The effects of anesthetics on brain activity and cognitive function

Wolfgang Heinke[a] and Stefan Koelsch[b]

Purpose of this review

This review presents an overview of recent findings related to changes in brain activity with increasing anesthesia mainly obtained with brain imaging and electrophysiological techniques in humans.

Recent findings

Recent studies have revealed that the brain as a whole is not affected to the same degree by anesthetics, but that specific brain regions (and particular cognitive processes mediated by these regions) are more sensitive to anesthesia and sedation than others. Inhibition of activity in multimodal association cortices (such as parietal and prefrontal association cortices) by sedative concentrations of anesthetics produces amnesia and attention deficits, whereas activity in unimodal cortices and in the thalamus remains largely unaffected by low doses of anesthetics. Activity in the midbrain reticular formation, thalamus, and unimodal cortices appears to be suppressed only by anesthetic concentrations causing unconsciousness. Besides those regional suppressive effects, anesthetics impair functional connections between neurons in distributed cortical and thalamocortical networks, which also contributes to the state of anesthesia.

Summary

Anesthetics produce changes in the patient's behavioral state by interacting with brain activity via at least two mechanisms: the dose-dependent global and regionally specific suppression of neuronal activity and the disruption of functional interactivity within distributed neural networks.

Keywords

auditory event-related potential, Bispectral Index, brain activity, functional magnetic resonance imaging, general anesthesia, positron emission tomography

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[a]Department of Anesthesiology and Intensive Care Therapy, University of Leipzig, Leipzig, Germany and [b]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Correspondence to Wolfgang Heinke, Department of Anesthesiology and Intensive Care Therapy, University of Leipzig, Liebigstraße 20, 04103 Leipzig, Germany
Tel: +49 341 9717700; fax: +49 341 9717709;
e-mail: heiw@medizin.uni-leipzig.de

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Abbreviations

AERP	auditory event-related potential
BIS	Bispectral Index
CBF	cerebral blood flow
EEG	electroencephalogram
ERP	event-related potential
ERAN	early right anterior negativity
LLAEP	long-latency auditory evoked potential
MMN	mismatch negativity
rCBF	regional cerebral blood flow

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Introduction

In the past, methods to assess the effect of anesthesia on brain activity were based only on behavioral outcome measures or on electrophysiological recordings, such as recordings of the electroencephalogram (EEG) or evoked potentials [1]. In the past decade, the progress in neuroscience techniques has extended this range of methods to include positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) [2]. These techniques measure the site of hemodynamic and metabolic changes caused by anesthesia-induced alterations in brain activity, while electrophysiological techniques reflect the electrical activity of the cortex with high temporal but low spatial resolution.

In the clinical setting, current developments in neuromonitoring [e.g. the Bispectral Index (BIS)] allow a general assessment of neuronal activity during surgery [3]. These techniques, however, do not predict movements or hemodynamic responses to stimulation, nor do they enable prediction of exactly when individual patients will regain consciousness [4]. Hence, awareness (i.e. explicit memory) [5] and implicit memory formation have been observed [6] even under apparently adequate anesthesia guided by neuromonitoring. Thus, important aspects of cerebral functionality during anesthesia still remain obscure [7]. Using the complementary features of electrophysiological and brain imaging techniques, this gap has partly been closed in recent years by exploring drug effects on neural networks involved in mediating attention, auditory language processing, memory and consciousness. Furthermore, elaborate studies with close control of the hypnotic state addressing unconscious memory formation have been performed. Therefore, this review summarizes recent findings obtained with different investigation techniques and presents a framework which integrates current information.

Brain activity during anesthesia as measured with functional neuroimaging

Functional neuroimaging refers mainly to modern brain imaging techniques like PET and fMRI. Both techniques were successfully employed in pharmacological research and research into anesthetic drug action during the past decade.

Changes of cerebral blood flow, cerebral metabolism and blood oxygenation level-dependent contrast

PET and fMRI studies indicate changes in brain activity due to anesthetics, provided that neurovascular coupling during anesthesia is preserved [8]. Using these techniques, dose-dependent decreases in cerebral blood flow (CBF), cerebral glucose metabolism and the blood oxygenation level-dependent (BOLD) signal have been demonstrated for nearly all anesthetics [9–14,15•,16•] except ketamine [17,18•] and nitrous oxide [19]. These actions point to a global decrease in neuronal activity with increasing anesthesia. The potency to decrease brain activity is presumably identical for intravenous and volatile anesthetics judging by the relatively similar reductions of the cerebral metabolism at comparable levels of sevoflurane and propofol anesthesia [19]. Loss of consciousness occurs at a cerebral glucose metabolism of around 60–65% [20]. Aside from the global decrease in neuronal activity, some brain regions located within the cortical association areas (e.g. parietal and frontal association cortex), the thalamus and the midbrain show a markedly higher decrease in CBF, cerebral metabolism or BOLD signal compared with the global reductions [9–14,15•,16•,19,21–24] (cf. Table 1). These actions indicate specific effects of anesthetics to produce unconsciousness, amnesia and attention deficits: convincing evidence exists that the thalamus plays a key role in anesthesia-induced unconsciousness [25,26] because relative metabolic reductions of regional glucose metabolism [12,25] and CBF [27] have been observed in this area associated with adequate anesthesia. By contrast, low anesthetic concentrations seem to have no or only little effect on the thalamus [22] and regions involved in primary information processing (Figs 1 and 2). Low drug doses, however, have been proposed to mediate amnesia either by a relatively unspecific depression of neuronal activity predominantly in the cortex [28] or by specific depressant effects on the hippocampus [29], the insula [22,30••], the amygdala [31••], and the prefrontal cortex [30]. These anesthetic actions seem to affect memory by an impaired encoding of new material into memory (unspecific drug effect due to sedation) and by the disturbed retention of encoded material in long-term memory. The latter effect appears to be independent of sedation and presumably reflects specific amnesic actions of anesthetics [32••].

Although these findings partly explain unconsciousness and amnesia, they do not provide any information about neuronal activity related to sensory stimulation during anesthesia. Animal studies suggest that evoked cortical activity may be detectable even during deep anesthesia [33]. In humans, neuronal activity has been observed using functional neuroimaging evoked by either auditory [15,30••,34•], visual [13] or noxious stimuli [35•] during light and adequate stages of anesthesia (Table 1). For example, we observed functional activation in both temporal lobes evoked by auditory language processing at an effect-site concentration of propofol of over 1.51 μg/ml (Fig. 1). This activation disappeared at concentrations exceeding 3.35 μg/ml. Similarly, sevoflurane decreased auditory evoked functional activation dose dependently. When compared with wakefulness, residual activation was observed bilaterally at the superior temporal gyrus, the thalamus, the striatum, and left frontal cortex at 1% sevoflurane, whereas this activity was totally suppressed at 2% sevoflurane [34•]. Recently, it was demonstrated that sedative propofol and thiopental doses do not alter the increase in CBF evoked by auditory stimuli, despite a 15% decrease in global CBF (gCBF) [41••]. Even during unresponsiveness (mean BIS = 66), a regional CBF (rCBF) response at the left temporal lobe was observed (although clearly diminished). Altogether, these findings suggest that auditory stimulation still evokes cortical activity, albeit reduced, during light stages of anesthesia.

Like auditory stimuli, somatosensory stimuli may also cause cortical activity during unresponsiveness, but this is apparently dependent on the stimulus used. Vibrotactile stimuli did not activate the cortex and caused merely thalamic activity at a propofol concentration of 1.5 μg/ml [39]. In contrast, noxious (heat) stimuli increased CBF in the somatosensory and midinsular cortex even at a propofol concentration of 3.5 μg/ml (i.e. during unconsciousness) [35•]. Interestingly, the anterior cingulate cortex, a region implicated in pain perception [42], was activated by heat at lower propofol concentrations. Thus, the insula might even be active during unconsciousness (although not mediating pain perception, but rather autonomic responses), whereas other structures mediating pain perception appear to be suppressed at propofol concentrations causing unconsciousness [35•].

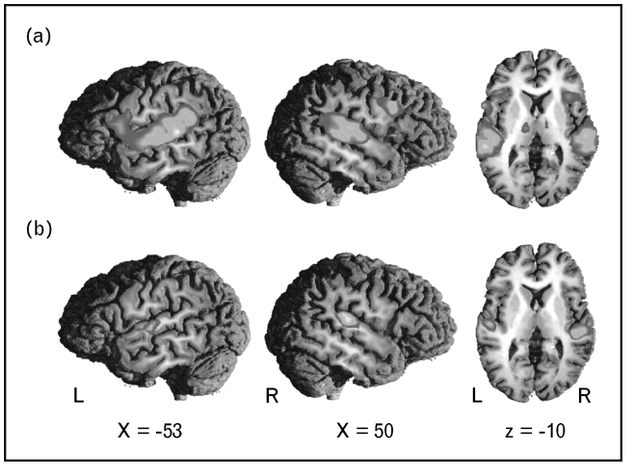
The effects of ketamine on CBF [17] and cerebral glucose metabolism [17,18,43] on resting brain activity are clearly distinguished from other anesthetics. Subanesthetic doses of ketamine produce a global increase in rCBF, the most profound changes in brain structures being related to pain processing [17]. Under noxious stimulation, however, subanesthetic ketamine decreased pain and stimulus evoked brain activity, with the greatest reductions observed in the thalamus and insula [44•]. Besides these analgesic actions, ketamine appears to interact at low doses with brain activity related to working memory, in brain regions comprising frontal and parietal cortical areas and the putamen [45], as well as with

Table 1. Changes in brain activity and cognitive function with increasing anesthesia

Anesthetic depth	BIS	Reduction in gCBF	Reduction in $gCMR_{glu}$	Behavioral effects	AERP components	Anesthetic concentrations: Propofol (μg/ml)	Anesthetic concentrations: Volatile (MAC)	Anatomical drug effect: Max drug effect on resting brain activity	Anatomical drug effect: Drug effect on evoked brain activity
Awake	100			Attention deficits, disturbed encoding of material into long-term memory, affected retention of encoded material within long-term memory [32••], auditory sensory memory intact [36•], working memory (although affected) preserved [32••]	P1 amplitude unchanged, N1, MMN and P3a amplitude slightly decreased	0.5	0.2	Multimodal association cortices [28], propofol – anterior brain regions, thiopental – posterior brain regions and cerebellum [32••]	Nearly unchanged evoked activity in word, language and music processing networks [15•,32••,36•], decreased activity in insular and parietal cortices during visual information processing [22]
Light sedation	90	15% [32••]							
	80								
Deep sedation				Increasing impairment of attention and episodic memory, auditory sensory memory preserved but clearly affected [36•], explicit and implicit memory formation possible	P1 amplitude unchanged; N1, MMN, ERAN detectable but markedly reduced, P3a detectable	1.5		Thalamus [16•]	Activity of (frontal) heteromodal association cortices clearly reduced [15•,36•], loss of anterior cingulate activation caused by noxious stimuli, preserved cerebellar, somatosensory, and insular cortex activation by noxious stimuli [35•], preserved thalamic activity [39] and preserved activity in the auditory cortices [15•,36•]
	70						0.4		
				Breakdown of (music) syntactic processing	P3b, ERAN undetectable				
							0.5	Disruption of interhemispheric connections causing disturbed synchronized brain activity [37,38••]. Thalamus, midbrain reticular formation, basal forebrain, cerebellum, occipital cortex [16•, 25], impaired thalamocortical connectivity [26]	
Hypnosis	60		40	Unconsciousness, memory function lost (no implicit or explicit memory formation) [40••]	P1 markedly reduced, MMN, P3 undetectable	2.5			Total suppression of innoxious evoked brain activity [39]
		22% [27]							
		–	–						
							1.0		Cortical (insula) activation by noxious stimuli still possible [35•]
		27% [28]		Movement in response to noxious stimuli possible					
			60% [9,11,12]						
	40			No movement in response to noxious stimuli		>4.0			

Summary of anesthetic actions on resting brain activity, evoked brain activity and cognitive functions depending anesthetic depth. Anesthetic depth is indicated by the Bispectral Index (BIS), effect site-concentration of propofol and minimum alveolar concentration (MAC is the minimum alveolar concentration of a volatile anesthetic at one atmosphere pressure needed to prevent 50% of patients from moving in response to a surgical skin incision). gCBF, global cerebral blood flow; $gCMR_{glu}$, global cerebral metabolic rate of glucose; aERP, auditory event-related potential; MMN, mismatch negativity; ERAN, early right anterior negativity.

Figure 1. Brain activation during language processing (awake versus sedation)



Functional brain activation elicited by auditory language processing obtained during wakefulness (a) and during deep sedation (i.e. when individuals did respond to the language processing task) (b). During wakefulness, auditory language processing elicited brain activity in a temporo-frontal network. Deep sedation (propofol effect-site concentration between 1.51 and 3.35 μg/ml) restricted the measurable brain activity to regions in and around the primary auditory cortex on both hemispheres. At propofol effect-site concentrations exceeding 3.35 μg/ml, no functional brain activation related to auditory stimulation was detectable. Adapted with permission from Heinke *et al.* [15•].

activity related to the encoding and retrieval of episodic information in frontal and hippocampal regions [46•].

Changes of functional interactivity during anesthesia

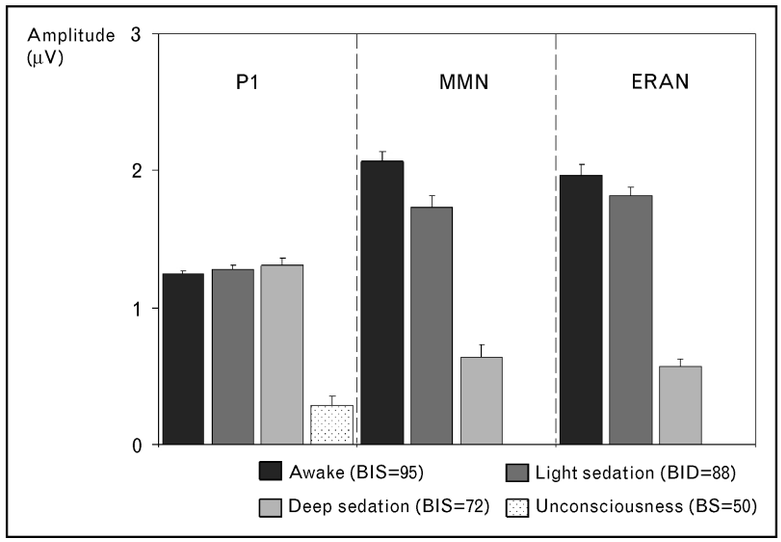
Neurons across the brain are thought to interact with one another, for example to forward information between cortical areas and to facilitate the binding of distinct perceptual attributes into a unitary, conscious percept [37,47]. Disconnections of these functional interactions within neural networks are probably important for drug effects such as amnesia and unconsciousness [48]. Neuroimaging studies indicate that functional connectivity can be examined under anesthesia, and that anesthesia may be associated with changes in network connectivity [26,38••]. White and Alkire [26] demonstrated impaired corticocortical and thalamocortical connectivity at anesthetic concentrations causing unconsciousness. More recently, it has been shown that a reduction of interactivity in motor networks by 0.5 minimum alveolar concentration (MAC) sevoflurane caused a functional dissociation between the two hemispheres (i.e. the network was confined to just one hemisphere). At 1 MAC sevoflurane, motor network connectivity was completely eliminated [38••]. These findings suggest a dose-dependent reduction of synchronized temporal correlations between neurons within functional networks during anesthesia. The hypothesis that connectivity disruption is a mechanism that decreases brain activity and produces behavioral changes is also supported by recent EEG work demonstrating the electrical uncoupling of diverse brain regions by anesthetics [49]. These studies show that besides the regionally suppressive actions of anesthetics, disconnecting effects appear to be equally important for producing anesthesia and depressing neuronal activity.

Brain activity during anesthesia assessed with electrophysiological methods

Because anesthetics affect the EEG in a characteristic manner, a variety of methods are available providing

Figure 2. Effect of increasing propofol sedation on auditory event-related potentials

Reflects primary auditory processing (P1), auditory sensory memory (MMN) and music-syntactic processing (ERAN). Amplitudes (mean ± SE) of P1, MMN, and ERAN during different levels of sedation adjusted with target-controlled infusion of propofol: wakefulness (propofol concentration 0.0 μg/ml, mean Bispectral Index (BIS) = 95), light sedation (propofol concentration 0.5 μg/ml, mean BIS = 89), deep sedation (propofol concentration 1.5 μg/ml, mean BIS = 72) and unconsciousness (propofol concentration 2.5–3.0 μg/ml, mean BIS = 50). The P1 amplitude was unchanged by sedation and markedly decreased, but still detectable, during unconsciousness. In contrast, amplitudes of the MMN and the ERAN were progressively decreased with increasing sedation and abolished during unconsciousness. This indicated differential effects of propofol sedation on auditory sensory memory and music-syntactic processing when compared with primary processing of the acoustic input. Adapted with permission from Heinke *et al.* [36•] (see reference for further details).



indices of anesthetic depth derived from the EEG or evoked potential waveform [4,50]. Although they allow a global estimation of brain activity, however, they may not be sufficiently accurate to differentiate between sedation levels or to assess specific brain function during drug administration. Recordings of long-latency auditory evoked potentials (LLAEPs) or auditory event-related brain potentials (AERPs) provide a way to differentiate between sedation levels [51•] and to precisely assess the cognitive state of a patient during sedation. In contrast to midlatency auditory evoked potentials, whose detection mainly reflects activity within the primary auditory cortex, LLAEPs (or AERPs) reflect neural mechanisms that may also involve other cortical areas (such mechanisms underlying, for example, auditory sensory memory, music and language processing, and orientation to novel stimuli) [52,53]. The first positive deflection in the waveform of the LLAEP is the P1, which is followed by a negative deflection, the N1. The P1 reflects the sensory encoding of auditory stimulus attributes [52,54], whereas the N1 appears to reflect the conscious detection of discrete changes in any subjective dimension of the auditory environment [55]. The N1 amplitude decreases with increasing sedation [36•,56,57] but is still detectable in individuals unresponsive to verbal commands [36•]. In contrast, the P1 amplitude is only affected by unconsciousness but appears to be unchanged during deep sedation (Fig. 2) [36•]. The presence of P1 and N1 at a BIS indicating unconsciousness (the neural generators of both components are assumed to be located in the auditory cortices, although both components receive contributions from different neural populations) confirms neuroimaging studies [15•,30••,34•], indicating neuronal activity in the auditory cortices during light stages of anesthesia (Figs 1 and 2).

An AERP which has in some studies been used to investigate effects of sedation on auditory processing is the mismatch negativity (MMN) [52,58]. The MMN is elicited by deviant stimuli that occur in a series of repetitive standard stimuli (e.g. in a repetitive series of standard tones, a frequency deviant elicits an MMN). The MMN is thought to reflect operations of the auditory sensory memory, a preattentive short-term store for acoustic information. Recently, a dose-dependent breakdown of auditory sensory memory has been shown by MMN recordings [36•,51•,56,57]. The MMN amplitude decreased with increasing sedation and was not detectable at a BIS of 50 (Fig. 2) [36•]. This suggests a continuous decrease in neuronal activity within the MMN-generating network located in temporal and frontal brain areas with increasing sedation as well as a collapse of this memory system during unconsciousness.

Due to methodological difficulties, the effects of sedative drugs on language processing have not yet been investigated with AERPs. Interestingly, however, the processing of syntactic information has been investigated using musical stimuli. Music-syntactic irregularities elicit an early right anterior negativity (ERAN); this component is generated in brain regions that also serve the syntactic processing of language. Recent studies show that the ERAN, like the MMN, continuously decreases with increasing sedation caused by propofol (Fig. 2), and that the ERAN is eliminated at higher BIS values (above 68) than the MMN (S. Koelsch, W. Heinke, D. Sammler, D. Olthoff, unpublished data). The latter finding suggests that language functions are impaired by lower sedative drug doses than the functions underlying auditory sensory memory, and that neural mechanisms important for syntax processing do not operate at BIS values of around 68.

Another event-related potential (ERP) widely used to evaluate cognitive function is the P3. Generally speaking, this ERP component has been suggested to represent the transfer of information to consciousness, a process that involves different brain regions [59]. The classical parietally distributed P3 (often labelled as P3b) occurs only when individuals consciously detect a target stimulus. This ERP has been taken to reflect the operations of a mechanism that updates a model of the environment or of a context in working memory [60]. Irrespective of attention, however, certain stimuli may nevertheless elicit an earlier, more frontally distributed P3 (labelled P3a) [61], which is taken to reflect an involuntary switch of attention to an unexpected or relevant stimulus [62,63]. Recently, the effect of propofol on the P3 has been thoroughly investigated: when individuals listened passively to a series of tones, a P3a was elicited by deviant stimuli during wakefulness and light sedation, but abolished during deep sedation [36•]. In another experiment in which individuals were trained to respond to deviant stimuli via a button press response, however, a P3a (but no P3b) was visible (although clearly reduced) even under deep sedation (mean BIS = 68; at this level, individuals did not respond behaviorally to the task) (S. Koelsch, W. Heinke, D. Sammler, D. Olthoff, unpublished data).

To sum up, these findings indicate that neural processes located at the level of the primary auditory cortex remain intact during sedation. In contrast, the cognitive processes underlying the generation of MMN, ERAN and P3 (which involve neural generators located beyond the level of primary sensory cortices) are significantly affected by sedation. The processes underlying the generation of MMN and P3 are observable, however, although clearly reduced at a BIS of 68. The total breakdown of these processes occurs at BIS values lower than 68, presumably in a BIS range of between 68 and 50.

Brain activity during anesthesia assessed with behavioral tests

Numerous studies have investigated explicit and implicit memory after anesthesia. Explicit memory is mainly the result of inadequate anesthesia [5,7,64•]. In contrast, the possibility of implicit memory formation remains controversial. Very close control of anesthetic depth (BIS 50–55), however, prevents implicit memory formation [40••]. This tallies with neuroimaging and EEG studies demonstrating a lack of cortical activity under adequate anesthesia and contrasts with previous studies reporting the possibility of memory formation during unconsciousness [6,65,66]. Most of the ERP and imaging studies, however, investigated volunteers in the absence of surgery and thus do not rule out the risk of implicit memory formation facilitated by surgical stimulation under adequate anesthesia [65,67].

Conclusion

Functional neuroimaging complements electrophysiological and behavioral assessments of brain activity during anesthesia, providing a better understanding of how anesthetic depth affects neuronal networks mediating specific cognitive functions.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 662–663).

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