delirium in adults: incidence, predictors and consequences. *Acta Anaesthesiol Scand* 2016; **60**: 1059-1066 [PMID: 26968337 DOI: 10.1111/aas.12717]

3 **Frost EA**. Differential diagnosis of delayed awakening from general anesthesia: a review. *Middle East J Anaesthesiol* 2014; **22**: 537-548 [PMID: 25668997]

4 **Kushikata T**, Hirota K. Mechanisms of anesthetic emergence: evidence for active reanimation. *Curr Anesthesiol Rep* 2014; **4**: 49-56

5 **Tarnal V**, Vlisides PE, Mashour GA. The Neurobiology of Anesthetic Emergence. *J Neurosurg Anesthesiol* 2016; **28**: 250-255 [PMID: 26274626 DOI: 10.1097/ANA.0000000000000212]

6 **Franks NP**. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. *Nat Rev Neurosci* 2008; **9**: 370-386 [PMID: 18425091 DOI: 10.1038/nrn2372]

7 **Diao S**, Ni J, Shi X, Liu P, Xia W. Mechanisms of action of general anesthetics. *Front Biosci* (Landmark Ed) 2014; **19**: 747-757

8 **Son Y**. Molecular mechanisms of general anesthesia. *Korean J Anesthesiol* 2010; **59**: 3-8 [PMID: 20651990 DOI: 10.4097/kjae.2010.59.1.3]

9 **Lee U**, Ku S, Noh G, Baek S, Choi B, Mashour GA. Disruption of frontal-parietal communication by ketamine, propofol, and sevoflurane. *Anesthesiology* 2013; **118**: 1264-1275 [PMID: 23695090 DOI: 10.1097/ALN.0b013e31829103f5]

10 **Imas OA**, Ropella KM, Ward BD, Wood JD, Hudetz AG. Volatile anesthetics disrupt frontal-posterior recurrent information transfer at gamma frequencies in rat. *Neurosci Lett* 2005; **387**: 145-150 [PMID: 16019145 DOI: 10.1016/j.neulet.2005.06.018]

11 **Murphy M**, Bruno MA, Riedner BA, Boveroux P, Noirhomme Q, Landsness EC, Brichant JF, Phillips C, Massimini M, Laureys S, Tononi G, Boly M. Propofol anesthesia and sleep: a high-density EEG study. *Sleep* 2011; **34**: 283-91A [PMID: 21358845 DOI: 10.1093/sleep/34.3.283]

12 **Akeju O**, Loggia ML, Catana C, Pavone KJ, Vazquez R, Rhee J, Contreras Ramirez V, Chonde DB, Izquierdo-Garcia D, Arabasz G, Hsu S, Habeeb K, Hooker JM, Napadow V, Brown EN, Purdon PL. Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. *Elife* 2014; **3**: e04499 [PMID: 25432022 DOI: 10.7554/eLife.04499]

13 **Scheib CM**. Brainstem Influence on Thalamocortical Oscillations during Anesthesia Emergence. *Front Syst Neurosci* 2017; **11**: 66 [PMID: 28959192 DOI: 10.3389/fnsys.2017.00066]

14 **Alkire MT**, McReynolds JR, Hahn EL, Trivedi AN. Thalamic microinjection of nicotine reverses sevoflurane-induced loss of righting reflex in the rat. *Anesthesiology* 2007; **107**: 264-272 [PMID: 17667571 DOI: 10.1097/01.anes.0000270741.33766.24]

15 **Lioudyno MI**, Birch AM, Tanaka BS, Sokolov Y, Goldin AL, Chandy KG, Hall JE, Alkire MT. Shaker-related potassium channels in the central medial nucleus of the thalamus are important molecular targets for arousal suppression by volatile general anesthetics. *J Neurosci* 2013; **33**: 16310-16322 [PMID: 24107962 DOI: 10.1523/JNEUROSCI.0344-13.2013]

16 **Alkire MT**, Asher CD, Franciscus AM, Hahn EL. Thalamic microinfusion of antibody to a voltage-gated potassium channel restores consciousness during anesthesia. *Anesthesiology* 2009; **110**: 766-773 [PMID: 19322942 DOI: 10.1097/ALN.0b013e31819c461c]

17 **Solt K**, Van Dort CJ, Chemali JJ, Taylor NE, Kenny JD, Brown EN. Electrical stimulation of the ventral tegmental area induces reanimation from general anesthesia. *Anesthesiology* 2014; **121**: 311-319 [PMID: 24398816 DOI: 10.1097/ALN.0000000000000117]

18 **Monti JM**, Monti D. The involvement of dopamine in the modulation of sleep and waking. *Sleep Med Rev* 2007; **11**: 113-133 [PMID: 17275369 DOI: 10.1016/j.smrv.2006.08.003]

19 **Solt K**, Cotten JF, Cimenser A, Wong KF, Chemali JJ, Brown EN. Methylphenidate actively induces emergence from general anesthesia. *Anesthesiology* 2011; **115**: 791-803 [PMID: 21934407 DOI: 10.1097/ALN.0b013e31822e92e5]

20 **Taylor NE**, Chemali JJ, Brown EN, Solt K. Activation of D1 dopamine receptors induces emergence from isoflurane general anesthesia. *Anesthesiology* 2013; **118**: 30-39 [PMID: 23221866 DOI: 10.1097/ALN.0b013e318278c896]

21 **Chemali JJ**, Van Dort CJ, Brown EN, Solt K. Active emergence from propofol general anesthesia is induced by methylphenidate. *Anesthesiology* 2012; **116**: 998-1005 [PMID: 22446983 DOI: 10.1097/ALN.0b013e3182518bfc]

22 **Taylor NE**, Van Dort CJ, Kenny JD, Pei J, Guidera JA, Vlasov KY, Lee JT, Boyden ES, Brown EN, Solt K. Optogenetic activation of dopamine neurons in the ventral tegmental area induces reanimation from general anesthesia. *Proc Natl Acad Sci USA* 2016; **pii**: 201614340 [PMID: 27791160 DOI: 10.1073/pnas.1614340113]

23 **de Lecea L**, Huerta R. Hypocretin (orexin) regulation of sleep-to-wake transitions. *Front Pharmacol* 2014; **5**: 16 [PMID: 24575043 DOI: 10.3389/fphar.2014.00016]

24 **Zhang LN**, Li ZJ, Tong L, Guo C, Niu JY, Hou WG, Dong HL. Orexin-A facilitates emergence from propofol anesthesia in the rat. *Anesth Analg* 2012; **115**: 789-796 [PMID: 22798527 DOI: 10.1213/ANE.0b013e3182645ea3]

25 **Kelz MB**, Sun Y, Chen J, Cheng Meng Q, Moore JT, Veasey SC, Dixon S, Thornton M, Funato H, Yanagisawa M. An essential role for orexins in emergence from general anesthesia. *Proc Natl Acad Sci USA* 2008; **105**: 1309-1314 [PMID: 18195361 DOI: 10.1073/pnas.0707146105]

26 **Zhang LN**, Yang C, Ouyang PR, Zhang ZC, Ran MZ, Tong L, Dong HL, Liu Y. Orexin-A facilitates emergence of the rat from isoflurane anesthesia via mediation of the basal forebrain. *Neuropeptides* 2016; **58**: 7-14 [PMID: 26919917 DOI: 10.1016/j.npep.2016.02.003]

27 **Bayer L**, Eggermann E, Serafin M, Saint-Mleux B, Machard D, Jones B, Mühlethaler M. Orexins (hypocretins) directly excite tuberomammillary neurons. *Eur J Neurosci* 2001; **14**: 1571-1575 [PMID: 11722619 DOI: 10.1046/j.0953-816x.2001.01777.x]

28 **Schwartz MD**, Nguyen AT, Warrier DR, Palmerston JB, Thomas AM, Morairty SR, Neylan TC, Kilduff TS. Locus Coeruleus and Tuberomammillary Nuclei Ablations Attenuate Hypocretin/Orexin Antagonist-Mediated REM Sleep. *eNeuro* 2016; **3**: pii: ENEURO.0018-16.2016 [PMID: 27022631 DOI: 10.1523/ENEURO.0018-16.2016]

29 **Vazey EM**, Aston-Jones G. Designer receptor manipulations reveal a role of the locus coeruleus noradrenergic system in isoflurane general anesthesia. *Proc Natl Acad Sci USA* 2014; **111**: 3859-3864 [PMID: 24567395 DOI: 10.1073/pnas.1310025111]

30 **Song AH**, Kucyi A, Napadow V, Brown EN, Loggia ML, Akeju O. Pharmacological Modulation of Noradrenergic Arousal Circuitry Disrupts Functional Connectivity of the Locus Ceruleus in Humans. *J Neurosci* 2017; **37**: 6938-6945 [PMID: 28626012 DOI: 10.1523/JNEUROSCI.0446-17.2017]

31 **Stanley EM**, Fadel J. Aging-related deficits in orexin/hypocretin modulation of the septohippocampal cholinergic system. *Synapse* 2012; **66**: 445-452 [PMID: 22213437 DOI: 10.1002/syn.21533]

32 **Yamanaka A**, Tabuchi S, Tsunematsu T, Fukazawa Y, Tominaga M. Orexin directly excites orexin neurons through orexin 2 receptor. *J Neurosci* 2010; **30**: 12642-12652 [PMID: 20861370 DOI: 10.1523/JNEUROSCI.2120-10.2010]

33 **Villano I**, Messina A, Valenzano A, Moscatelli F, Esposito T, Monda V, Esposito M, Precenzano F, Carotenuto M, Viggiano A, Chieffi S, Cibelli G, Monda M, Messina G. Basal Forebrain Cholinergic System and Orexin Neurons: Effects on Attention. *Front Behav Neurosci* 2017; **11**: 10 [PMID: 28197081 DOI: 10.3389/fnbeh.2017.00010]

34 **Marchant N**, Sanders R, Sleigh J, Vanhaudenhuyse A, Bruno MA, Brichant JF, Laureys S, Bonhomme V. How electroencephalography serves the anesthesiologist. *Clin EEG Neurosci* 2014; **45**: 22-32 [PMID: 24415399 DOI: 10.1177/1550059413509801]

35 **Yeom SK**, Won DO, Chi SI, Seo KS, Kim HJ, Müller KR, Lee SW. Spatio-temporal dynamics of multimodal EEG-fNIRS signals in the loss and recovery of consciousness under sedation using midazolam and propofol. *PLoS One* 2017; **12**: e0187743 [PMID: 29121108 DOI: 10.1371/journal.pone.0187743]

36 **Baria AT**, Centeno MV, Ghantous ME, Chang PC, Procissi D, Apkarian AV. BOLD temporal variability differentiates wakefulness from anesthesia-induced unconsciousness. *J Neurophysiol* 2018; **119**: 834-848 [PMID: 29212921 DOI: 10.1152/jn.00714.2017]

37 **Hight DF**, Voss LJ, García PS, Sleigh JW. Electromyographic activation reveals cortical and sub-cortical dissociation during emergence from general anesthesia. *J Clin Monit Comput* 2017; **31**: 813-823 [PMID: 27444893 DOI: 10.1007/s10877-016-9911-z]

38 **Cascella M**. Mechanisms underlying brain monitoring during anesthesia: limitations, possible improvements, and perspectives. *Korean J Anesthesiol* 2016; **69**: 113-120 [PMID: 27066200 DOI: 10.4097/kjae.2016.69.2.113]

39 **McCarthy MM**, Brown EN, Kopell N. Potential network mechanisms mediating electroencephalographic beta rhythm changes during propofol-induced paradoxical excitation. *J Neurosci* 2008; **28**: 13488-13504 [PMID: 19074022 DOI: 10.1523/JNEUROSCI.3536-08.2008]

40 **Hight D**, Voss LJ, Garcia PS, Sleigh J. Changes in Alpha Frequency and Power of the Electroencephalogram during Volatile-Based General Anesthesia. *Front Syst Neurosci* 2017; **11**: 36 [PMID: 28611600 DOI: 10.3389/fnsys.2017.00036]

41 **Amzica F**. What does burst suppression really mean? *Epilepsy Behav* 2015; **49**: 234-237 [PMID: 26195335 DOI: 10.1016/j.yebeh.2015.06.012]

42 **Kroeger D**, Amzica F. Hypersensitivity of the anesthesia-induced comatose brain. *J Neurosci* 2007; **27**: 10597-10607 [PMID: 17898231 DOI: 10.1523/JNEUROSCI.3440-07.2007]

43 **Brown EN**, Lydic R, Schiff ND. General anesthesia, sleep, and coma. *N Engl J Med* 2010; **363**: 2638-2650 [PMID: 21190458 DOI: 10.1056/NEJMra0808281]

44 **Sloan TB**. Anesthetic effects on electrophysiologic recordings. *J Clin Neurophysiol* 1998; **15**: 217-226 [PMID: 9681559 DOI: 10.1097/00004691-199805000-00005]

45 **Purdon PL**, Pierce ET, Mukamel EA, Prerau MJ, Walsh JL, Wong KF, Salazar-Gomez AF, Harrell PG, Sampson AL, Cimenser A, Ching S, Kopell NJ, Tavares-Stoeckel C, Habeeb K, Merhar R, Brown EN. Electroencephalogram signatures of loss and recovery of consciousness from propofol. *Proc Natl Acad Sci USA* 2013; **110**: E1142-E1151 [PMID: 23487781 DOI: 10.1073/pnas.1221180110]

46 **Breshears JD**, Roland JL, Sharma M, Gaona CM, Freudenburg ZV, Tempelhoff R, Avidan MS, Leuthardt EC. Stable and dynamic cortical electrophysiology of induction and emergence with propofol anesthesia. *Proc Natl Acad Sci USA* 2010; **107**: 21170-21175 [PMID: 21078987 DOI: 10.1073/pnas.1011949107]

47 **Chander D**, García PS, MacColl JN, Illing S, Sleigh JW. Electroencephalographic variation during end maintenance and emergence from surgical anesthesia. *PLoS One* 2014; **9**: e106291 [PMID: 25264892 DOI: 10.1371/journal.pone.0106291]

48 **Liang Z**, Huang C, Li Y, Hight DF, Voss LJ, Sleigh JW, Li X, Bai Y. Emergence EEG pattern classification in sevoflurane anesthesia. *Physiol Meas* 2018; **39**: 045006 [PMID: 29513276 DOI: 10.1088/1361-6579/aab4d0]

49 **Xi C**, Sun S, Pan C, Ji F, Cui X, Li T. Different effects of propofol and dexmedetomidine sedation on electroencephalogram patterns: Wakefulness, moderate sedation, deep sedation and recovery. *PLoS One* 2018; **13**: e0199120 [PMID: 29920532 DOI: 10.1371/journal.pone.0199120]

50 **Sleigh JW**, Vacas S, Flexman AM, Talke PO. Electroencephalographic Arousal Patterns Under Dexmedetomidine Sedation. *Anesth Analg* 2018 [PMID: 29933272 DOI: 10.1213/ANE.0000000000003590]

51 **Maeda S**, Tomoyasu Y, Higuchi H, Ishii-Maruhama M, Egusa M, Miyawaki T. Independent predictors of delay in emergence from general anesthesia. *Anesth Prog* 2015; **62**: 8-13 [PMID: 25849468 DOI: 10.2344/0003-3006-62.1.8]

52 **Radtke FM**, Franck M, Hagemann L, Seeling M, Wernecke KD, Spies CD. Risk factors for inadequate emergence after anesthesia: emergence delirium and hypoactive emergence. *Minerva Anestesiol* 2010; **76**: 394-403 [PMID: 20473252]

53 **Mason KP**. Paediatric emergence delirium: a comprehensive review and interpretation of the literature. *Br J Anaesth* 2017; **118**: 335-343 [PMID: 28203739 DOI: 10.1093/bja/aew477]

54 **Chen L**, Xu M, Li GY, Cai WX, Zhou JX. Incidence, Risk Factors and Consequences of Emergence Agitation in Adult Patients after Elective Craniotomy for Brain Tumor: A Prospective Cohort Study. *PLoS One* 2014; **9**: e114239 [PMID: 25493435 DOI: 10.1371/journal.pone.0114239]

55 **Pandit JJ**, Andrade J, Bogod DG, Hitchman JM, Jonker WR, Lucas N, Mackay JH, Nimmo AF, O'Connor K, O'Sullivan EP, Paul RG, Palmer JH, Plaat F, Radcliffe JJ, Sury MR, Torevell HE, Wang M, Hainsworth J, Cook TM; Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland. The 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. *Anaesthesia* 2014; **69**: 1089-1101 [PMID: 25204236 DOI: 10.1111/anae.12826]

56 **Cascella M**. Emergence from anesthesia: a winding way back. *Anaesthesiol Intensive Ther* 2018; **50**: 168-169 [PMID: 29953576 DOI: 10.5603/AIT.2018.0020]

57 **Zhang J**, Tan H, Jiang W, Zuo Z. Amantadine alleviates postoperative cognitive dysfunction possibly by increasing glial cell line-derived neurotrophic factor in rats. *Anesthesiology* 2014; **121**: 773-785 [PMID: 25251457 DOI: 10.1097/ALN.0000000000000352]

58 **Cortese GP**, Burger C. Neuroinflammatory challenges compromise neuronal function in the aging brain: Postoperative cognitive delirium and Alzheimer's disease. *Behav Brain Res* 2017; **322**: 269-279 [PMID: 27544872 DOI: 10.1016/j.bbr.2016.08.027]

59 **Kushikata T**, Yoshida H, Kudo M, Kudo T, Hirota K. Plasma orexin A increases at emergence from sevoflurane-fentanyl anesthesia in patients undergoing ophthalmologic surgery. *Neurosci Lett* 2010; **482**: 212-215 [PMID: 20655366 DOI: 10.1016/j.neulet.2010.07.037]

60 **Wang ZH**, Ni XL, Li JN, Xiao ZY, Wang C, Zhang LN, Tong L, Dong HL. Changes in plasma orexin-A levels in sevoflurane-remifentanil anesthesia in young and elderly patients undergoing elective lumbar surgery. *Anesth Analg* 2014; **118**: 818-822 [PMID: 24651236 DOI: 10.1213/ANE.0000000000000109]

61 **Tsai HJ**, Chen CC, Chang KY. Patients and surgery-related factors that affect time to recovery of consciousness in adult patients undergoing elective cardiac surgery. *J Chin Med Assoc* 2011; **74**: 345-349 [PMID: 21872814 DOI: 10.1016/j.jcma.2011.06.009]

62 **Cascella M**, Muzio MR, Bimonte S, Cuomo A, Jakobsson JG. Postoperative delirium and postoperative cognitive dysfunction: updates in pathophysiology, potential translational approaches to clinical practice and further research perspectives. *Minerva Anestesiol* 2018; **84**: 246-260 [PMID: 28984099 DOI: 10.23736/S0375-9393.17.12146-2]

63 **Johansen SL**, Iceman KE, Iceman CR, Taylor BE, Harris MB. Isoflurane causes concentration-dependent inhibition of medullary raphé 5-HT neurons in situ. *Auton Neurosci* 2015; **193**: 51-56 [PMID: 26213357 DOI: 10.1016/j.autneu.2015.07.002]

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Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**Table 1 Suggestions for additional research on emergence from anesthesia**

|  |  |
| --- | --- |
| Type of study | Topic(s) |
| Multicenter RCTs | Effects of drugs on AE time, features, and postoperative complications including mental status changes |
| Multicenter RCTs | Effects of antinociceptive interventions (*e.g*., neuraxial anesthesia) on accelerating emergence and improving patient outcomes |
| Animal research (molecular/behavioral research) | Effects of AE modulation on molecular targets of neuroinflammation |
| Animal research (behavioral research) | Effects of AE modulation on early postoperative behavioral changes |
| Animal research (molecular/imaging/behavioral research) | Anesthetics mechanisms; Linkage between brain areas involved in cognitive functioning and AE features |
| Animal research/in humans | Neurophysiological changes under general anesthesia (*e.g*., by combining EEG approaches with electrodiagnostic methods, including EMG and EPs, or with brain activity measures such as fNIRS, and neuroimaging modalities like fMRI)  |
| *In vitro*/*In vivo* (*e.g*., mutant analysis in Drosophila) | Anesthetic mechanisms (*e.g*., genes encoding for second-messengers, memory formation substrates, ion channels, synaptic proteins)  |

RCT: Randomized controlled trial; AE: Anesthesia emergence; EMG: Electromyography; EPs: Evoked potentials; fNIRS: Functional near-infrared; fMRI: Functional magnetic resonance imaging.