Neuroimaging consciousness and anaesthesia

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Anaesthesia offers an important tool for the scientific study of consciousness. Recent works will be discussed with an aim towards answering basic questions regarding the nature of consciousness and how it is removed by anaesthesia. What brain areas and systems must be turned off to remove consciousness? What brain regions or key processes must be turned back on to restore consciousness? How will a better understanding of the neurobiology of consciousness allow the clinician to give a better and safer anaesthetic? What new monitoring technology might enhance the safety of anaesthesia delivery and reduce the risks of intraoperative awareness? This lecture will touch upon these key topics in order to provide the background needed for understanding future developments in anaesthesia research.

Theoretical considerations in monitoring depth of anaesthesia

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It is surprising that anaesthesiologists routinely monitor the cardiorespiratory effects of anaesthetic agents, but do not consistently attempt to monitor the brain, which is the target organ of general anaesthesia. One possible explanation might be that there are controversies surrounding the efficacy, effectiveness, and cost-effectiveness of currently available brain monitors, most of which are based on processed EEG indices. Another possible reason is that practitioners have generally not received formal training in EEG interpretation and might therefore be reluctant to incorporate the EEG into their practice. However, recent research has shown that with appropriate structured training, anaesthesiologists can learn to recognize features of anaesthesia from a single EEG channel, and can frequently glean useful information from the EEG trace. One of the chief goals of brain monitoring is to track anaesthetic depth and to use the brain monitor to guide the appropriate titration of anaesthetic agents. Hypothetically, depth of anaesthesia (DOA) monitors would allow practitioners to decrease the amount of administered anaesthesia without incurring an increased risk of unintended intraoperative awareness.

An ideal DOA monitor would need to have certain key attributes, including:

(i) As state transitions occur rapidly (e.g. arousal from unresponsive to awake), the index would have near perfect discrimination between consciousness and unconsciousness; or between wakefulness and unresponsiveness, which are clinically relevant surrogates.

(ii) A high correlation coefficient would reliably be observed (i.e. in all patients) between the DOA index and the anaesthetic concentration in the brain. If the index were to display significant variability at various anaesthetic concentrations in individual patients, this would curtail its utility.

(iii) The DOA index would be sufficiently sensitive (the slope of the concentration response curve would be sufficiently steep) in individual patients to allow reasonably accurate estimation of relative anaesthetic concentration based on the index.

(iv) The relationship (slope) between anaesthetic concentration and the DOA index would be relatively robust among patients, with parallel shifts to the left and right representing increasing and decreasing anaesthetic sensitivity, respectively.

(v) The index would have a rapid response time so that the practitioner would be alerted expeditiously to state changes (e.g. sudden arousal).

(vi) The index would retain accuracy for all anaesthetic agents and combinations of agents.
(vii) It would remain robust in the face of artifacts and drugs that currently confound DOA indices (e.g. surgical cautery and neuromuscular blocking agents).

(viii) The monitor would detect changes in relevant brain regions, and would also track alterations in connectivity between brain areas.

Currently available candidate DOA indices meet each of these key requirements to varying extents. An important challenge facing anaesthesiologists and other neuroscientists is to address the deficiencies of currently available monitors. Future technology should ideally be transparent, biologically explicable, and non-proprietary. Our objective should be to devise accurate brain monitors that reliably track DOA, and allow anaesthesiologists to incorporate interpatient variability in anaesthetic sensitivity into the scientific practice of anaesthesia.

**Brain-region specific effects of GABA on sleep, wakefulness, and anaesthesia**

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Most drugs used to produce sleep, sedation, or general anaesthesia act by enhancing transmission at GABAA receptors. Preclinical studies demonstrate that the effects of GABA on behavioural states of arousal are brain-region specific. For example, GABAA receptor agonists cause sleep when administered directly into the posterior hypothalamus yet produce wakefulness when delivered into the anterior hypothalamus.1 Pharmacologically enhancing GABAergic transmission within the pontine reticular formation (PRF) increases wakefulness, decreases sleep, and increases time to loss of righting for isoflurane and propofol.2–5 Similarly, decreasing GABAergic transmission in the PRF decreases wakefulness, increases sleep, and decreases isoflurane and propofol induction time.2–5 These data indicate that endogenous GABA acting at GABAA receptors in the PRF functions to promote wakefulness. The finding that altering GABAergic transmission in the PRF does not change recovery time from isoflurane6 or propofol7 anaesthesia supports the concept that induction of and emergence from general anaesthesia are not mirror-image processes,7 and suggests that GABAergic transmission in the PRF contributes to the maintenance, but not the initiation, of wakefulness.

The hypothesis that GABA in different brain regions functions to promote different behavioural states is further substantiated by measuring levels of endogenous GABA across behavioural states. Comparing levels of endogenous GABA during wakefulness, non-rapid eye movement (NREM) sleep, and REM sleep has revealed the greatest levels occur in the PRF during wakefulness,8 in the cerebral cortex during NREM sleep,9 and in the dorsal raphé nucleus during REM sleep.10 Comparing GABA levels during wakefulness and isoflurane anaesthesia shows that in the PRF and posterior hypothalamus, GABA levels are greater during wakefulness.4–11

Behavioural states are generated by complex interactions between multiple transmitters in many brain regions. Acetylcholine (ACh) promotes the brain-activated states of wakefulness and REM sleep. In the PRF, ACh participates in the generation of REM sleep and endogenous GABA acting at GABAA receptors in the PRF inhibits both REM sleep and ACh release.2,12 REM sleep is characterized by relatively high levels of ACh and relatively low levels of GABA in the PRF, supporting the interpretation that high cholinergic tone and low GABAergic tone in the PRF are both important for generating REM sleep. Figure 1 shows that the ratio of ACh/GABA across states differs between brain regions. Data in Figure 1a are from ref. 8. For Figure 1b, GABA data are from ref. 9 and ACh data are from ref. 13.

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**References**

 Isoflurane alters multimodal integration in the primary auditory cortex

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Introduction. A key component of sensory awareness is the comparison of intracortically generated predictions about our environment with sensory information from the outside world. In the auditory cortex, an important example of this process is modulation of auditory responses by descending cortical input from the visual system. Evidence suggests that upon anaesthetic-induced loss of consciousness, ascending sensory pathways are relatively unaffected, but descending and intracortical pathways are disrupted, potentially leading to a disruption of the prediction process and thus sensory awareness. Here, we investigated the laminar profile of synaptic activity in the primary auditory cortex to determine the effect of isoflurane (iso) on visual–auditory integration.

Methods. Five Sprague–Dawley rats were chronically implanted with single-shank electrode arrays (Neuronexus; 16 × 100 μm spacing) in left A1. After a 1 week recovery period, animals were placed on a heating pad in a sound-proof enclosure and local field potentials were recorded in response to tones (50 ms free-field at best frequency), LED flashes (1 ms, contralateral eye), and paired stimulation with visual preceding auditory stimuli by 50–100 ms. Current source density was estimated using the spline inverse CSD method. During each recording session, data were collected under control conditions for 1 h followed by a drug condition for 45 min (iso 0.4%, 0.8%, or 1.6% applied in room air) followed by a 1 h recovery condition.

Results. CSD analysis revealed stereotyped spatiotemporal patterns of current sinks for auditory and visual stimuli. In control, auditory stimuli elicited earliest sinks in middle layers at 10 ms that spread first to supragranular and then to infragranular layers over the next 40 ms, presumably reflecting intracolumnar information transfer. Strong sinks were rarely observed after stimulus offset. Visual stimuli elicited longer latency (50–100 ms) current sinks in infragranular layers followed 100 ms later by sinks in supragranular layers. Preceding visual stimuli shifted the auditory-evoked CSD profile towards deeper layers, with supragranular sinks suppressed and infragranular sinks enhanced. Under iso at 0.8% and 1.6%, similar early sinks were observed in response to auditory stimuli, but additional strong current sinks moved from superficial layers to deep layers over the next 100 ms. Early responses to visual stimuli were qualitatively similar under iso, but late reverberatory activity was also observed, and auditory responses were no longer modulated by preceding visual stimuli, with the shift to deeper layers in the CSD profile absent. These effects were not apparent at 0.4% iso.

Discussion and conclusion. Our data show that iso does not suppress cortical responses to sensory stimuli, but does alter the spatiotemporal activation pattern within the cortical column, with late reverberatory activity present under hypnotic doses but not subhypnotic or control conditions. Modulation of auditory responses in A1 by preceding visual stimuli is apparent at subhypnotic doses of iso, but is disrupted at 0.8% iso, which is the concentration that causes loss of righting reflex (and presumably consciousness) in rats. We suggest that these effects on intracortical processing contribute to loss of consciousness under general anaesthesia.

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Framework for a cognitive psychology of anaesthesia

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The problem of implanted cognitions during states of general anaesthesia remains. From exposure to auditory information to nociceptive registrations within the brain, the problem becomes one of empirical test. To what extent are relevant events registered and alter the unconscious knowledge base perturbing it in interesting ways? The framework will examine two areas: language understanding and pain registration during anaesthesia, and their consequences.
A patient has a preload of thoughts, feelings, and expectations within the nervous system before surgery. This nervous system is then subject to anaesthesia. Does it cooperate or resist? With knowledge activated before conscious attention, pertinent information to the nervous system is possible during some but not all states of general anaesthesia. These cognitive activations have been studied extensively and recently summarized. 1

Studies of atomistic stimulation miss, in my opinion, the semantic activations in studies of priming and the like. In 1995, working with Ted Eger and Ben Chortkoff, we published the Levinson replication. 2 I will review this study as it contains valuable findings for human learning and memory research in anaesthesia. While there was no recall or hypnotic retrieval of any auditory information from the demonstrably unconscious and anaesthetized subjects, that is, the ‘surgical crisis’ of the original Levinson study, there were two positive findings: (i) Levinson was correct as to who had received the crisis or not, and (ii) behavioural instructions to touch the ear or chin when we take your blood pressure during the interview tomorrow presented during anaesthetic unconsciousness in the higher scoring subjects on the SCHS scale of hypnotizability were acted out, but without any conscious recall by the subject.

A functional and pertinent activation of knowledge should be assumed. ‘You couldn't get the black stuff out’ is a perfect example. A woman recovering from abdominal cancer surgery was depressed to the point of suicidal ideation, had psychiatric consult soon after, and had no response to medications. A final surgical follow-up weeks later was benign, reflecting the surgeon’s opinion that all malignancy was removed. The surgeon had expressed this also during the hospitalization. Yet the woman presented in severe depression, convinced she was going to die, weeping, and then, she said, blurtting out, ‘But you couldn’t get all the black stuff out’. The surgeon was stunned. Cancer is not black; he had resected with clean margins. A unique moment in the care of the patients, they also show how difficult it is to distinguish different states of consciousness.

Cerebral connectivity in disorders of consciousness
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Introduction. During the last decade, functional neuroimaging of disorders of consciousness (i.e. coma, vegetative state, and minimally conscious state) has evolved from measuring resting cerebral blood flow or electrical activity to studying functional response to sensory stimuli and to active paradigm asking patients to concentrate on doing a task like playing tennis. While these methods have improved the care of the patients, they also show how difficult it is to distinguish different states of consciousness.


Results. I will cover results obtained using a range of functional and effective connectivity approaches based on positron emission tomography, functional magnetic resonance imaging, high-density EEG, and TMS-EEG recordings. Experimental work performed in other unconscious states (i.e. anaesthesia and deep sleep) will also be introduced.

Conclusions. Current evidence suggests that loss of consciousness is associated with a loss of cerebral integration, a loss of brain activity differentiation (stereotypical activity), or both. Future research should aim at acquiring normative data in order to compare the sensitivity and specificity of the different techniques, and at getting closer to neural mechanisms, for example, using multimodal approaches. It could also be of interest to combine experiments to a theoretical approach and to integrate current knowledge about neural correlates of consciousness into a unified diagnostic framework. This would allow moving from exploratory to explanatory correlates of consciousness, and hopefully improve the patients’ diagnosis, and their management at the clinical bedside.
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Anaesthesia awareness registry: patient responses to awareness
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Introduction. The Anesthesia Awareness Registry (www.awaredb.org) was established in October 2007 to better understand the patient experience and the psychological impact of anaesthesia awareness.

Methods. After IRB approval, subjects 13 yr or older who self-reported explicit recall during general anaesthesia (GA) were recruited. A survey included questions about the awareness experience and psychological sequelae. Medical records were requested. Overall patient characteristics, awareness experience, and psychological sequelae were based on survey data. Type of anaesthesia was determined from medical records. The Michigan Awareness Classification1 was used to report levels of sensation. Fisher's exact test was used to compare awareness recall and psychological sequelae between GA and non-GA [monitored anaesthesia care (MAC), sedation without an anaesthesia provider, or regional anaesthesia] for patients who experienced awareness in 1990 or later and submitted medical records.

Results. As of March 3, 2011, 251 subjects had enrolled in the Registry. Seventy-five per cent were women age 38 (14) so, and 68% reported awareness experiences since 1990 (range 1961–2010). Of 266 experiences reported by 251 subjects, 82% experienced tactile sensations and 60% also had pain or burning. Eighty-six per cent felt paralysed/unable to move and 88% felt anxiety, fear, or panic. Seventy-six per cent (n=202) of subjects reported one or more psychological symptoms (anxiety, flashbacks, trouble sleeping) after their awareness experience. From 81 medical records received for cases between 1990 and 2010, 69% of anaesthetics were GA (n=56) and 31% were non-GA [MAC=10, sedation=9, regional=6 (4 SAB, 2 epidural)]. Patients who self-reported awareness under GA were more likely to experience pain and paralysis (71%). Patients who self-reported awareness under non-GA were more likely to experience auditory or tactile sensations (20%, P=0.01). There was no difference in emotional distress between GA and non-GA (Fig. 2).

Discussion. A vast majority of patients experienced distress during their awareness experience regardless of their type of anaesthetic. Similar to findings from a single-centre quality improvement study,2 our data suggest that a patient’s understanding of intraoperative awareness may differ from that of an anaesthesiologist and that the disparity of expectations may lead to considerable patient distress.

Improved communication and patient education may be helpful.

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References

Effects of intraneuronal Ca2+: chelation on isoflurane actions in old and young rats
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Introduction. Our previous reports indicated that ageing potentiation of anaesthetic actions can be opposed by decreasing intraneuronal Ca2+ concentration ([Ca2+]i) using manoeuvres to block voltage-dependent Ca2+ influx.1 In keeping with this concept, we hypothesize that decreasing [Ca2+]i, using intraneuronal Ca2+ chelators can reverse ageing-induced enhancement of anaesthetic actions.

Methods. First, we determined the effects of intraneuronal Ca2+ chelator, BAPTA-AM (50 µM) on anaesthetic actions in hippocampal slices taken from young (2–3 months) and aged (22–24 months) Fisher 344 rats. Anaesthetic actions were measured by analysing the changes in field excitatory postsynaptic potentials evoked in hippocampal slices. Slices were incubated either in BAPTA-AM or its vehicle DMSO (0.12%). Secondly, young and
old Fisher 344 rats were split between two groups, the BAPTA-AM-injected group and a DMSO-injected control group. Isoflurane anaesthesia was induced and then maintained at various concentrations until MAC was determined using the flick tail test. Meanwhile, the EEG was recorded for every isoflurane concentration used during the experiment. In addition, two other determinants of recovery from the anaesthetic action were measured by time required to eye opening and regain the righting reflex. During the study, we also measured end-tidal isoflurane and CO₂ concentrations.

**Results.** Aged slices incubated and perfused with BAPTA-AM showed that isoflurane actions were partially reversed compared with those perfused with DMSO. On the contrary, isoflurane actions were enhanced in young slices perfused with BAPTA-AM.

Intraperitoneal injections of BAPTA-AM enhanced MAC for isoflurane by 28.78 (4.6) [mean (SD)]% and increased the number of bursts during isoflurane-induced EEG burst suppression in old animals. Such effects of BAPTA-AM were not observed in young animals. The latency to eye opening and righting reflex after administration of isoflurane 2 MAC for 1 h was not affected by BAPTA-AM injections in old and young animals (Fig. 3).

**Discussion.** The intraneuronal Ca²⁺ chelator, BAPTA-AM, improves synaptic efficiency and plasticity in aged neurones. Such effect might have attenuated the ageing-induced decrement in the MAC values for isoflurane.

**Keywords:** ageing; intraneuronal calcium chelation; MAC

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**Unconscious synaesthesia: a layered perspective**

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The focus of this paper is to present the unconscious experience from the perspective of the patient experiencing pain. Based on my research and on my own extensive experience as a patient, this will be a first person perspective explaining how sensory perceptions may not translate into the unconscious experience in the same manner that they would be interpreted by the conscious mind. This transformation is reminiscent of the phenomenon of synaesthesia, although not precisely. Synaesthesia is the cross-modal transformation of sensory information—the stimulation of one sensory modality that produces a sensation in one or more dissimilar sensory modalities. I propose the concept of unconscious synaesthesia, a phenomenon in which sensory input may cross sensory modalities in the unconscious brain. Measures that access specific recollections of specific sensory elements such as sound and language may miss the essence of the patient’s sensory experience—an experience that may be a mix of sensations from different sensory modalities that are too complex to be easily understood or easily communicated. Other measures, which ask open-ended questions about possible memories, may still access only some of the information of an unconscious event. Thus, the current testing and interview measures that rely on recall that is more explicit or sensory specific may provide data that suggest much less mental processing than might be occurring.

These personal experiences are presented with the hope that this insight may guide researchers into probing more fruitful measures of the unconscious patient’s memory. In addition, I hope that this analysis might stimulate a broader conceptualization of the unconscious experience and diversify research objectives and strategies to include phenomenon beyond those traditionally investigated.

**Keywords:** memory; pain; perception; synaesthesia; unconsciousness

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Target-controlled propofol infusion linearly suppresses auditory-evoked potentials and bispectral index

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Introduction. The purpose of the study is to evaluate auditory-evoked potentials (AEPs) (N1P2) and bispectral index (BIS) scores during target-controlled propofol infusion (TCI).

Methods. A total of 14 subjects participated in this study. The propofol administration (0.4, 0.8, 1.2, 1.6 µg ml⁻¹) was provided with a TCI device. For AEP recording, a 40 channel EEG and a stimulus unit (EMISU) were used.1 The auditory stimuli (1500–1600 Hz, 85 dB SPL) were applied with headphones. Central location was analyzed. BIS recording was performed. One-way analysis of variance was used for statistical analysis.

Results. The amplitude of N1P2 was found to be 13.9 µV at 0.0 (no-drug) dosage level, 11.33 µV at 0.4 µg ml⁻¹, 6.00 µV at 0.8 µg ml⁻¹, 3.58 µV at 1.2 µg ml⁻¹, and 2.77 µV at 1.6 µg ml⁻¹ dosage levels, respectively (Fig. 4). At (0.0) level, the BIS value was significantly higher than the other dosage level (P<0.001). Beyond 1.2 µg ml⁻¹, all subjects reached loss of consciousness.

Discussion. The vital sign monitoring is most commonly used method in anaesthesia.2 Besides that EEG and AEP-based methods were used.3,4 There are a number of AEP studies during anaesthesia which have more focus on early/middle latency responses.3,4 In the current study, we tested the suppression effect of propofol on late latency AEP responses while monitoring BIS. This way we have obtained a linear decrease in potentials as anaesthetics suppression, accompanied by a direct correlation with BIS values. These AEP responses disappeared reaching a level of 1.6 µg ml⁻¹ propofol. Accordingly, these late auditory responses should not be expected at regular anaesthesia levels of typical surgery (>2 µg ml⁻¹ propofol). Henceforth, the correlation between the BIS and AEP may provide a suitable analysis platform to study the transition between conscious states and their functional properties.

Keywords: AEP; BIS; N1P2; propofol; suppression of consciousness; target controlled infusion

Funding

References

Fig 4 The BIS values at different propofol dosage levels are plotted (left primary axis) against AEP (N1P2) at secondary axis at right. The horizontal axis denotes the propofol target doses (µg ml⁻¹).
Electrode position for the auditory-evoked potentials extraction in awake subjects

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Introduction. Recording auditory-evoked potential (AEP) signals is challenging: AEP waves show low amplitudes (1–3 μV) and are embedded in the EEG signal, whose amplitude is significantly higher (typically 10–100 μV). We hypothesize that using the earlobe position instead of the cheekbone position would improve the quality of the extracted AEP.

Methods. Records of brain electrical activity were performed with three pre-gelled electrodes placed in two different positions. The reference electrode was always placed above the eyebrow and the two active electrodes were placed in the following positions: frontal and cheekbone (1) and frontal and earlobe (2). Volunteers were stimulated bilaterally with randomized 1 kHz clicks during 7 min. They had the eyes closed during each test, except from 1 min in the middle in order to make sure they were not falling asleep. Visual inspection was used to evaluate the quality of the obtained AEP: the main peaks (V, Na, Pa, Nb, Pb) were manually detected in the average AEP wave and the detection rate was used to assess the quality of the obtained AEP.

Results. Forty volunteers were included in the study. Figure 5 shows the success rate in the AEP peaks detection. For all the considered peaks, the configuration using the earlobe position showed a higher detection rate.

Discussion. The earlobe position appears to be a better option for high-quality AEP recordings. The percentage of peaks detected decreases with latency: the higher the latency, the lower the detection rate. This conclusion is consistent with the results of other researchers¹ stating that Nb and Pb peaks do not appear in a high percentage of the population.

Reference


Meyer–Overton meets quantum physics: conscious awareness, memory, and anaesthetic binding in tubulin hydrophobic channels

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Introduction. Anaesthetic gases selectively erase conscious awareness and memory, largely sparing non-conscious brain activities. At the turn of the 20th century, Meyer and Overton found anaesthetic gas potency correlated with solubility/binding in a non-polar, hydrophobic environment, subsequently shown to be hydrophobic pockets within proteins,¹ including 70 receptors, ion channels, and tubulin in cytoskeletal microtubules.² Anaesthetic gases bind in protein hydrophobic regions by quantum London forces, electron cloud dipole couplings with non-polar amino acid residues, for example, electron resonance rings of phenylalanine and tryptophan. Theories suggest anaesthetics act in protein hydrophobic regions by preventing endogenous quantum effects,³ and that quantum computations in microtubules support consciousness.⁴ Evidence for functional quantum effects in warm biology include ballistic conductance at megahertz resonant frequencies in microtubules.⁵ Quantum processes in microtubule hydrophobic regions are potential sites for consciousness and anaesthetic action.

Methods. We used molecular modelling to identify tryptophan, phenylalanine, and anaesthetic binding sites in tubulin, and calculated anaesthetic-tubulin binding energies and affinities.

Results. Within tubulin, eight tryptophans and 32 phenylalanines cluster and align (<2 nm separation) along tubulin–tubulin helical microtubule lattice pathways. Predictive
anaesthetic binding energies are between \(-2.54\) and \(-3.12\) kcal mol\(^{-1}\), corresponding to dissociation constants (binding affinity) between 6 and 16 mM. Anaesthetics bind at five putative sites per tubulin, for example within 6 Å (0.6 nm) of an aligned tryptophan with a binding energy of \(-2.74\) kcal mol\(^{-1}\) (11.7 mM).

**Discussion.** Anaesthetic-tubulin binding is 10–100 times weaker than anaesthetic binding to other neuronal proteins, for example, GABA\(\alpha\) receptors. However, there are 100 times more tubulins than GABA\(\alpha\) receptors per neurone. Intratubulin hydrophobic channels match microtubule lattice helical pathways, and may account for ballistic conductance\(^5\) and topological quantum computing implicated in consciousness and memory.\(^6\)\(^7\) Microtubule hydrophobic channels (possibly quantum entangled with GABA\(\alpha\) receptors and other neuronal proteins) are viable candidate sites for consciousness, memory, and anaesthetic action.

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**Molecular substrates of general anaesthetics**

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Although considerable progress has been made since their discovery in the 19th century, current understanding of the molecular and cellular mechanisms that underlie the pharmacology of general anaesthetics is incomplete. This lack of knowledge limits both our ability to use these important drugs with optimal safety and efficacy and to design potentially safer and more efficacious drugs. Considerable evidence now implicates agent-specific effects on discreet molecular targets to modulate synaptic transmission and the function of neuronal networks central to each of several specific anaesthetic endpoints. Major progress in understanding the molecular pharmacology of i.v. anaesthetics has come with the application of genetic approaches, but the actions of the inhaled anaesthetics have been more difficult to resolve. There is now ample evidence that clinical concentrations of most general anaesthetics influence the function of specific proteins, in particular ligand-gated ion channels. However, there is still relatively little information about how modulating these channels alters central nervous system function at the cellular and network levels, and even less about how these changes lead to the state of general anaesthesia. Advances in systems neuroscience should extend our knowledge of anaesthetic effects from the molecular and synaptic levels to their actions on cognitive and motor functions of the intact organism.

**Keywords:** anaesthetics, general; ion channels; ligand-gated ion channels

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**Unconsciousness and EEG burst suppression**

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Unconsciousness is produced by several different mechanisms such as physiological sleep, metabolic disorders, and intoxications such as general anaesthesia, diffuse ischaemic damage, and seizures. In all of these, the EEG pattern of burst suppression is seen, but during sleep only in premature babies, and is then called trace discontinuity.

Burst suppression is defined as bursts of high-amplitude EEG interrupted by relative quiescence, suppressions. Another essential feature is that the duration of a burst or suppression is variable and unpredictable, unless a burst is induced with stimulation. A third characteristic feature is that two causes of burst suppression strengthen each other, that is, together produce longer and sometimes lower amplitude suppression than either one alone. Thus, the effect of two anaesthetics is often additive. Even subclinical hypoxic ischaemia increases duration of suppressions in trace discontinuity of neonates. On the other hand, typical ischaemic burst suppression in neonate may gradually develop into normal physiological discontinuous sleep pattern of quiet sleep upon recovery.

The development of EEG before birth, recovery from general ischaemic brain damage, or recovery from generalized tonic clonic seizure, and also recovery from very deep anaesthesia, follow the same pattern. First, during continuous suppression, low-amplitude slow waves appear, then series of waves of increasing amplitude bursts. The suppressed periods become shorter until they disappear, and finally turn into continuous slow activity. In this development, burst suppression EEG and brain activity may become epileptic in anaesthesia, intoxications, ischaemic damage. These developments can also occur focally in focal brain damage and focal seizures, and this is easy to understand, keeping in mind that burst suppression and epileptic patterns are closely related to sleep slow-wave oscillations. These are essentially a local event in the cortex, although often synchronized in the whole cortex. Notice that the patient may be conscious during focal burst suppression.

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The suppressions may be of variable amplitude, often under 5 µV with conventional EEG band. However, EEG patterns well over 5 µV are often seen. With propofol and isoflurane, suppression consists of low-amplitude arrhythmic alpha–theta activity. In propofol anaesthesia, also sleep spindles are seen. In diffuse brain damage, regular alpha frequency rhythm can dominate during suppression: alpha coma. In epileptic disorders, focal recruiting rhythm, up to 1 mV spikes, or periodic epileptiform discharges can be seen during suppression. Anaesthetics such as sevoflurane may, in fact, produce all such characteristic EEG patterns of status epilepticus with the difference that in anaesthesia, the changes are transient during induction and in status epilepticus, they continue.

Sometimes in seizure disorders, we see patterns very similar to burst suppression: high amplitude more or less epileptiform high-amplitude bursts of variable duration and responsive to stimulation. The suppressed periods are then a clue to consciousness: the EEG may be normal or near normal and the patient then fully conscious even during discharges. This reminds us that there is no simple correlation between EEG and any other measure of brain activity—a fact that is increasingly evident from recent studies of minimal consciousness in brain damage. And when unconsciousness during anaesthesia is studied, the patterns of sleep on the one hand and the development from prenatal patterns to adult patterns must be considered. Normal and pathological physiology of sleep and arousal systems are essential keys for understanding unconsciousness during anaesthesia, including the level of EEG burst suppression.

**Electrical fields of the sleep-related slow-wave EEG patterns in anaesthesia**

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**Introduction.** Understanding the electrical fields of EEG during anaesthesia is necessary, among others, for understanding the function of indexes of depth of anaesthesia, and to avoid misinterpretation of EEG signals recorded from outside and inside the brain.

**Methods.** We have developed a computer simulation of electrical fields generated by the EEG slow oscillations of deep anaesthesia, slow waves, and burst suppression, which correspond to the slow waves of deep physiological sleep, delta activity, and discontinuous EEG of neonatal sleep. The model consists of a sphere, where a hole in the cortex and bony cranium at the bottom corresponds to the brainstem and foramina under the hemispheres. The slow oscillations of anaesthesia, including burst suppression, are modelled with a synchronously active dipole surface in the cortex.

**Results.** The currents generated by the cortex create a closed loop by flowing from under the surface of the cortex inside of hemispheres down and turn through cerebrospinal fluid and scalp to the outer surface of the cortex. The current density is highest at the bottom of the cranium, that is, near the thalamus. For this reason, an electrode pair oriented in the direction of current at, for instance, the subthalamic nucleus, records cortical activity with a relatively high voltage. Correspondingly, electrodes outside the scalp also record cortical EEG. As an example, the burst suppression pattern of propofol anaesthesia was recorded from electrodes located vertically with a distance of 3 cm on the masseter muscle below the zygomatic arch (Fig. 6).

**Discussion.** Our model explains why relatively high-amplitude cortical EEG can be recorded from two...
electrodes in the subthalamic nucleus, and low-amplitude pattern even from electrodes on the cheek. It also explains why the burst suppression pattern is sometimes difficult to measure accurately from a recording made between two frontopolar electrodes, popular in monitoring. For interpretation of EEG during anaesthesia, understanding the electrical fields of cortical EEG on the scalp and subcortically is necessary.

**Keywords:** anaesthesia; EEG; sleep

**Reference**


**Information flow as electrophysiological signature of cortical connectivity during consciousness and propofol-induced unconsciousness**

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**Introduction.** Recently, functional connectivity analysis of resting state networks (RSNs) under propofol-induced loss of consciousness (LOC) reported a decreased connectivity of higher cortical networks.1 The neurophysiological correlates of observed haemodynamic changes on the systemic information processing level remain unclear. The present investigation analyses effects of propofol-induced unconsciousness on fMRI blood oxygen level-dependent (BOLD) connectivity and on EEG information flow based on symbolic transfer entropy (STEn).2

**Methods.** Approved by the ethics committee, 15 volunteers were enrolled into the study. After a resting period, volunteers were instructed to relax and close eyes while BOLD 3T-fMRI and 64-channel EEG baseline (BL) recordings were performed 15 min. Subsequently, propofol was infused until LOC using a target-controlled infusion pump. At this level, concentration was maintained 15 min and BOLD fMRI/EEG was measured. Independent RSN components of fMRI were identified and differences between BL/LOC tested.3 STEn quantifies the mutual information flow between two signals and was computed over all channel pair combinations on EEG of 10 s length (0.5–30 Hz total bandwidth) and 50 ms time delay reflecting mainly information processing within the β-band. Thereby, information is coded by amplitude order sequences, where the degree of prediction of actual information from past signal content is reflected by a generalized Markov property. Effects of propofol (BL/LOC) were indicated by non-parametric tests based on bootstrap.

**Results.** fMRT analysis revealed a decreased connectivity within the frontoparietal network (P<0.05). Figure 7 shows density of STEn at BL (A) and LOC (A). Lower absolute values of STEn indicate balanced information exchange (STEn=0, color coded in white), higher values (STEn positive and negative) unidirectional coupling. Below the main diagonal, EEG from electrodes on the horizontal axis drives EEG from electrodes on the vertical axis if STEn<0 (blue), and EEG from electrodes on the horizontal axis is driven by EEG from electrodes on the vertical axis if STEn>0 (red).

**Discussion.** STEn reveals effects related to the information flow between cortical areas. A decrease in balanced flow in EEG and in corticocortical fMRI connectivity could be caused by loss of feedback connection.4 Thereby, long-range communication pathways according to default and executive control networks seem to be particularly affected, whereas local interactions are mainly preserved during propofol-induced unconsciousness.

**Keywords:** consciousness; electroencephalogram; functional connectivity; information

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**Fig 7** Density of STEn at BL (A) and LOC (A). Lower absolute values of STEn indicate balanced information exchange (STEn=0, color coded in white), higher values (STEn positive and negative) unidirectional coupling. Below the main diagonal, EEG from electrodes on the horizontal axis drives EEG from electrodes on the vertical axis if STEn<0 (blue), and EEG from electrodes on the horizontal axis is driven by EEG from electrodes on the vertical axis if STEn>0 (red).
Changes in brain electrical activity, and memories formation under the influence of anaesthetic drugs

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Abstract

Introduction. The mechanisms underlying loss of consciousness and amnesia created by various anaesthetics drugs are not fully understood yet. Different types of anaesthetics create different states of unconsciousness: Midazolam, a GABA receptor agonist, has potent amnesic effect; whereas ketamine, an NMDA antagonist, creates a state of dissociative anaesthesia.

Awareness during anaesthesia is a feared anaesthesia complication. This is a stressful condition, and was found to be related to postoperative PTSD.1

The amygdala, a set of nuclei in the medial-temporal-lobe, is involved in the acquisition and consolidation of emotional memories, especially in aversive memories.2 3 We therefore hypothesized that it has a major role in memory formation during anaesthesia and awareness episodes.

Methods. In order to study the mechanisms involved in memory formation during anaesthesia, we recorded extra-cellular electrical activity in the amygdala of Macaque monkeys. Recordings were performed during the execution of classical conditioning paradigm utilizing tone and aversive odours. We used odours as aversive stimuli because they have a direct anatomical route into the primate amygdala and underlie intense emotional states. We compared the activity under the influence of midazolam (i.m. 0.1 mg kg–1) and ketamine (i.m. 6 mg kg–1). The aversive odour was delivered by an olfactomeric system and applied via a nasal mask. We monitored the respiratory rate and tidal volume with a pressure sensor. We used the local field potentials (LFPs) to estimate the synaptic activity in the amygdale. The anatomical location of the electrodes was pre-established by MRI scans. All procedures were approved by the IRB/IACUC.

Results. Behaviour: Breathing pattern tracings conducted before, during, and after an auditory stimulation under aversive olfactory conditions were compared before and after administration of ketamine or midazolam. Preconditioning performed under midazolam exerted similar breathing patterns before and after the execution of the paradigm.

In contrast, breathing patterns changed after administration of ketamine, indicating the possibility that midazolam blocks the formation of aversive memory, whereas ketamine does not.

Neuronal activity: LFP from 50 electrodes were recorded in two monkeys. Fourteen sessions were recorded under the effect of midazolam and 13 under ketamine.

We observed a radical change in the pattern of LFP after ketamine injection: The intermediate-frequency waves (alpha and beta frequencies) were diminished. A gamma band, of 40–60 Hz, appeared and slow frequency (1–3 Hz) oscillations became prominent.

The changes after midazolam injection were less prominent: the alpha waves remained, but slow waves (3–4 Hz) became dominant. On top of these changes, peaks of higher frequency oscillations in the beta and low gamma range appeared during odour release.

Discussion. We suggest that the differential changes that occur after midazolam vs ketamine may explain the different states of anaesthesia observed with these drugs.

Preliminary behavioural results suggest that learning and memory formation are possible under the influence of ketamine, but not after midazolam administration.

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Collapse of neural inertia, a precursor for awareness?

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We have previously demonstrated that hysteresis in volatile anaesthetic dose–response curves cannot be fully explained solely by pharmacokinetics. Rather, we demonstrate in both mammals and invertebrates the existence of a behavioural state barrier that opposes transitions from the anaesthetized state back to the conscious wakeful state. This barrier, which we have termed neural inertia, is subject to both pharmacological and genetic regulation.1 In Shaker minisleep flies, ShMNS, which are known to be partially resistant to induction of anaesthesia, neural inertia is collapsed. Presently, we demonstrate that a homozygous mutation in the sleepless gene, sssP1, phenocopies the shaker mutant flies. Specifically, sssP1 flies also exhibit a small right shift in their EC50 for induction of isoflurane anaesthesia, and a massive right shift in the EC50 for emergence, awakening at relatively high doses of isoflurane at concentrations where their wild-type siblings remain anaesthetized. As with ShMNS flies, this combination leads to collapsed neural inertia, which we interpret to indicate instability in the barrier separating the
unconscious state from that of conscious wakefulness. The sleepless gene product (SSS) is known to interact with Shaker to modulate potassium currents. Hence, loss of function changes in either gene product is predicted to cause a relative depolarization of resting membrane potentials in affected neurones in mutant flies.

We hypothesized that the processes underlying anaesthetic induction and emergence may be anatomically separable. Capitalizing on the UAS-Gal4-inducible gene expression system in flies, we conducted a series of tissue-specific rescues of wild-type SSS protein in various subsets of neurones in the sss\textsuperscript{P1} mutant fly brain. While the majority of Gal4 driver lines did not affect anaesthetic induction or emergence, we demonstrate three groups of rescuing driver lines. Group 1 typified by the endogenous sleepless promoter driving Gal4 rescued induction, emergence, and neural inertia. Group 2, characterized by selective rescue of sleepless in glutamatergic neurones, caused a significant but parallel shift in both induction and emergence dose–response curves, thus fully restoring wild-type induction sensitivity, but failing to rescue neural inertia. Group 3 drivers, such as D42, failed to alter anaesthetic induction but fully restored emergence and neural inertia. Cumulatively, these results suggest that distinct sets of neurones are capable of modifying the ways in which the state of anaesthesia arises and dissipates. We suggest that populations of flies with collapsed neural inertia (Sh\textsuperscript{MNS} and Sss\textsuperscript{P1}, but not their wild-type siblings, Group 2 flies but not those in Group 1 or 3) may be especially vulnerable to awareness under anaesthesia, a hypothesis currently under investigation.

References

Propofol-induced activity changes in the hippocampus and neocortex

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Introduction. Non-linear, bivariate parameters can evaluate anaesthetic-induced changes on inter-channel regularity in EEG and cortical local field potential (LFP) recordings.\textsuperscript{1, 2} In this work, effects of propofol on LFP inter-channel regularity in the hippocampus and neocortex are evaluated. Therefore, the classical frequency bands were analysed with Bivariate Permutation Entropy BP\textsubscript{En}, in order to illustrate possible differences of propofol-induced effects.

Methods. LFP sequences were simultaneously recorded from four-channel electrode arrays placed in neocortical and hippocampal regions from nine mice. An artifact-free 5 s LFP sequence was extracted from each recording at control conditions and under hypnotic concentrations of propofol. Each sequence was evaluated with BP\textsubscript{En} (d=5) at the following frequencies: (i) $\theta$: 4–8 Hz, (ii) $\alpha$: 8–12 Hz, (iii) $\beta$: 12–24 Hz, and (iv) 5–15 Hz. BP\textsubscript{En} is an extension of the ordinal parameter permutation entropy\textsuperscript{3} with order d to two channels. It evaluates the mutual concordance of the distribution of the different d! permutations in both signals. BP\textsubscript{En} was calculated for every possible channel combination within each region. Effects of propofol were indicated by a two-sample Wilcoxon test (P<0.05).

Results. In the hippocampus, BP\textsubscript{En} averaged over all channel combinations was significantly affected in each analysed frequency band (Fig. 8). BP\textsubscript{En} increased at $\alpha$-frequencies and decreased in the $\theta$- and $\beta$-bands, whereas neocortical analysis only showed a significant increase in the $\alpha$-band. A 5–15 Hz analysis showed a significant increase in the hippocampus and a not significant increasing trend in the neocortex. The plot illustrates changes in BP\textsubscript{En} for the single-channel combinations of the averaged significant changes. Hippocampal $\theta$- and $\alpha$-activity showed a unitary propofol-induced trend and neocortical $\alpha$-activity. Hippocampal $\beta$-activity was unspecific despite a significant averaged effect. Functional structures seem to be unaffected by propofol in $\theta$- and $\alpha$-bands.

Discussion. Propofol seems to affect hippocampal LFP stronger than neocortical LFP. In both areas, BP\textsubscript{En}(\alpha) increases significantly, indicating higher irregularity among the channels. Synchrony in frequencies of 2–15 Hz apparently represents a key mechanism for interactions between the hippocampus and neocortex.\textsuperscript{5, 6} The higher irregularity in the $\alpha$-band under propofol may represent a disruption of these interactions.

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Corticocortical-evoked potential monitoring as a tool to investigate anaesthetic-induced unconsciousness: a preliminary report

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**Introduction.** Intracortical information transfer was disrupted during sleep and sedation with midazolam in earlier human studies using high-density EEG and transcranial magnetic stimulation. We studied the effects of sevoflurane on the cortical information transfer in a patient implanted with subdural electrodes, which might reveal more direct electrophysiological events on the cerebral cortex during anaesthesia and wakefulness.

**Methods.** A 22-yr-old male patient with intractable epilepsy underwent chronic implantation of subdural electrodes around the left temporal and frontal lobes under sevoflurane–remifentanil anaesthesia. After the end of surgery, we recorded corticocortical-evoked potentials (CCEPs) via a sheet electrode placed at the base of the left frontal lobe, along with somatosensory-evoked potentials (SSEPs), at end-tidal sevoflurane concentrations 1.5%, 1.0%, and 0.72%. We also evaluated behavioural awareness with observer’s assessment of alertness and sedation (OAA/S) and recorded bispectral indices.

**Results and discussion.** The patient was not responsive at all at 1.5% and 1.0%, but turned fully alert at 0.72% sevoflurane concentrations. Although the SSEP showed a concentration-dependent suppression, the CCEP appeared relatively unaffected by sevoflurane. More detailed analysis will be presented as preliminary results.

**Keywords:** anaesthesia; consciousness; evoked potentials

**References**

Dexmedetomidine, adenosine, and sleep: convergence or conflation?
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Background. States of consciousness are objectively defined by a constellation of physiological and behavioural traits. Since 1994, we have been systematically evaluating the hypothesis that neuronal networks that evolved to generate traits of sleep are preferentially involved in generating traits that define states of sedation and anaesthesia. This hypothesis has been tested using ketamine, potent agents, opioids, and sedative/hypnotic GABA A agonists. The present study extends evaluation of this hypothesis to the α-2 adrenoceptor agonist dexmedetomidine (Dex). Adenosine is an endogenous sleep-promoting molecule and in the substantia innominata (SI) of the basal forebrain adenosine levels accumulate during wakefulness and significantly decrease during sleep. This study is testing the hypothesis that Dex causes changes in SI adenosine levels, sleep architecture, and EEG power equivalent to those observed during sleep.

Methods. All procedures involving Sprague–Dawley rats were reviewed and approved by the University of Michigan Committee on the Use and Care of Animals and by the National Institutes of Health. Dependent measures were quantified before and after Dex was administered systemically or by microdialysis to the SI. Control conditions were provided by systemic administration of saline or by microdialysis with Ringer’s. As previously described, SI levels of adenosine were quantified using microdialysis and high-performance liquid chromatography with UV detection. States of sleep and wakefulness and EEG power were objectively assessed using standard electrophysiological criteria.

Results. Microdialysis delivery of Dex to the SI of isoflurane anaesthetized rat did not decrease SI adenosine. In contrast to sleep, systemic administration of sedating doses of Dex to unanaesthetized rat also did not significantly decrease adenosine levels in the SI. Dex significantly disrupted the temporal organization of sleep for >24 h. Dex significantly increased EEG delta power compared with EEG delta power recorded during non-random eye movement sleep.

Conclusions. Dex-induced sedation and sleep are equivalent only if one accepts a poorly nuanced comparison. Fine-grained quantification of lower level neurochemical and electrophysiological phenotypes that define states of consciousness do not support the equivalency of sleep and Dex-induced sedation.

Funding
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Novel approaches to the physiological monitoring of anaesthetic depth based on neural field theory
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To date, depth of anaesthesia (DoA) monitoring based on the analysis of spontaneous or evoked EEG activity has relied on a range of heuristic measures and methods to objectively assess the hypnotic state. Because these measures and methods are not derived from an understanding of how rhythmic activity arises in the EEG, or how such activity is modified by anaesthetic agents, the performance of such heuristic methods must necessarily be suboptimal. Therefore, the development of physiologically better-motivated approaches to DoA monitoring is expected to offer more robust and comprehensive solutions for the assessment of anaesthetic effect. One emerging physiologically motivated approach showing promise is based on the somewhat recon- dite branch of biomathematics known as cortical neural field modelling. Cortical neural field models attempt to characterize the spatio-temporal activity of cortical neural tissue at a scale intermediate between that of the single neuron and the whole brain. In particular, they model the mean activity of appropriately circumscribed populations of cortical neu- rones. For this reason, they have found great utility as a framework for understanding the dynamical genesis of EEG activity. Further, because these models contain generaliza- tions of the physiology of single neurones and their synaptic interactions, the bulk effects of many of the identified cellular, sub-cellular, and molecular targets of anaesthetic action can be meaningfully incorporated. In this manner, neural field models can act as a mesoscopic bridge between the microscopic targets of anaesthetic action and their macro- scopic, or whole brain, effects (Fig. 9). One specific neural field approach of particular relevance to DoA is attributed to Bojak and Liley. This model posits that the rhythmic activity observed in the EEG emerges from the reverberant activity of spatially distributed networks of interconnected excitatory and inhibitory cortical neurones. Not only is this theory able to describe the resting EEG, it is also able to account for a number of electroencephalographic phenomena that are of relevance to better understand and monitor anaesthetic action—the ‘beta’ buzz, the ‘biphasic’ power surge during in- duction and emergence and anaesthetic agent-induced
ictogenesis. Although the full theory is mathematically elaborate, it nevertheless suggests a quite explicit, and easily implemented, method for the analysis of spontaneous EEG, which can be readily utilized to monitor DoA. Specifically, it gives rise to two measures that uniquely parameterize anaesthetic action: cortical state (CS, a measure of cortical responsiveness) and cortical input (CI, a measure of the magnitude of cortical input). Initial results suggest CS best measures the hypnotic component of anaesthesia, whereas CI may be useful as a measure of analgesic efficacy and the nociceptive–antinociceptive balance. 2

Keywords: consciousness monitors; electroencephalogram; mathematical model

References

Brain networks mediating information and integration for consciousness during propofol sedation

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Introduction. Current theories and empirical data¹ ² suggest that consciousness is determined by a system’s capacity for information integration, and disrupting cortical information integration may account for the mechanism of general anaesthesia in suppressing consciousness. Yet, it remains unclear how the neural correlates sustaining information and integration are partitioned in the brain for a specific task. Based on the theoretical implications¹ and the unique neuroanatomical features of the thalamocortical system,³ we hypothesize that the specific and non-specific thalamic divisions are specifically concerned with the two criteria of consciousness, namely, information and integration, respectively. We sought to test this hypothesis in a paradigm in which propofol sedation suppresses auditory verbal memory by preserving sensory reactivity but disrupting cortical integration in the brain.

Methods. Eight healthy volunteers underwent fMRI scans at 1.5 T while listening to and attempting to remember a distinct set of 40 English words during each of the three sequential states of consciousness: wakefulness, deep sedation (0.75 or 1.0 μg ml⁻¹ propofol plasma concentration, STANPUMP), and recovery of consciousness. Conversational unresponsiveness and global loss of memory were achieved in deep sedation. Seed regions representing the specific and non-specific thalamic nuclei were manually defined in the coronal plane of each individual’s high-resolution anatomical images. Functional connectivity analyses were performed to examine the integrity of the thalamic networks across the three states of consciousness.

Results. Task-related responses persisted in the primary auditory cortex (PAC) but vanished in the inferior frontal gyrus (IFG) and premotor areas in deep sedation. As anticipated, the two divisions of the thalamocortical system exhibited distinctly different patterns of the change of functional connectivity in response to propofol administration (Fig. 10). The integrity of the specific thalamic network is largely preserved; the non-specific network is severely suppressed in deep sedation and is subsequently reinstated in recovery.

Discussion. This study bridges the neuroanatomical findings of the thalamocortical system³ with the information...
Theoretical account of consciousness. Given the formulation of anaesthetic mechanisms at a critical depth of anaesthesia as ‘information received but not perceived’, we demonstrate that this concept is well represented by the differential changes of the integrity of the specific (for functional specialization, information) and non-specific (for integration) thalamic networks during propofol sedation. Together, our methodology and results offer a promising framework for considering and identifying the potential neural substrates in the brain that sustain consciousness from the perspective of information and integration as suggested by the theories.

**Funding**
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**Increased functional connectivity in the limbic network of isoflurane-anaesthetized rats during electrical stimulation of the nucleus pontis oralis**

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**Introduction.** The nucleus pontis oralis (PnO) is a major component of the functionally classified mesopontine tegmental anaesthesia area of the brainstem. In addition, the PnO is a key component of the ascending arousal system, and has been implicated in the regulation of the state of consciousness across normal sleep–wake cycles of the central nervous system. Here we investigated whether electrical stimulation of the PnO would facilitate electroencephalographic arousal and alteration functional connectivity (FC) in the MRI signal during light isoflurane anaesthesia in rats.

**Methods.** A total of eight male Sprague–Dawley (SD) rats weighing 280–350 g were used in this study. Platinum epidural electrodes were implanted above the left frontal cortex for EEG recording and a home-made bipolar carbon-fibre electrode was implanted in the left PnO for electrical stimulation. EEG signals were acquired throughout the experiment. A 9.4 T spectrometer (Biospec Avance 94/31; Bruker, Germany) was used for MR imaging. Isoflurane concentration (1.2–1.4%) required for the presence of electroencephalographic slow δ waves was determined in each animal and kept constant throughout the experiment. Electrical stimulation of the PnO consisted of square pulses at 300 Hz, 5–7 V, 0.1 ms width, 3 s on, and 57 s off for 10 cycles. The nucleus basalis of Meynert (NBM), chosen for its suggested role in the regulation of the state of consciousness, was used as a seed for FC correlation coefficient analysis of the low-frequency BOLD time courses.

**Results.** PnO stimulation produced EEG desynchronization for 10–30 s. Compared with the unstimulated state, stimulation-induced significant BOLD increase in the somatosensory cortex, and significant FC increases between the left NBM and caudate putamen (CPu), major regions of the limbic system including the medial prefrontal cortex (PFC), anterior cingulate cortex (AC), hippocampus (Hipp), retrosplenium (Retro), amygdala (Amyg), and thalamus (Thal) as shown in Figure 11 (P < 0.05). The average FC increased from 0.18 (0.10) to 0.49 (0.21) in correlation coefficient value.

**Discussion.** Electrical stimulation of the PnO was accompanied by cerebral BOLD, and EEG alterations. An increase in FC between the NBM and key regions of the limbic system may allow affective and episodic information processing between the cortex and related subcortical networks. Moreover, these results further implicate a critical role of the PnO in anaesthetic state modulation.

**Funding**
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Sleep homeostasis, general anaesthesia, and synaptic downscaling

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There has been a renewed interest in the relationship of sleep homeostasis and general anaesthesia. Past studies demonstrated that propofol satisfies the need for both rapid eye movement (REM) and non-REM sleep. More recent studies have focused on volatile anaesthetics and have found a selective influence on non-REM sleep and slow-wave homeostasis. Notably, inhalation anaesthesia titrated to burst suppression or isoelectricity is associated with a decreased delta power long after the anaesthetic is terminated. One paradigm of homeostasis suggests that an important function of slow-wave sleep is ‘synaptic downscaling’, in which synaptic weight is renormalized after prolonged wakefulness. The regulation of sleep-homeostatic processes during general anaesthesia may therefore have cognitive implications for the perioperative period.

Keywords: general anaesthesia; homeostasis; memory; sleep

Role of sleep deprivation in cognitive decline accompanying an episode of acute illness, injury, or both

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Sedation regimens allow critically ill patients to tolerate painful or otherwise uncomfortable interventions including mechanical ventilation. Building upon our earlier studies of the mechanisms for the hypnotic properties of sedative agents1–7 and the recent studies addressing restorative properties of NREM sleep,8–12 I provide a rational basis upon which to select a sedative regimen in intensive care unit (ICU) and postoperative settings. By unravelling the mechanism whereby some, but not all, sedative agents can produce cognitive dysfunction I will identify therapeutic targets for optimizing the most appropriate sedative regimen for the individual patient.

I will also explore whether sleep deprivation, by either enforced wakefulness or possibly through the use of non-restorative sedative agents, affects the neuroinflammatory response to surgery that causes cognitive decline.13 14 Two clinical studies have reported higher levels of proinflammatory cytokines and CRP in the serum of patients with sleep disturbances and considered that these analytes could be contributing to the associated cognitive decline. Data from the preclinical studies can inform strategies for mitigating cognitive decline in surgical patients with either preoperative or postoperative sleep deprivation. For example, surgical patients suffering from sleep deprivation from obstructive sleep apnoea may require attenuation of the innate immune response to surgery while for the postoperative sleep-deprived patient, it may be necessary to use sleep-maintenance interventions, both pharmacological (e.g. with restorative-sleep enhancing sedatives) and non-pharmacological means to mitigate postoperative delirium.

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Fig 11 PnO stimulation induced FC increase maps with seed voxels in the left nucleus Basalis of Meynert (NBM). Voxelwise t-test was applied to the NBM FC maps of each animals of both stimulated and unstimulated states. Colour bar indicates t-range as on the left. Compared to the unstimulated state, PnO electrical stimulation induced significant FC increases between the left NBM and caudate putamen (CPu), in addition to the major regions of the limbic system including the prefrontal cortex (PFC), anterior cingulated (AC), hippocampus (Hipp), retrosplenium (Retro), amygdala (Amyg), thalamus (Thal), and the reticular formation (p1Rt and mRt) (P < 0.05).
Anaesthetic interventions for prevention of awareness during surgery: a Cochrane review

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Background. A recent task force defined awareness as ‘when a patient becomes conscious during a procedure performed under general anaesthesia and subsequently has recall of these events’ (ASA Task Force 2006).

Objectives. The objective of this review is to evaluate the efficacy of two types of anaesthetic interventions on reducing clinically significant awareness: anaesthetic drug regimens and intraoperative anaesthetic depth monitors (ADM).

Search methods. We will search MEDLINE using the search terms described in Appendix 1 and EMBASE using the terms found in Appendix 2. We will search CENTRAL using the search terms found in Appendix 3.

Selection criteria. Selection criteria were that the study had to be a randomized controlled trial (RCT) of either anaesthetic drug or ADM, performed after skin incision, with a post-operative assessment for awareness.

Data collection and analysis. Titles and abstracts of reports were identified by electronic and manual searching and by contact with experts. We will evaluate full-text versions of potentially relevant studies.

Results. The search covered from 1950 up to January 2011 in 6658 studies of which 3017 came from PubMed, and 3641 came from Embase. Of these, 6218 were rejected for being irrelevant to the topic of this review or duplicates. There were 440 full papers that were considered for this review; of which, 132 were included and 308 were excluded.

Included studies. There were 132 included RCTs. Seventy-two per cent randomized TIVA vs other techniques and 22% randomized on anaesthesia depth monitors (ADMs). Eighty-six per cent used neuromuscular blocking agents (NBAs) on induction, 53% and 51% randomized NBAs on maintenance or both. Only 7% of the RCTs used the isolated forearm technique (IFT). Twenty-nine per cent of the RCTs were minor to moderate risk surgery, 53% were moderate to major risk surgery, and 15% were mixed. The majority of studies were conducted in Germany and the USA (29%).

Conclusions. The primary outcomes, awareness/wakefulness as defined using an awareness classification system, were as follows: wakefulness in the merged studies was 22-fold more frequent than awareness. There was no significant difference between ADMS and SCPs with regard to the frequency of awareness in that merged series of studies. TIVA was 4.4-fold more frequently associated with awareness than was inhalation with low-dose narcotic techniques. Thiopental was 7-fold more frequently associated with awareness than newer hypnotic sedative drugs.

None of the secondary outcomes were identified in any of the included studies: full or partial forms of post-traumatic stress syndrome (PTSD), suicide, myocardial infarction and/or cardiac arrest, and death.

Strategies to avoid awareness during anaesthesia

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Awareness during anaesthesia is an uncommon event, one or two cases per 1000 anaesthesias, but it leads often to long-lasting neuro-psychological problems including post-traumatic stress disorder (PTSD). Therefore, it is important to develop strategies to prevent unintended awareness during anaesthesia.

A growing literature comprising case-reports, awareness incidence studies, and reviews have revealed several possible causes and risk factors for awareness. Based on knowledge about these causes and risk factors, the following strategies have been suggested to avoid awareness:

(a) Before operation: preoperative risk assessment for awareness (patient evaluation), patient information, premedication with benzodiazepines, proper maintenance of anaesthesia delivery systems, and preoperative checkout protocols.

(b) Intra-operatively: sufficient anaesthetic dosing, no unnecessary use of neuromuscular blocking agents, monitoring purposeful movement, use of brain monitoring for at-risk patients, use of brain monitoring routinely during TIVA, use of the isolated forearm technique,
use of inhalation anaesthetics rather than TIVA, if possible, routine monitoring of end-tidal anaesthetic gas concentration (at least 0.5 or 0.7 MAC), setting an alarm for low MAC, considering alternative treatments for hypotension rather than decreasing anaesthetic concentration, re-dosing i.v. anaesthetics during prolonged intubation or bronchoscopy, application of benzodiazepines or scopolamine for amnesia, if anaesthesia cannot be administered because of haemodynamic compromise (prospectively—no evidence for retrospective amnesia after BZ administration), offering music via headphones and, offering reassurance in case the patient unexpectedly becomes conscious.

(c) Other: Training of anaesthesia personnel about awareness risk.

The current literature does not give an unambiguous picture about the causes and risk factors for awareness and the recommended strategies for how to prevent awareness vary. Most authors agree that an overly light anaesthetic, especially combined with the use of neuromuscular blocking agents, increases the risk of awareness. Furthermore, each patient should be evaluated individually for possible risk factors. Since there is no 100% sensitive brain monitor to rule out that a patient is awake during general anaesthesia, the development of multiple strategies to prevent awareness and training of the anaesthesia team are needed.

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Determining consciousness in terms of brain responsiveness
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Introduction. The assessment of the state (or the level) of consciousness is still an arbitrary concept in the field of neuroscience. The current advances in the electrophysiological signal processing enables some further insight into this domain.

Methods. Twelve subjects who went under lumbar-disc operation were studied. Target-controlled propofol was administered while EEG and bispectral index (BIS) were recorded. As a separate healthy group (12 subjects), the sleep was monitored by polysomnography and BIS. The ongoing variable auditory stimulations were analysed offline. The sLORETA procedure was applied to the epochs obtained under different conditions.

Results. The loss of consciousness (LOC) was gradually preceded by suppression of evoked responsiveness. The precuneus area showed a significant decrease in activity before and after LOC. The gradual (deccremental) BIS vs AEP change was present both in sleep and anaesthesia. Furthermore, similar frequency and temporo–spatial patterns in these two states were noted.

Discussion. The continuous and dynamic responsiveness analysis of the brain provides insight into milliseconds to longer time domains. The information processing in the brain becomes critical with this approach, as the ongoing activity and dynamic changes during a certain state in response to the inputs from the outside world—that can be processed by the brain—are elucidated. The comparative analysis of similar and different features of brain responsiveness during sleep and anaesthesia may also become a useful tool in different states and pathological conditions (i.e. stupor, coma, etc.).

Keywords: AEP; BIS; consciousness; precuneus; propofol; sleep; sLORETA

Funding

Determination of minimum alveolar concentration for isoflurane and sevoflurane in a rodent model of human metabolic syndrome
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Introduction. Subtherapeutic anaesthesia is considered a primary cause of intraoperative awareness with explicit recall (AWR). Morbid obesity has been considered as a risk factor for AWR. We tested the hypothesis that obesity significantly affects the minimum alveolar concentration (MAC) for isoflurane and sevoflurane. The experiments were
conducted in rats developed through artificial selection for inherent low aerobic capacity (LCR) and high aerobic capacity (HCR). The LCR rat is a model for human metabolic syndrome characterized by obesity and low running endurance. In contrast, HCR rats have high running endurance and improved health and cardiovascular performance.

Methods. LCR and HCR rats of both sexes (n = 20) were used in this study. The rats were tracheally intubated and maintained on mechanical ventilation with either isoflurane or sevoflurane. A bracketing design using tail-clamp as mechanical stimulus was used to determine MAC. The tail-clamp was always preceded by an anesthetic equilibration period of 30 min. The MAC between LCR and HCR rats was statistically compared using parametric (two-tailed unpaired t-test) and non-parametric (Mann-Whitney test) tests. The data are reported as mean (SD) along with the 95% confidence interval.

Results. The isoflurane-MAC in LCR rats [1.52% (0.13); 95% CI: 1.42–1.62] was similar to the previously reported MAC for isoflurane in normal rat [1.51% (0.12)] but was significantly lower than the isoflurane-MAC in HCR rats [1.90% (0.19); 95% CI: 1.76–2.03] (P<0.0001). The sevoflurane-MAC was not significantly different between LCR and HCR rats and was similar to the previously published sevoflurane-MAC for normal rat. There was no effect of sex on MAC (Fig. 12).

Discussion. MAC for isoflurane and sevoflurane are not affected by obesity and the associated co-morbidities in an animal model of metabolic syndrome. However, isoflurane-MAC was higher in rats with high aerobic capacity, which may be a risk factor for subtherapeutic dosing.

Keywords: isoflurane; obesity; sevoflurane

Funding
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How we recall (or do not): the hippocampal memory machine and anaesthetic amnesia
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Far from being a ‘simplified’ or ‘poor man’s’ version of the neocortex, the hippocampal formation is distinctly specialized to process (relevant) sensory input into retained, remembered and consciously retrievable information. Arguably, conscious awareness/explicit recall would not exist without hippocampal learning and memory. The mechanisms by which anaesthetic drugs interfere with these processes are now emerging. In this talk, I will briefly review the essentials of the role the hippocampal formation in the generation of memory traces. I will then discuss how anaesthetics might interfere with its function. Finally, I will present recent experimental data that shed light on the dynamics of isoflurane interference with short-term vs long-term memory and speculate about possible implications for clinical issues.

Norepinephrine infusion into nucleus basalis elicits micro-arousal in desflurane-anesthetized rats
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Introduction. The nucleus basalis of Meynert (NBM) of the basal forebrain is a major component of the AAS, and has been implicated in the regulation of the state of

Fig 12 Differential sensitivity of LCR and HCR rats to inhaled anaesthetics.
consciousness across normal sleep–wake cycles. The possible role for NBM in the modulation of general anaesthesia has been scarcely examined. Here we investigated whether microinfusion of the excitatory neurotransmitter norepinephrine into the NBM would facilitate EEG and behavioural arousal during light desflurane anaesthesia in unrestrained rats.

**Methods.** Adult male Sprague–Dawley rats were chronically implanted with bilateral infusion cannulae in the NBM and with epidural electrodes to record EEG activity in the frontal and visual cortices. Desflurane concentration required for the loss of righting reflex was determined in each animal and kept constant throughout the experiment. Norepinephrine (7.5 ng) or artificial cerebrospinal fluid (aCSF) was infused into the NBM at 0.2 μl min⁻¹ for 1 min, repeated five times at 1 min intervals. The behavioural response to drug infusion was measured by scoring the orofacial, limb, and head movements, and postural changes.

**Results.** Rats lost their righting reflex at 4.6 (0.5)% desflurane. Behavioural scores were higher after norepinephrine than after aCSF treatment (P<0.01, t-test). Eight of 11 animals showed behavioural arousal after norepinephrine treatment (P<0.0001, χ² test) that coincided with EEG activation (P<0.05, t-test). The average decrease in δ power in the frontal cortex was significantly larger after norepinephrine (P<0.05, t-test) than after aCSF; there was no significant change in the visual cortex. This δ power decrease significantly predicted the behavioural response (logistic regression, P<0.05). Behavioural arousals were relatively brief (1–2 min), but recurred several times during the 60 min post-infusion period. Norepinephrine also increased the EEG cross-approximate entropy between frontal and visual cortices (P<0.01, t-test), while aCSF had no effect.

**Discussion.** In rats anaesthetized with a hypnotic dose of desflurane, microinfusion of norepinephrine into the NBM produced behavioural arousal that was predictable by a simultaneous decrease in EEG δ power in the frontal cortex. Furthermore, an increase in cross-approximate entropy in responsive rats suggested that the repertoire of cortical states was enhanced by norepinephrine. The transient nature of arousals suggested a similarity with micro-arousals previously observed during natural sleep. We speculate that these results implicate a possibility for transient episodes of awareness and memory formation under anaesthesia.

**Funding**

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**Insights into mechanisms of anaesthesia from intracranial EEG recordings from the human brain**

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Recording of the EEG from the scalp has led to a better understanding of the effects of general anaesthetics on the brain. These recordings, however, offer low spatial resolution and are highly vulnerable to contamination from artifacts arising from scalp muscles. Invasive recording of the EEG (iEEG) with intracranial electrodes is an established procedure for the pre-surgical evaluation of patients with drug-resistant epilepsy. This technique aims to identify the location and boundaries of the epileptogenic zone. The electrodes cover widely distributed cortical areas that usually include both pathological tissue and regions where no abnormalities are found. There are two types of electrode: the depth electrode, which consists of a semi-rigid shaft with multiple recording sites along the main axis and which is inserted in the brain at right angle relative to the surface; and the subdural electrode, which consists of multiple recording sites arranged in a grid pattern and which is placed on the cortex. The electrodes are typically left in place for 7–21 days.

Patients undergoing such evaluation offer an opportunity to use iEEG to study anaesthetic action. Cases will be presented to illustrate the use of iEEG to examine the effects of sevoflurane anaesthesia on high-frequency oscillations in the gamma (30–80 Hz) and high-gamma (80–200 Hz) range and on evoked auditory responses. Care is taken to ensure that the recordings are obtained from brain regions where no abnormalities are found. The main advantages of this approach are (i) high spatial resolution and precise localization of the recording sites, factors that facilitate comparisons with animal studies; (ii) attenuation of the impact of muscle artifacts. The main limitations are (i) the heterogeneity of recording sites (which are determined solely on the basis of clinical need independently of any research considerations) and (ii) the impact of anti-epileptic medications. Strategies to address these limitations will be presented. The combination of iEEG with the powerful electrophysiology recording equipment now available offers promising opportunities for unravelling the mechanisms of anaesthetic action in the human brain.

**Keywords:** consciousness; epilepsy; gamma oscillations; high-frequency EEG oscillations

**References**

Propofol anaesthesia decreases GABA and increases glutamate in the thalamus: MRS study in volunteers

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Introduction. Receptor mechanism for anaesthetic action is well established. Glutamate (excitatory) and GABA (inhibitory) together constitute ~90% of the neurons in mammalian brain. I.V. anaesthetics such as propofol and etomidate act primarily on GABA receptors while ketamine and nitrous oxide act on glutamate. Volatile anaesthetics act on both receptor groups. Our aim in this study was to measure the change in GABA and glutamate concentration in the thalamus with propofol anaesthesia. Our working hypothesis was ‘Propofol anaesthesia will cause an increase in GABA and decrease in glutamate level in the thalamus’.

Methods. The Yale University Human Investigation Committee approved study protocol. In 15 healthy ASA I volunteers (19–35 yr), propofol was administered using a STANPUMP (Marsch protocol) aiming for a target plasma Propofol concentration of 2 μg ml⁻¹ (0.5 MAC). Standard ASA monitors were connected (EKG, NlAP, SpO₂, ECO₂) in all subjects. Magnetic resonance spectroscopy (MRS) data were acquired on a 3 T Tim Trio scanner with a 12-channel phased-array head RF coil. GABA, glutamate/glutamine (glu/gln), and water level in the right thalamus (30 × 30 × 30 mm voxel) was measured using the MEGA-PRESS method. The GABA and glu/gln level was normalized by dividing the water level measured in the same voxel. Two cycles of imaging were carried out—awake and anaesthesia.

Results. At 2 μg ml⁻¹ plasma propofol (TCI), all subjects were asleep (no response to call) and had no memory of the event. GABA level was significantly increased by propofol from 0.26 (0.03) (a.u.) to 0.29 (0.04) (P<0.05, paired t-test), while the change in the glu/gln concentration was not significant [from 0.2 (0.05) in the awake condition to 0.19 (0.05) under anaesthesia] (Fig. 13).

Discussion. A decrease in activity in the thalamus has been correlated with narcosis related to anaesthesia. This study confirms that the mechanism increases in GABA-mediated inhibitory response. Glutamate change is not significant at 0.5 MAC.

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EEG: come so far, so far to go

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The EEG was discovered in 1873 by Caton. Using a sensitive galvanometer, he demonstrated low-frequency oscillations on the exposed cerebral cortex of monkeys. Advances in electronic technology slowly enabled compressed displays (e.g. the compressed and the density spectral displays) and the real-time quantification of some statistical aspects of the EEG increasing understanding of the EEG’s relationship to anaesthetic pharmacokinetics and dynamics. In 1950, Bickford and Faulconer at Mayo Clinic reported 50 clinical anaesthesics, where diethyl ether administration was controlled by EEG using a simple analogue computer. An advance in clinical EEG applications came from Chamoun of Harvard who replaced the notion of deriving a monitoring parameter from observation of anaesthetic dose–response in the EEG with a mathematical iterative search for which derived indices perform best in discriminating between specific behavioural endpoints such as recall or response to verbal command. This functional framework removed the wide variations between individual PK/PD responses and to a large extent, the variation between different anaesthetics. Thus, the ‘BIS’ index is a completely empirical derivation with no a priori explication of underlying physiology. Designed with thousands of subject correlations of EEG with target behaviour, the BIS monitoring system survived several prospective clinical trials to win FDA approval for reducing the risk of unintended perioperative recall.

Unintended recall or ‘awareness’ is an uncommon (one to two cases per 1000 unselected general anaesthetics), and often subtle complication of anaesthesia and is of more direct interest to the anaesthesia practitioner than say, ischaemia monitoring. The risk of recall is particularly acute in TIVA-based anaesthetics due to the large population variance in response to propofol and opiates. The current data suggest that BIS monitoring can reduce the incidence of

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recall by 80%, and this is borne out by a recent Cochrane review.

The performance of the current EEG systems can be improved several ways. First, provide steeper response curves. Minimize the circumstances under which the system degrades. Foremost is biological variability; some subjects have unusually high or low EEG scalp voltages. A few anaesthetic drugs do not produce the classic pattern of EEG change with increasing anaesthetic dose. Ketamine and nitrous oxide are in this category. Improve the detection and automatic rejection of many types of electrical interference in the EEG signal. EMG activity from spontaneous activity in the muscles of facial expression and the masseter resembles the EEG waveform and the frequency content of these signal overlap the EEG.

An area where potential growth for clinical applications of EEG monitoring might be found is in the prevention of excessive depth of anaesthesia. Obviously, one may save time and money by using patient-specific dosing. More intriguing is the suggestion, initially from Monk and colleagues, that excessive anaesthetic depth may be associated with increased long-term mortality. Another finding was that of Sessler and colleagues that a low BIS reading combined with low arterial pressure, and low anaesthetic requirement also signalled an increase in long-term patient morbidity.

The EEG is well past its centennial mark and for many clinicians, it remains a niche product. For others, it is of daily utility. BIS monitoring are available to many, perhaps even most clinicians working in large hospitals in the USA. The cost-effectiveness of the monitor is sensitive to the perspective of the analyst. To this author, the near future of the EEG as a clinical monitor will be driven more by culture than by the literature.

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### Differential effects of remifentanil and propofol on the neuronal activity in the subthalamic nucleus of parkinsonian patients

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**Introduction.** Implantation of deep brain stimulation (DBS) electrodes in the subthalamic nucleus (STN) for the treatment of Parkinson’s disease (PD) is often performed using micro-electrode recording (MER).1 The extent to which sedative drugs interfere with MER is controversial.2 We recorded the activity of STN neurones during remifentanil and propofol sedation and examined its effect on the neuronal activity, oscillations, and synchronization.

**Methods.** During DBS surgery for PD, we administered either propofol or remifentanil at a constant electrode location in the STN. We recorded the electrical activity, and calculated the root mean square (RMS), power spectrum, and coherence of the multi-unit activity. We compared the activity before, during, and after sedation.

The experiment was approved by the institutional review board and all patients signed informed consent.

**Results.** Activity was recorded from 24 electrode trajectories in 16 patients during propofol sedation, and 16 electrode trajectories in 10 patients during remifentanil sedation. The average normalized RMS decreased by 23.2 (9.1)% [mean (so)] during propofol administration (P<0.001) and 22.1 (11.4)% during remifentanil administration (P<0.001). Propofol administration either increased or did not change the power of oscillatory activity in the β range. However, remifentanil administration inhibited the oscillatory activity in this range dramatically. In instances of significant coherence of the β oscillations between two electrodes, we found that propofol administration maintained this coherence whereas remifentanil caused it to decrease dramatically.

**Discussion.** The RMS of STN activity decreased significantly and to a comparable extent after administration of both propofol and remifentanil, indicating a similar reduction in STN multi-unit neuronal activity. Oscillatory activity and synchronization in the β range was previously described in the STN of PD patients and is thought to underlie some of the disease manifestations.3 Remifentanil interferes with the oscillatory pattern of the parkinsonian STN activity, whereas propofol does not. The synchronization between two electrodes was also affected by remifentanil but not by propofol. The different changes of oscillatory activity and synchronization observed during a similar decrease in the RMS suggest that the synchronized oscillations are independent of the firing rate of the neuronal population. These observations also suggest that the typical parkinsonian STN activity is impacted less by propofol than by remifentanil.

**Amnestic concentrations of etomidate block in vitro hippocampal long-term potentiation in mice expressing etomidate-insensitive β3 GABA<sub>A</sub>-receptor subunits**

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**Introduction.** Long-term potentiation (LTP) is a commonly used in vitro model of learning and memory. GABA<sub>A</sub>ergic inhibition is considered to be a prime target of anaesthetics
affecting memory. Etomidate has been shown to cause amnesia at low concentrations (0.25 μM) in a manner consistent with acting on β2- and β3-containing GABAA receptors. The present experiments sought to test whether amnestic concentrations of etomidate block LTP, and to assess the effects of etomidate on paired-pulse facilitation of synaptic transmission.

**Methods.** The 500 μm thick coronal brain slices from WT and genetically modified (β2,N265M) mice were perfused in a microfluidic chamber. A 16-channel recording electrode was inserted in the CA1 region orthogonal to the hippocampal layers. Schaffer collateral/commissural fibres (SC) were stimulated to evoke fEPSP at 0.03 Hz, using a stimulus intensity adjusted to evoke responses approximately half-maximal fEPSP amplitude. LTP was induced by a-burst stimulus at half-maximal fEPSP amplitude (TBS: 40 pulses total; bursts of four pulses at 100 Hz, repeated every 200 ms, 10 times), in the presence or absence of 0.25 μM. Paired-pulse ratio (PS2/PS1) of half-maximal population spikes (PS) was assessed at inter-pulse intervals ranging from 2 to 500 ms.

**Results.** In slices from WT mice under control conditions, TBS elicited a 170 (27)% (n=6, mean (SEM)) increase in the fEPSP slope assessed at 60 min post-tetanus. LTP was significantly reduced in slices from WT animals exposed to 0.25 μM etomidate [129 (11)%], P<0.001, n=8] increase in the fEPSP slope. In slices from β2,N265M mice in the absence of etomidate, TBS resulted in a 168 (7)% (n=2) increase in the fEPSP slope. Similar to slices from WT, exposure to 0.25 μM etomidate significantly reduced TBS-evoked LTP [117 (13)%], P<0.001, n=4]. At 0.25 μM etomidate, paired-pulse ratio in slices from WT mice was not changed compared with control. Interestingly, 0.25 μM etomidate increased paired-pulse ratio in slices from β2,N265M animals at inter-pulse intervals from 10 to 200 ms.

**Discussion.** There is a partial block of LTP in the presence of 0.25 μM etomidate. The β2,N265M mutation does not prevent this amnestic concentration of etomidate from blocking LTP in vitro. Thus, the amnesic actions of etomidate may involve β2-containing GABAA receptors. The observed effect of etomidate on paired-pulse ratio in the β2,N265M knock-in suggests that there may be opposing effects of inhibition on pyramidal neurone spiking mediated by β2- and β3-containing GABAA receptors.

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14% of responsive patients reported pain. In the most recent and largest study, responsiveness was noted in a non-paralysed patient but overt wakefulness (eye opening or gross patient movement) or reflex motor activity was not present.1

Discussion. In studies of the isolated forearm technique with clinically relevant stimuli during anaesthesia, external awareness occurs with similar frequency to internal awareness (dreaming).2 Interestingly, patients may become externally aware without overt wakefulness.3

Keywords: anaesthesia; awareness; consciousness

Funding
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Detecting thalamocortical oscillations in the EEG during anaesthesia
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There are at least two concepts for utilizing the EEG for monitoring and understanding the mechanism of anaesthesia. One concept is to use mathematical processes to extract a parameter which is presumed to correlate with the amount of anaesthetic effect. This is the quantitative EEG or ‘qEEG’ approach. The mechanism of anaesthesia which this parameter is presumed to correlate with is a progressive dysfunction of the brain. The original brain dysfunction or depression theory was Meyer–Overton which proposed disruption when ether dissolved in the lipids of neurone membranes. Today, the depression theory is that anaesthetic agents affect ion channels enhancing inhibitory and reducing excitatory synaptic processes.

An alternative view is that the EEG contains signals created by oscillatory processes in the thalamus and cortex. These thalamocortical oscillations, in particular spindle oscillations, occur during natural slow wave sleep. There is evidence that anaesthetic agents affect ion channels that control these natural thalamocortical oscillations in ways that prevent the natural wake-up process from terminating the oscillations.

Spindle oscillations are not compatible with consciousness but are not brain dysfunction or brain depression. They imply a functional state that is different from that of the brain which creates consciousness. Spindle oscillations are not a total mechanism of anaesthesia. They may occur after loss of consciousness and be terminated before return of consciousness. Thalamocortical oscillations are not a mechanism of surgical immobility. However, detecting spindle oscillations during anaesthesia could be to be a reliable way to insure a lack of awareness for individual surgical patients.

The proposed method for detecting spindle oscillations in the EEG during anaesthesia is to evaluate the shape of the EEG spectrum on a log–log graph. In this presentation, the EEG spectrum can be approximated by two straight lines. The low frequency approximation line has a shallow slope and a peak in the 7–14 Hz range rises above it that results from spindle oscillations. The high-frequency approximation line has a steep slope. This is the shape that occurs in the anaesthetic range with maximum spindle activity. If the anaesthetic agent concentration is increased or decreased, the shape of the spectrum will change in predictable ways. The limited number of, and the consistent progression of log–log EEG spectral shapes enables an alternative to the parameter approach. This alternative is an EEG spectral feature analysis method which could be called ‘visual qEEG’. The patient’s log–log EEG spectrum would be compared with a library of spectra from other patients to determine the anaesthetic state. Also, the patient’s EEG spectra can be recorded during the procedure and used for comparison to track changes in the anaesthetic state.

Beta ratio of bispectral index correlates with the slope of the high-frequency segment of a log–log EEG spectrum
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Introduction. The bispectral index (BIS) is created by combining multiple parameters derived from the EEG, including the beta ratio. The beta ratio is the log of the ratio of the EEG power in the 30–47 Hz range divided by power in the 11–20 Hz range.1 The beta ratio dominates BIS from 60 to 1002 and is more effective at detecting loss of consciousness than the complete BIS algorithm.3 During surgical anaesthesia, the EEG spectrum on a log–log graph can be approximated by two straight lines. The high-frequency segment

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Table 2 Isolated forearm technique positive responses from 654 patients included in 14 studies
(HF) contains most of the range of the beta ratio (Fig. 14). The slope of that line should correlate with the beta ratio and should correlate with BIS between 60 and 100.

**Methods.** Thirteen surgical cases that were previously recorded with IRB approval were evaluated. The criterion for inclusion was BIS between 60 and 100 for the last 5 min and patient verbal response in the last minute. The cases were processed by a custom Programme (Log 2T M ) to obtain the beta ratios and log–log EEG spectrum approximation line slopes every 5 s during emergence. Total data points were $n=1367$.

**ANOV A was used to determine $R$ values and significance.**

**Results.** The median $r$ values for BIS vs beta ratio, BIS vs HF slope, and beta ratio vs HF slope were 0.90, 0.92, and 0.93, respectively. The significance was $P<0.01$ for all $r$ values.

**Discussion.** The HF slope, a parameter generated from the log–log EEG spectrum has been shown to correlate highly with both BIS and the beta ratio during emergence from anaesthesia. The HF slope has the advantage over BIS that the clinician can visualize it directly from the log–log EEG spectrum rather than rely on a ‘black box’ proprietary algorithm to produce a number which is subject to artifact.

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**EEG as a monitor of anaesthetic effects**

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The EEG signal is measured on the scalp and is derived from the surface of the hemispheres. Most prominent generators are vertically oriented pyramidal cells which are mainly located in the cortical layer V and generate open dipoles directed towards the surface of the scalp. For scalp recordings following the 10–20 system, a close correlation between cerebral topology and electrode position has been demonstrated. This allows spatial identification of anatomical structures underlying anaesthesia-induced changes of the EEG.

Traditionally, the EEG is assessed with respect to frequency and amplitude of the signal. In addition, characteristic EEG patterns (grapho elements) are identified. On this basis, EEG-based classification of sleep stages has been applied to anaesthesia-induced changes of the EEG. Such a classification requires the analysis of multi-channel recordings of the EEG. A frequency-based approach, that is, analysis of the EEG spectrum, allows an identification of anaesthetic effects on the basis of a single-channel recording of EEG. Recently, spectral and bispectral analysis, or analysis of spectral entropy, have been used to monitor anaesthetic effects on the brain.

These recent approaches are mainly based on statistical approaches to EEG analysis, that is, observed changes in EEG characteristics are related to those in the level of anaesthesia. This approach may be useful for the clinical application of such a monitor. Still, a more reliable assessment should be possible with a monitoring method which is based on underlying mechanisms of anaesthesia. Recent theories about mechanisms of anaesthesia-induced unconsciousness suggest that anaesthesia-induced changes of cortico-cortical communication are a key aspect of general anaesthesia. Therefore, a monitor should be able to capture a change of signal characteristics at this level. For
this purpose, analysis of EEG regularity and irregularity may be useful. This is related to the theory that the potential information content of a signal decreases with increasing regularity of this signal. EEG approximate entropy (ApEn) or permutation entropy (PeEn) are examples for such an approach. Analysis of a single EEG channel may limit the potential value of EEG analysis as a monitor of anaesthetic effects. On the basis of multi-channel EEG recordings, similarity of signal characteristics between different EEG channels can be analysed. Cross approximate entropy (XApEn) is an extension of ApEn to the analysis of multi-channel recordings, which quantifies synchrony between two EEG channels. Another example is symbolic transfer entropy (STEn), which is suggested as a measure of information flow between different cortical areas. In the future, a combination of imaging techniques (fMRI) and EEG analysis may allow identification of anaesthesia-induced changes of cortical activity and related changes of the EEG.

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Are indirect memory studies in anaesthesia subject to the decline effect?

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The possibility of a decline effect being a factor in failure to replicate scientific findings came to widespread public attention in December 2010 in an article in The New Yorker (The Truth Wears Off, J Lehrer, December 13, 2010, 52–7). The literature concerning memory and awareness has been particularly subject to the phenomenon of failure to replicate. The original observation by Levinson that patients could, under hypnosis, recall emotionally charged information presented during anaesthesia without direct recall of hearing the information. However, Eger and colleagues could not replicate this finding. Similarly, findings of reduced morphine utilization for postoperative pain after hysterectomy could not be replicated.

Failure to replicate studies is often ascribed to small changes in protocol or data collection between studies. However, it is possible that surprising findings occur as a result of an initial study group that was in some way ‘out of the ordinary’, a statistical anomaly. This may result in a study receiving a lot of attention and being subject to replication attempts. If we accept a one in 20 chance of rejecting a null hypothesis incorrectly, then a relatively large number of scientific papers may have spurious findings.

There may also be an issue in selective reporting. It has been suggested that researchers like to validate their hypotheses, especially when grants, prestige, or personal financial gain may be at stake. Data can be presented in the best possible light to satisfy a priori beliefs and convictions.

One area of significant concern to scientists is fraud and this is obviously an area of research subject to the decline effect. There have been several incidents recently of systematic fraud which has driven certain clinical practices. When a large number of papers in a particular field have been retracted, the evidence basis becomes shaky and the field can be left in disarray.

Dynamic changes of network ‘backbones’ across wakefulness, anaesthesia, and recovery

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Introduction. Understanding consciousness is a topic of current interest in the neurosciences. Network analysis of brain activity in different states of consciousness is one technique to approach this problem. General anaesthesia is a unique method to reversibly suppress consciousness. We propose a quantitative method to study dynamic brain networks during consciousness and anaesthesia.

Methods. We define functional backbones as the most probable subgraphs in a brain network. In order to identify network backbones, we first extract a dynamic series of static networks that correspond to a given time point. Next, we identify all subgraphs of the network. Finally, we obtain the most frequent subgraphs of the dynamic network series. We can then study the functional circuit time-series by tracing the appearance of backbones, or alternatively visualize the functional backbones’ rank transition.

Results. We measured the inter-regional brain activities as high-resolution time-series using EEG from anaesthetized patients during surgery (n=9 induced with propofol, n=9 induced with sevoflurane). The functional backbones of brain networks were derived from the EEGs across five states of consciousness from baseline wakefulness to general anaesthesia to recovery. We identified ‘constitutive backbones’ that are present during all states, and ‘variable backbones’ that appear during specific states. There were robust backbone networks unaffected by anaesthetics, whereas some backbone networks occurred only in the baseline state or anaesthetized state.

Discussion. Our data suggest that there exist state-dependent network backbones. General anaesthesia is not
a process in which one network is disrupted or activated, but rather a composite picture of dynamic backbone changes.

**Keywords:** consciousness; human information processing; propofol; sevoflurane

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**Sleep spindles and general anaesthesia: signs of a closed thalamic gate?**

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If a patient is aware during a general anaesthetic, it is necessary that information from the external world must have access to—and influence on—the neuronal networks and assemblies that make up the neurobiological substrate for consciousness. Are there specific features in the EEG that reliably indicate that the patient is cognitively disconnected from the external world? We propose that the occurrence of waxing-and-waning alpha frequency oscillations—spindles—is an EEG signature of a hyperpolarized thalamo-cortical system; and hence one sign that the ‘thalamic gate’, which lies between the cerebral cortex and the outside world, is closed. Whether it is the change in mode of the thalamus itself, that reduces information flow from the outside world; or whether it is the thalamo-cortical hyper-synchronization that restricts the information flux, is not clear as yet. The quantification of EEG spindle activity is not straightforward, but may be measured by using the spectral peak, the biocoherece, or in the time domain. The neuro-physiological basis for these oscillations during general anaesthesia seems to be similar to that of natural slow-wave sleep; namely that the anaesthetic drugs precipitate thalamic hyperpolarization by switching off the endogenous arousal neuromodulators and/or via direct actions on ion channels. The hyperpolarized thalamus then activates various intrinsic currents and thus moves into a burst firing mode—which is seen in the scalp EEG as spindles. We present some preliminary data that indicate a genetic influence on spindle amplitude and frequency. There is good evidence that the noxious stimulation of surgery tends to diminish the spindles in the EEG, unless appropriately blocked with anaesthetic drugs—either opioids or volatile agents. However, there is marked variability between different patients as to their propensity to show spindle activity; many patients are completely unresponsive to the outside world without any obvious spindles on the EEG. It is unclear if this a simple variation in anaesthetic dose–response, or whether it indicates an underlying difference in neurology in these patients. We present a number of intraoperative illustrative case examples.

**Strain differences in regional EEG during induction and emergence from isoflurane anaesthesia**

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**Introduction.** Two rat strains, SS/JrHsdMcwi (abbreviated as SS) and BN/NhsdMcwi (abbreviated as BN), are parental groups for a consomic (chromosomal substitution) model that is useful for future pharmacogenomic anaesthetic studies. We previously observed that these strains differ significantly in loss of consciousness (LOC) and EEG response during volatile anaesthetic administration. Compared with BN, SS exhibited LOC at lower levels of volatile anaesthesia during both induction and emergence, whereas EEG differences were primarily observed during emergence (but not induction). EEG was measured globally (as a decay constant of an exponential model), and differences were observed in the parietal (but not motor) cortex. In the present study, our objective was to identify the EEG frequency ranges associated with the anaesthetic sensitivity differences between the strains, and to exclude secondary causes such as hypotension and anaesthetic concentration differences.

**Methods.** Chronically instrumented SS and BN rats (aged 9–12 weeks) were prepared with concentric bipolar electrodes in the primary motor cortex (M1) and stainless steel screw electrodes in the parietal association cortex (Pta), as well as indwelling femoral arterial cannula. EEG was recorded concurrently with arterial pressure measurement, and arterial blood samples were drawn for anaesthetic concentration measurement. Loss of righting reflex as an index of loss of consciousness was tested at 0%, 0.3%, 0.6%, 0.8%, and 1% inhaled isoflurane. Average band powers were calculated for δ (2–4 Hz), θ1 (4–8 Hz), θ2 (9–12 Hz), β (13–30 Hz), and γ (30–55 Hz) bands from 30 s EEG recordings, and expressed in percent of the total power of the spectrum up to 60 Hz. Induction and emergence were studied in separate experiments.

**Results.** There was no difference between BN and SN in mean isoflurane plasma concentrations during induction or emergence. Mean arterial pressure was equal or higher in BN groups for a consomic (chromosomal substitution) model. EEG was recorded concurrently with arterial pressure measurement, and arterial blood samples were drawn for anaesthetic concentration measurement. Loss of righting reflex as an index of loss of consciousness was tested at 0%, 0.3%, 0.6%, 0.8%, and 1% inhaled isoflurane. Average band powers were calculated for δ (2–4 Hz), θ1 (4–8 Hz), θ2 (9–12 Hz), β (13–30 Hz), and γ (30–55 Hz) bands from 30 s EEG recordings, and expressed in percent of the total power of the spectrum up to 60 Hz. Induction and emergence were studied in separate experiments.

**Results.** There was no difference between BN and SN in mean isoflurane plasma concentrations during induction or emergence. Mean arterial pressure was equal or higher in SS compared with BN (never lower) at all levels of isoflurane (Fig. 15). Mean EEG power did not differ between the SS and BN groups at 0% isoflurane. Likewise, there was no difference between SS and BN in γ fraction of the EEG. In Pta (but not M1), the δ fraction was significantly greater in SS compared with BN at isoflurane levels above 0.3% during emergence but not during induction. The (slow) θ fraction was significantly greater in SS compared with BN at isoflurane levels above 0.3% during induction, and (in contrast to δ fraction) differences in θ2 were observed in M1 but not Pta.
Conclusions. The data support earlier conclusions that induction and emergence from isoflurane involve distinct pathways. Previously observed decreased dynamic slope analysis attributed prolonged emergence in SS compared with BN to mechanisms that enhance δ activity rather than decreasing γ activity. Slow θ2 activity has been associated with a state of quiet immobility. Cellular/network mechanisms leading to increased θ2 fraction would be logical candidates for explaining differences in consciousness, and could also account for why this difference is observed in motor rather than parietal cortex. The observed strain differences appear related to direct effects of isoflurane on cortical pathways and not on secondary (hypotensive or anaesthetic concentration-related) effects.

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Keywords: anaesthesia; electroencephalography; inbred strains; pharmacogenetics; rats

Inflammation and underlying postoperative cognitive decline
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Introduction. Impairments of cognition often occur after surgery and acute hospitalization. Activation of the innate immunity, cytokines, and neuroinflammation associate with aseptic surgical trauma and become putative mechanisms to underlie the processes of cognitive decline. Tumour necrosis factor-α (TNF) in particular is a pivotal initiator of several inflammatory conditions; herein, we report on its role in postoperative cognitive dysfunctions.

Methods. Adult C56BL/6J male mice were randomly assigned into groups: (i) untreated animals; (ii) general anaesthesia (GA) with isoflurane + buprenorphine for analgesia; (iii) stabilized tibial fracture under GA and analgesia; (iv) anti-TNF prophylaxis 18 h before surgical intervention. Separate cohorts of mice per group were assessed for plasma and hippocampal cytokines (ELISA), microglial activation (CD11b), and hippocampal-dependent memory using trace fear conditioning.

Results. Administration of anti-TNF monoclonal antibody (Ab) before surgery significantly reduced release of IL-1β (Fig. 16A) at 6 and 24 h after tibial surgery. TNF ab also reduced neuroinflammation, including IL-1β expression and CD11b activation, in the hippocampus. Postoperative

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cognitive decline in contextual fear response was significantly ameliorated after TNF ab prophylaxis ($P<0.05$ vs S, Fig. 16A). Prophylaxis with anti-TNF in mice-lacking expression of MyD88−/− fully ablated the inflammatory response, highlighting a synergism between TNF and MyD88-dependent pathways.

**Conclusions.** TNF is an early marker during postsurgical aseptic peripheral inflammation. Prophylactic targeting suppresses generation of downstream IL-1β, thus preventing neuroinflammation and cognitive decline.

**Keywords:** delirium; innate immunity; surgical complications

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**References**

**Evaluation of analgesic effects of (s)-ketamine and sevoflurane on somatic pain indicated by cerebral source localization of contact heat-evoked potentials**

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**Introduction.** Pain is a complex sensation including cognitive, affective, and sensory aspects which are influenced differently during general anesthesia. Based on low-resolution brain electro-magnetic tomography (LORETA) source localization,¹ the present study analyses the effects of the dissociative drug (s)-ketamine and the hypnotic sevoflurane in subanaesthetic concentrations on specific brain areas after painful heat stimulation. During wakefulness, the cerebral correlates of contact heat-evoked potentials (CHEP) have already been identified by imaging techniques.²

**Methods.** After approval by the ethics committee, 30 healthy male volunteers participated in this study. Standard monitoring parameters were recorded and 29-channel EEG was acquired (average reference) using a 32-channel amplifier (BrainAmp MR, Brain Products, Gilching, Germany). For CHEP, heat pain was applied at the individual pain threshold by a CHEP stimulator (CHEPS® Medoc, Israel). At baseline, CHEP were registered without drug. Then, for each of the 15 subjects, CHEP were recorded under either (s)-ketamine (0.25 mg kg⁻¹ h⁻¹) or sevoflurane (0.40 vol%). Cerebral activity of CHEP was analysed by LORETA power estimation (0.5–30 Hz EEG bandwidth, 350–500 ms post-stimulus) in the frontal and somatosensory cortices and in the limbic system. Drug-induced changes were analysed with a Wilcoxon two-sample test ($P<0.05$).

**Results.** Estimated LORETA power of specific cerebral regions is affected differently by (s)-ketamine and sevoflurane. For (s)-ketamine, LORETA power decreases significantly in the gyrus cinguli (Fig. 17A vs B). For sevoflurane, there is only a significant decrease in the frontal cortex (Fig. 17C vs D).

**Discussion.** The current results provide a differentiated evaluation of analgesic effects. In accordance with previous findings, the reduced activity in the gyrus cinguli caused by (s)-ketamine can be seen as a drug-specific modulation of cognitive activity.
the affective component of pain. In contrast, sevoflurane seems to influence conscious processing of pain, indicated by the reduction in frontal cortical activity. In both cases, volunteers reported a reduction in pain. In accordance with the multidimensional sensation of pain, the current findings by LORETA analysis indicate different, drug-specific modulation of cerebral processing of pain, which both clinically result in analgesic effects.

Keywords: CHEP; electroencephalogram; LORETA; pain; (s)-ketamine; sevoflurane

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Anaesthetic amnesia: where is a memory to hide?

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What happens to experiences registered in the presence of amnesic drugs? Are they present somewhere in the brain and not readily accessible, or do they experience some other fate? Normally, almost unlimited amounts of information may be stored in long-term memory indefinitely. Memory has been subdivided into two broad categories, explicit and implicit, with explicit memories being dependent on hippocampal function, and implicit memories being independent of the hippocampus. Explicit memories consist of general knowledge about the world (semantic memories) and episodic memory (i.e. personal memories which occurred in a particular place and time). Amnesic drugs disrupt episodic memory function, and no (or impaired) recollection of experiences that occur in the presence of amnesic drugs is possible. A review of the possible neurobiological effects that may explain amnesia for episodic memory will be briefly presented. The importance of hippocampal–neocortical interactions in support of memory function will be highlighted. On the other hand, implicit memory will be briefly presented. The importance of hippocampal–neocortical interactions in support of memory function will be discussed. A different conceptualization of memory taxonomy will be presented, which focuses on dynamic information processing rather than static classification of different types of memory.

Cross-correlogram analysis reveals state-dependent neuronal connectivity in the rat cerebral cortex

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Introduction. Local computations through functional interconnections are believed to be an important component of cognitive functions and modulation of global activity in the brain. How anaesthetics affect cortical neuronal interactions within a network, in vivo, is currently unknown. Multiple studies have shown that most anaesthetics modulate ligand-gated ion channels by enhancing inhibitory and suppressing excitatory synaptic transmission. Here, we examined the effects of desflurane anaesthesia on excitatory and inhibitory spike transmission probabilities in the rat cerebral cortex.

Methods. Multishank (8 × 8) silicon probes (200 μm shank separation, 200 μm electrode contact separation, depth: 2.1 mm) were chronically implanted in the rat primary visual area (n = 8). Spontaneous extracellular spikes were recorded (Fs = 30 kHz) for 10 min (Cyberkinetics Inc., Foxborough, MA, USA) in three anaesthetized states (6%, 4%, 2%) and wakefulness. Cross-correlogram (CCG) analysis was performed on all active (>1 spikes s⁻¹) neuronal pairs. A jittering resampling method was applied to remove random correlations between neuronal pairs and determine significant monosynaptic connections. Significant peaks or troughs observed within a short-latency interval of [+1, +5] ms in the histogram putatively classified monosynaptic connections as excitatory or inhibitory, respectively. The state-dependent effect on the number of excitatory and inhibitory connections was tested using repeated-measures ANOVA (NCSS).

Results. In the unconscious state, 80% of the excitatory connections were found within the same electrode contact, whereas all inhibitory connections were between contacts and the spanned longer distances (200–1400 μm). Pairwise t-tests determined that the connection distance distribution of excitatory interactions was unaffected by changes in state (Z < 2.63, Dunn’s test), whereas inhibitory connections were limited to shorter lengths in the unconscious state compared with all others states (P < 0.001, ANOVA; Z > 2.63, Dunn’s test). As the state level progressed from unconsciousness to awake, a concentration-dependent increase in inhibitory
connections was observed (P < 0.05, Tukey–Kramer), whereas an abrupt increase in excitatory interactions was found (P < 0.01, Tukey–Kramer).

**Discussion.** In summary, we found a state-dependent effect on the number of functional connections. A gradual increase in the number of inhibitory connections was observed from unconsciousness to wakefulness, whereas excitatory connections increased abruptly from unconscious to sedated states. Although anaesthetics are known to enhance inhibitory synaptic transmission, the net effect of excitatory and inhibitory synaptic modulation may be a reduction in inhibitory spike transmission in the intact cortical neuronal network. Overall, the effect of state modulation by general anaesthesia on functional communication between cortical neuronal cells should help better explain how changes in spike interactions modulate population activity as a function of state.

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**References**


**Implicit–explicit dissociation after conscious sedation: implications for inadequate general anaesthesia**

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Intraoperative consciousness followed by postoperative amnesia is a more common circumstance than that of full awareness with postoperative explicit memory, and with some techniques, may have an incidence of more than 50%. It has been suggested that such a circumstance has no consequence and constitutes ‘ideal surgical conditions’. Others have raised ethical concerns. Moreover, accounts have been accumulating of psychological disturbance after surgery with circumstantial evidence of inadequate anaesthesia but absence of explicit intraoperative recall. These accounts raise the possibility that a state of dissociation of implicit from explicit memory during inadequate general anaesthesia may make the patient vulnerable to implicit emotional association, giving rise to cued emotional distress in subsequent waking life. Such distress may be particularly insidious since the patient may have no understanding of the origin of the problem.

We have been investigating this state of memory dissociation in other clinical contexts involving benzodiazepine sedation: specifically, colonoscopy and intensive care unit (ICU) sedation. Typically, these patients have impaired explicit recall to the extent they may believe, erroneously, that they have received a general anaesthetic. We have been investigating the proposition that the discomfort and emotional distress of patients in these settings may, by classical conditioning, become associated with words or other sound stimuli presented while patients are in this dissociated state. In some studies, we have detected such an emotional association in post-endoscopy skin conductance responses to words previously presented during endoscopy (of which the patient has no conscious, explicit recall). In another study, we have demonstrated differential emotional responses to sounds from the ICU in comparison with control sounds and control groups, in discharged ICU patients. Sedated ICU patients have also been presented with the Robinson Crusoe story in a partial replication of the Schwender and colleagues study. These studies and their findings will be reviewed.

There are similarities with the ‘date-rape’ literature in which women are assaulted in the same, drug-induced, dissociated state with impaired explicit recall but preserved implicit memory. Cued and breakthrough memories are common occurrences in these cases.

The implications of this literature and the recent conscious sedation studies from Leicester will be discussed in relation to inadequate general anaesthesia.

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**Implicit emotional memory for intensive care unit sound in discharged intensive care unit patients**

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Introduction. Intensive care unit (ICU) patients are commonly sedated during their stay. Although they often have little in the way of explicit memory post-discharge, in part due to the amnesic effects of benzodiazepines and opioids, some studies suggest that as much as 25% experience psychological disturbance at follow-up. Despite amnesia, ICU patients experience high levels of consciousness during their stay, along with pain and emotional distress. We hypothesize that these conditions of implicit–explicit memory dissociation and distress may give rise to implicit emotional memory that can be cued by external stimuli, which may explain some of the post-discharge psychopathology. We set out to investigate such implicit emotional memory in ICU patients at follow-up by presenting ICU sounds while monitoring skin conductance responses, which provide an indication of emotional arousal.

Methods. Twenty-one ICU patients were followed up between 4 and 5 weeks after discharge. Three sounds were presented from an MP3 player through closed headphones in 1 min sound blocks, balanced for order. These included the sound of a steam train, rain on a window, and sound recorded from the ICU environment, including heart monitor, mechanical ventilation, and alarm sounds. All three sound recordings were balanced for volume and sound density. Skin conductance was monitored during sound presentation. Silver–silver chloride electrodes were attached to the first and second medial phalanges of the dominant hand. Psychlab (Contact Precision Instruments) physiological measurement equipment was used to record the skin conductance signal and analyse for skin conductance level and spontaneous fluctuation rate during the 1 min sound presentation epochs. In addition to the ICU patient group, a patient relative sample (n=11) and age-matched non-clinical population sample (n=20) were recruited for comparison and played the same sound stimuli.

Results. Discharged ICU patients showed no significant differences in their skin conductance levels in response to ICU sound in comparison with the other two sounds. There were no significant between-group differences in the skin conductance data using a 3×3 factorial MANOVA.

Discussion. These results do not support the implicit emotional memory hypothesis: it was not apparent that distressing experience during episodes of consciousness had become associated with the sound heard on the ICU by patients.

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