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Abstracts

ABSTRACTS

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Minding the mind of subconscious self

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The neuroscience of anaesthesia and how it relates to all levels of consciousness has focused on the major issues of anaesthetic pharmacology and how cognitive binding may be affected, using a wide range of techniques from the molecular scale to whole-brain neuroimaging modalities. All anaesthetic actions start with binding of various receptors and modification of their functions via inhibitory and excitatory mechanisms. Anaesthetic actions on target neurones, ranging from the periphery to the central nervous system, modify their emergent functions. The whole brain is indeed turned off (or at least inhibited to various degrees) in critical aspects of electrical activity and metabolism under sedation to the deepest anaesthesia. We seek associations between behaviour and the wide array of heterogeneous, incomplete neuronal suppressions, trying to find clues as to the mechanisms or substrates of anaesthetic-induced sedation, amnesia, and unconsciousness. Such strategies have been regarded as solid science; yes, we all simply do it.

Science deals only with what we can observe and communicate to each other (i.e. shared experience); hence, by this nature it is limited. Consciousness and self-awareness cannot ever be observed or shared, as colour cannot be communicated to the blind unless they have had the personal experience before blindness. There exist no clues regarding definite causal relationships between an 'objective' neuronal or cerebral event and personally relevant elements of conscious experience; thus, the 'hard problem of consciousness'.[1]

I see analogies with the nature of 'hard problem of anaesthesia awareness'. Despite apparent unconsciousness, measured crudely by unresponsiveness, there might be some part of our existence that cannot ever be shut down, which we cannot even conceive by ourselves. Who knows whether there should be no 'self' even when no single neurones or brain networks are active? Who knows how we should be after we die? Who knows what the world should look like when there are no live observers? No wonder if the core part of our existence, 'subconscious self', is resistant to even the highest doses of anaesthetics. Awareness during anaesthesia might potentially involve not only human errors in anaesthetic management, but also the limitation of anaesthetic agents to suppress the human 'soul'. Such a soul should include the most important part of our humanity and personality, that is, 'subconscious self'.

Above is my definition of the 'hard problem of anaesthesia awareness'. Any solution? Science? Yes and no. Monitoring? Yes and no. Respect? Yes. We must not only be aware of the inherent limitation of science and technology but, most importantly, also of the inherent dignity of each personal 'self'. How can we know if this 'self' is active under the deepest stage of anaesthesia, and possibly even until after bodily 'death'? To begin to answer this question, we need to respect and care for such souls in addition to the more accessible, apparently conscious or unconscious, animals or human beings, observations of whom we share in the anaesthetic literature.

Our approach to memory and awareness, both in practice and science, should be this way. Would there be a neurobiological equivalent to 'subconscious self' that is resistant to anaesthetics? It is a new question that deserves further inquiry.

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On the 'incidence' and 'nature' of accidental awareness during general anaesthesia

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Backgound: Active questioning of patients using the modified Brice questionnaire has yielded an incidence for accidental awareness during general anaesthesia (AAGA), consistent over several decades, of ~1:600 general anaesthetics, which is quite high.[1] Yet anecdotally, this is not the perception of most anaesthetists, who regard AAGA as very rare. The 5th National Audit Project in the UK and Ireland was designed in part to ascertain the incidence of spontaneous reports of AAGA made to health-care staff. Its main components were a baseline survey of senior anaesthetists, an activity survey of practice (to provide denominator data), and a prospective collection of data on AAGA reports.
Methods: A team of local coordinator anaesthetists, one in each of ~370 centres in the UK and Ireland, collected data between 2011 and 2013 on the following: (i) senior anaesthetist experience of patients reporting AAGA (to inform the baseline survey); (ii) data on each anaesthetic intervention over a 2 day period in 2013 (to inform the activity survey); and (iii) anonymous details of each new case of AAGA spontaneously reported to the hospital.
Results: The Activity Survey estimated that the number of general anaesthetics administered to patients annually in the UK was ~2 800 000 (almost identical to a previous survey),[2] 46% of whom received neuromuscular block (NMB). In Ireland, the estimated number of general anaesthetics administered to patients was ~300 000, 41% of whom received NMB. The baseline surveys estimated an incidence of reports of AAGA in the UK of ~1:15 000 and in Ireland of ~1:23 000.[3] Prospectively, the incidence of AAGA reports was ~1:19 000 (UK) and 1:31 000 (Ireland). However, there were variations in estimates by type of anaesthesia or subspecialty (e.g. when NMBs were used, the incidence was ~1:8000 in the UK and ~1:15 000 in Ireland).
Conclusions: It is striking that estimates based on spontaneous reports (using different methodologies and across countries) differ so much from those based on semi-direct, repeated questioning. It appears that the vast majority who respond positively to the latter would not spontaneously report AAGA. It is not known whether this is primarily because the AAGA experience is too trivial or too traumatic to report spontaneously. There are several other possibilities, as follows: (i) Brice questioning is flawed and overestimates AAGA; (ii) relying on spontaneous reports is flawed and underestimates AAGA; or (iii) Brice questioning and spontaneous reports reflect different types of AAGA; in other words, AAGA is not a single entity but a spectrum of experiences, perhaps reflecting diverse brain states that existed during the episode of 'awareness'. One example of this might be the notion of 'dysanaesthesia'[4 5] as a state of mind that is predicted to lead to a neutral recall of events and therefore a propensity not to report spontaneously but to respond to direct questioning. The over-representation of certain anaesthesia techniques (e.g. NMB use, total i.v. anaesthesia, and rapid sequence induction using thiopental) or specialties in which these are used (e.g. cardiothoracic and obstetric) suggests that AAGA and its causes are heterogeneous. The diverse responses of patients to the experience (from neutral to severe distress) also indicates a spectrum of mental states at the time of AAGA.

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The effectiveness of anaesthetic interventions for prevention of wakefulness and awareness during surgery

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Background: General anaesthesia is usually associated with unconsciousness. 'Awareness' is when patients have postoperative recall of events or experiences during surgery. 'Wakefulness' is when patients become conscious during surgery, but have no postoperative recollection of the period of consciousness. This systematic review, therefore, distinguishes between intraoperative wakefulness and degrees of postoperative recall (awareness). However, wakefulness with pain, distress, or both is ethically unacceptable even if there are no postoperative psychological sequelae.[1] We systematically obtained evidence for the efficacy of anaesthetic interventions to lower the probability of intraoperative wakefulness and awareness; these interventions included anaesthetic drug regimens and anaesthetic depth monitors.[2]
Methods: We included randomized controlled trials, that is, studies that randomized patients to anaesthetic drug regimens or anaesthetic depth monitors.
Results: The meta-analysis of anaesthetic depth monitors (BIS) *vs* standard clinical parameters (SCP) for the risk of definite and possible and definite-only awareness (grade 4 and 5) contained five studies.[3–7] A blinded, expert panel adjudicated, for each patient, the outcome as no awareness,

possible awareness, or definite awareness after reviewing the questionnaires. Either definite or possible instances of awareness were 151 (0.4%) out of 34 181 (BIS, 73/17 432; SCP, 78/16 749). Definite instances were 64 (0.2%) out of 34 181 (BIS, 23/17 432; SCP, 41/16 749). The effect size favoured neither BIS nor SCP, with little precision in the odds ratio (OR) estimates {OR 0.96, 95% confidence interval (CI) [0.51–1.80], 95% prediction interval (PI) [0.26–3.54]; OR 1.13, 95% CI [0.56–2.26], 95% PI [0.56–2.26], respectively}. The protocols of three studies[4 5 7] included alarms or alerts and the use of inhalation anaesthesia, with the OR estimates (OR 1.50, 95% CI [0.82–2.75], 95% PI [0.65–3.48]; and OR 1.13, 95% CI [0.56–2.26], 95% PI [0.56–2.26]) widely spanning the line of identity. The protocols of two studies[3 6] did not include alarms or alerts and used predominantly or exclusively total i.v. anaesthesia. The OR estimates (OR 0.54, 95% CI [0.29–1.02], 95% PI [0.23–1.28]; and OR 0.20, 95% CI [0.20–0.20], 95% PI [0.19–0.21]) were consistent with a large clinical effect, but the upper bound of the 95% CI slightly exceeded the line of identity in definite and possible instances. The quality of evidence was moderate.

Conclusions: Interventions that reduce the frequency of awareness in the anaesthetic dose ranges of inhalation and total i.v. anaesthetic techniques studied are BIS monitoring with total i.v. anaesthesia but not with inhaled agents with or without alarms, alerts, or both.

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Awareness during anaesthesia: current status in Japan

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Background: The incidence of intraoperative awareness in Japan has not been evaluated. Therefore, questionnaire surveys were performed at three time points. From these surveys, I deduced the status of awareness in Japan.

Methods: A questionnaire survey was conducted via the Internet. Letters were sent to hospitals with staff anaesthetists to encourage response.

Results: The first survey was conducted in 2008. Since the introduction of remifentanil in Japan in 2007, widespread changes have occurred, including a reduction in the maintenance doses of anaesthetics. The survey showed that 27% of anaesthetists experienced definite or possible awareness. This indicated that intraoperative awareness might be high during the introduction period of remifentanil.

The second survey was conducted to evaluate the first survey in detail. The survey was designed to obtain information regarding patients who experienced awareness in 2008. A total of 172 anaesthetists answered. The total number of reported anaesthetic patients was 85 156. Twenty-four instances of definite or possible awareness were reported by 21 anaesthetists, of which 14 were instances of definite and 10 of possible awareness. The most surprising finding was that total i.v. anaesthesia (TIVA) was used in 21 of the 24 patients.

The third survey was conducted in 2011 as a continuous survey. Ten instances of definite or possible awareness were reported. Five patients were maintained by TIVA and three with sevoflurane. The survey showed that 76% of anaesthetists routinely use BIS for TIVA, but for sevoflurane only 27% of anaesthetists routinely use BIS.

Conclusions: The incidence of intraoperative awareness was compatible with previous study. The surveys show that meticulous care should be taken when anaesthesia is performed by TIVA even with BIS monitoring. The results of these surveys should be verified, in addition to further continuous and prospective study.

Epidemiology of intraoperative awareness

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Awareness or explicit recall during general anaesthesia is important to patients and anaesthetists alike because it has psychological and medicolegal sequelae. The incidence of awareness in the general surgical patient population is 0.1–0.2% (1–2 per 1000 patients) in European[1] and US[2] studies, when evaluated prospectively using structured postoperative interviews at several points in time. The incidence is greatly underestimated when evaluated by patient self-reports via quality-improvement data[3 4] or by voluntary reporting by anaesthetists (1 per 15 000 patients).[5] Patients may not voluntarily report awareness if they were not disturbed by it. In addition, the memory for awareness may be delayed[1] or patients may not voluntarily report awareness.[6] Studies in Spain[7] and China[8] have reported a higher incidence (0.4–0.6%), probably associated with lighter anaesthetic techniques and lack of benzodiazepines. A higher incidence of awareness occurs in cardiac, Caesarean section,[7 9] and trauma surgery, and in patients with significant impairment of cardiovascular status, severe end-stage liver disease, difficult intubation, and known heavy alcohol intake, chronic benzodiazepine or opioid use (1% or 1 per 1000 patients).[10] Other patient factors associated with awareness are increasing ASA status and younger age, but not gender.[2 7 8 11] The incidence of awareness is higher in children (0.5–1%).[11] Patients with a history of awareness also have an increased risk of intraoperative awareness.[12] Emergency surgery, surgery performed at night, ophthalmic surgery, and

admission to the intensive care unit are also associated with an increased risk of awareness.[2 7] Anaesthetic technique has an important role in the association with awareness, in that awareness has a higher incidence with neuromuscular block (0.18 *vs* 0.10% without neuromuscular block),[1] probably attributable to the prevention of movement, a sign of light anaesthesia. Although results are conflicting,[13] some studies have shown an increase risk of awareness with total i.v. anaesthesia (TIVA).[14] Nitrous oxide is also associated with an increased risk of awareness.[11]

Intraoperative awareness is caused by light anaesthesia, equipment problems (e.g. vaporizer malfunction or TIVA delivery problems), or increase patient anaesthetic requirements. Review of 96 instances of awareness from 1990 and later from the Anesthesia Closed Claims database of 10 093 (Anesthesia Quality Institute) found that light anaesthesia and anaesthetic delivery problems were the most common aetiologies for awareness, when a cause was identified. Light anaesthesia was associated with 38% of instances of awareness, no volatile anaesthetic with 8%, difficult intubation and low induction doses with 3%, haemodynamic instability limiting anaesthetic doses with 8%, and low drug doses for no obvious reason with 18%. Anaesthetic delivery problems occurred in 30% of instances of awareness, vaporizer problems in 15%, drug error in 12%, and technical problems with TIVA in 3%. The aetiology of the remaining 32% of instances of awareness was not identified by review of the hand-written anaesthetic records. However, electronic anaesthetic records have demonstrated low anaesthetic gas concentrations in several instances of awareness, whereas the hand-written records did not.[15] Other studies have also found that light anaesthesia is a common aetiology of awareness.[16] Chronic alcohol, benzodiazepine, and opioid use leads to tolerance and increases anaesthetic requirements. In addition, genetic differences in anaesthetic sensitivity occur in animals[17] and may exist in humans in some instances of awareness.[18]

The incidence of awareness can be reduced by use of deeper levels of volatile anaesthetics (age-adjusted end-tidal gas concentrations of 0.7–1.3 MAC),[19–21] and use of brain function monitoring-guided anaesthesia using the bispectral index.[10 19–21] Administration of bispectral index-guided anaesthesia may be most effective in reducing awareness during TIVA.[22]

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Implicit emotional memory in intensive care unit patients: replication of the Robinson Crusoe study

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Background: Schwender and colleagues[1] demonstrated implicit memory by presenting a synopsis of the Robinson Crusoe story to cardiac surgical patients during general anaesthesia: when in recovery, they were asked 'what is the first thing that comes into your mind if I say 'Friday'? Many said: 'the weekend, etc.' but some said: 'desert islands' despite having no knowledge that they had been presented with the story. We sought to replicate the study, but this time in intensive care unit (ICU) patients.

Methods: Twenty-five sedated ICU patients were randomized into two groups; one group was presented with a synopsis of the Robinson Crusoe story through headphones and the other a synopsis of the Cinderella story. A bispectral index monitor was used to ensure that patients were approaching consciousness (bispectral index between 60 and 80) at the time of story presentation. They were followed up at 1 and 3–4 weeks post-ICU discharge, when they were asked to associate with the words 'Friday' and 'glass'.

Results: No patient had conscious explicit recall of the story presentation. Three patients responded with 'Robinson Crusoe' to 'Friday', but two of these had been presented with

the Cinderella story (and not Robinson Crusoe) while in the ICU. No patient responded with 'slipper' to the prompt 'glass'.
Conclusions: The fact that two patients in the Cinderella group responded with 'Robinson Crusoe' to the prompt 'Friday' raises the issue of the base rate of 'Robinson Crusoe' responses to 'Friday' in the local population. A baseline study has now commenced to determine this. However, even disregarding the two false positives, the rate of only one in 25 is disappointing. An important difference between this study and the study by Schwender and colleagues[1] is the time interval between story presentation and word association testing. In our study, we tested twice, 1 and 3–4 weeks after presentation, whereas Schwender and colleagues[1] tested within hours of the presentation. Nevertheless, we consider the delay in our study justified, because the disappearance of ephemeral emotional memory after only a few hours is unlikely to be significant clinically.

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Propofol induced spike synchrony of pyramidal cells in rat cerebral cortex

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Background: Recent data have revealed that the general anaesthetic propofol (PRO) increases frontal α rhythm at a dose that is sufficient to induce loss of consciousness.[1 2] However, the neural mechanisms of PRO-induced α rhythm in the cerebral cortex remain unknown. We previously demonstrated that inhibitory connections from fast-spiking cells (FS) to excitatory pyramidal cells (Pyr) are the most sensitive to PRO-induced facilitation of unitary inhibitory postsynaptic currents (uIPSCs).[3] Taken together with the finding that direct chemical inhibitory postsynaptic potentials (IPSPs) can promote a high degree of synchrony,[4] it is reasonable to propose the hypothesis that PRO-induced facilitation of uIPSCs results in firing synchrony among postsynaptic Pyr that receive inhibition from the same presynaptic FS.
Methods: We performed whole-cell patch-clamp recording from one FS and two Pyr (Pyr1 and 2 in Fig. 1) in rat insulocortical slices. In the pairs where a presynaptic FS projected to postsynaptic Pyr1 and 2, action current induction in the FS evoked unitary IPSPs in Pyr1 and 2. Pyr1 and 2 were depolarized to generate repetitive spike firing, and we examined how presynaptic FS action potentials modulate the timing of spike firing in Pyr1 and 2.
Results: Figure 1 shows an example in which the FS was connected to both Pyr1 and 2. In the control traces, inhibitory inputs from FS had little effect on spike timing synchrony between Pyr1 and 2. Bath application of 10 μM PRO significantly reduced the coefficient of variation of spike timing in Pyr1 and 2 during FS activation (arrows; $P<0.01$, Mann–Whitney *U*-test; $n=14$ pairs). In contrast, spontaneous firing of Pyr1 and 2 was not affected by PRO.

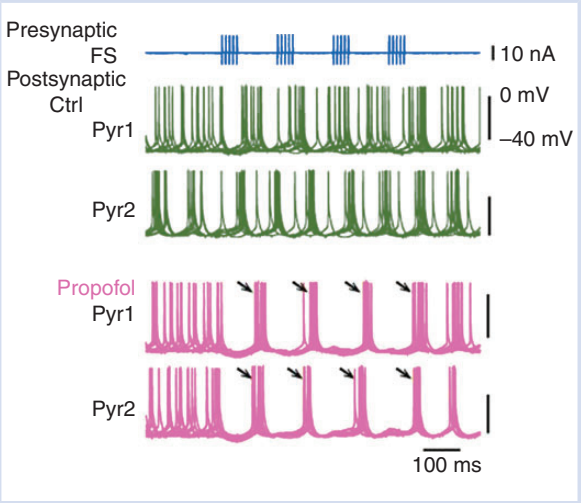

Fig 1 An example of propofol induced spike synchrony between two pyramidal cells. A presynaptic fast-spiking cell (FS) was connected to two postsynaptic pyramidal cells (Pyr1 and Pyr2). In control, inhibitory inputs from FS had little effect on spike timing synchrony between Pyr1 and Pyr2. Both application of 10 μM propofol significantly reduced the coefficient of variation of spike timing synchrony between Pyr1 and Pyr2 (arrows).

Conclusions: Propofol facilitates Pyr firing synchrony by enhancing inhibitory inputs from FS. This synchrony of Pyr may induce the frontal α rhythm that is associated with loss of consciousness.

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Awareness during general anaesthesia: risk factors and prevention

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Awareness during general anaesthesia is a rare event (1 or 2 per 1000 anaesthetics), but it may cause severe distress for the patient; in the worst case, post-traumatic stress disorder. Several possible causes and risk factors for awareness have been discussed in the literature. The increased risk for awareness can relate to the patient's condition, the type of surgery, or the management of anaesthesia. Risk of

awareness has been reported to be increased in patients with reduced cardiovascular capacity, those with accelerated metabolism of anaesthetics (e.g. patients with chronic pain), history of awareness (five-fold increased risk!), or obesity. Also, females and children have been reported to have increased risk of awareness.

Surgical procedures such as cardiac surgery, Caesarean section, emergency operations, and ophthalmological surgery may be associated with increased risk because of the lower doses of anaesthetics used in these operations.

The management of anaesthesia may cause increased risk. Underdosing of anaesthetics and use of neuromuscular blocking agents have resulted in awareness, as have difficult and prolonged laryngoscopy and intubation. Total i.v. anaesthesia has been reported to cause more awareness, perhaps because the drug concentrations that induce unconsciousness cannot be measured. Patients who have not received benzodiazepines have reported more often about awareness than those who have had premedication with benzodiazepines. Misuse of a machine or equipment malfunction may sometimes remain unnoticed and cause awareness.

Based on knowledge about the causes and risk factors, the following strategies have been suggested to avoid awareness. Before surgery, patients should be evaluated concerning the risk for awareness, and those with increased risk of awareness should be informed about it. The anaesthesia delivery systems should be checked. Checklist protocols increase the safety of anaesthetic delivery. During surgery, the dosing should be adjusted individually, and no unnecessary neuromuscular blocking agents should be used. The anaesthetist should monitor the vigilance and purposeful movements of anaesthetized patients. Brain monitoring should be used for at-risk patients and during total i.v. anaesthesia. The isolated forearm technique should be considered if neuromuscular blocking agents are used. Inhalation anaesthesia may be safer for the patient with increased risk for awareness rather than total i.v. anaesthesia. Anaesthetic gas end-tidal concentrations should be more than 0.5 or 0.7 MAC, and setting an alarm for low MAC is useful. In the event of hypotension, treatment other than decreasing the anaesthetic should be considered. Continuous application or re-dosing of the hypnotic agent is important during the whole induction and anaesthetic procedure, especially if intubation is prolonged. Benzodiazepines should be given for amnesia if the patient is in poor condition and adequate dosing of the anaesthetic agents cannot be administered (e.g. trauma). Finally, the whole anaesthesia team should be trained about the causes of awareness, risk factors, and prevention.

Mechanisms of anaesthetic action and memory: molecular and animal models

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Current understanding of the molecular and cellular mechanisms that underlie the pharmacology of general anaesthetics is incomplete. Understanding the mechanisms of anaesthetic action is critical to our ability to use these important drugs with optimal safety and efficacy. Genetic methods have led to major advances in identifying the targets for general anaesthetics and their role in producing unconsciousness and amnesia. Anaesthetics have agent-specific effects on discreet molecular targets to modulate synaptic transmission and the function of neuronal networks central to each of the specific anaesthetic end points. While these approaches have led to major progress in understanding the molecular pharmacology of i.v. anaesthetics, the actions of the inhaled anaesthetics have been more difficult to resolve. Ample evidence indicates that clinical concentrations of most general anaesthetics can alter the function of ligand-gated ion channels, in particular the $GABA_A$ receptor. Recent evidence has identified receptor subtype-specific effects involved in the amnestic effect of specific agents. However, there is still relatively little information about how modulation of 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. Further progress in defining anaesthetic effects at the molecular and synaptic levels is critical to understanding their cognitive actions in the intact organism.

Computational modelling of anaesthesia

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Background: The understanding of how general anaesthetics act on neurones and global brain function has increased significantly over the last two decades. Yet how they act at intermediate scales is poorly understood and therefore anaesthetic-induced unconsciousness and amnesia remain a mystery. Current experimental techniques are limited in their ability to observe phenomena directly at this intermediate scale, but advances in computational modelling are helping us to understand the processes linking neural activity to overall brain function. We describe three discrete models of the brain that we have examined to study the effects of propofol and volatile anaesthetics.
Methods: The effects of propofol were simulated by $GABA_A$ receptor potentiation and indirect reductions of excitatory input drive in a computer model of a cortical network[1] and an anatomically realistic model of the rat hippocampus. A particle swarm optimization algorithm was developed to match the output of a simple thalamocortical model to local field potentials measured *in vivo* from rat thalamus and cortex during emergence from isoflurane anaesthesia.[2]
Results: Potentiation of $GABA_A$ inhibition in the cortical network prevented the firing of spatiotemporally defined neuronal groups that were present at baseline. The hippocampal model spontaneously exhibited θ and γ rhythms that were altered in amplitude and frequency in the

presence of the simulated effects of propofol. The electrical effects of alterations in the concentration of inhaled isoflurane in the rat were reproduced in the thalamocortical model by modulating the strength of connections between the thalamus and cortex and between populations of excitatory neurones.

Conclusions: Facilitation of $GABA_A$ receptors both directly and indirectly inhibits the ability of neurones to form groups spontaneously. A lack of group formation is consistent with some theories of anaesthetic-induced loss of memory formation and consciousness. Changes in the native θ and γ hippocampal rhythms by $GABA_A$ facilitation may prevent memory formation during propofol anaesthesia. The use of particle swarm optimization to match *in vivo* data to *in silico* modelling allows the development of novel insights into the systems effects of anaesthetic agents.

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The role of dopamine in reanimation from general anaesthesia

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In current clinical practice, emergence from general anaesthesia is treated as a passive process dictated by the pharmacokinetics of anaesthetic drug elimination. As the mechanisms underlying anaesthetic emergence are poorly understood, related problems, such as postoperative delirium and cognitive dysfunction, remain significant causes of morbidity in surgical patients.[1–3] No effective methods to treat these problems are currently available.

There are multiple ascending arousal pathways in the brain, and recent findings suggest that many of these neural circuits are involved in emergence from general anaesthesia.[4–6] The arousal-promoting neurotransmitters orexin/hypocretin,[7 8] acetylcholine,[9–11] histamine[12 13] and norepinephrine[14 15] have all been implicated in emergence. However, the specific contributions of different arousal pathways to the process of regaining consciousness after general anaesthesia remain unclear.

We previously reported that methylphenidate (an inhibitor of the dopamine reuptake transporter) restores conscious behaviours in rats under general anaesthesia and induces EEG changes consistent with arousal.[16 17] We term this active emergence process 'reanimation', distinct from the passive emergence process in current clinical practice. A D1 dopamine receptor agonist also induces reanimation from general anaesthesia,[18] providing further evidence for a dopamine-mediated arousal pathway.

Our most recent work using intracranial stimulation shows that an arousal pathway projecting from the ventral tegmental area induces reanimation from general anaesthesia.[19] Our long-term goal is to provide clinicians with new tools to control the process of emergence. These tools may be useful to treat or obviate emergence-related problems, such as delirium and cognitive dysfunction, and may also benefit patients suffering from disorders of consciousness attributable to brain injury.

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Cortical acetylcholine, connectivity, and states of consciousness

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Previous studies have demonstrated the association between states of consciousness and changes in anterior–posterior brain connectivity.[1–4] However, most investigations regarding consciousness and connectivity have been conducted in humans, which limits insight into the underlying neurochemical processes. Concentrations of the neurotransmitter acetylcholine (ACh) in the cortex are correlated with electroencephalographic and behavioural

arousal.[5–8] Therefore, in a series of studies I investigated the association between cortical ACh and brain connectivity during conscious, anaesthetized, and sleep states in rats. Using microdialysis coupled with high-performance liquid chromatography and electrochemical detection, I measured cortical ACh before, during, and after unconsciousness induced by propofol and sevoflurane. In addition, concurrent monopolar EEG was recorded from frontal, parietal, and occipital cortices and analysed using non-directional and directional connectivity measures. I also investigated brain connectivity changes during the sleep–wake cycle, which is characterized by an endogenous modulation of cortical ACh. Preliminary results indicate that brain connectivity in the θ bandwidth is correlated with changes in cortical ACh, whereas the changes in γ connectivity appear to be independent of cortical ACh but are linked with behavioural arousal. These studies provide a comprehensive profile for concurrent changes in brain connectivity and cortical ACh across states of consciousness. A clear understanding of the coupling between brain connectivity and neurochemical changes, especially in the cortex, is imperative in order to understand the general neurobiological principles underlying mechanisms of anaesthetic- and sleep-induced unconsciousness.

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Ketamine induced synchronous oscillations in the cortex–basal ganglia network

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Background: Ketamine is commonly used for sedation and analgesia. It is an *N*-methyl-D-aspartate receptor antagonist, but its effect on the brain network activity is not documented. Measurements by currently available monitors of anaesthetic depth (such as bispectral index) are not reliable when using ketamine.

Methods: We recorded local field potentials and spiking activity from the primary motor cortex (M1) and external globus pallidus (GPe) of four vervet monkeys during administration of ketamine.

Results: Ketamine induced synchronized γ (30–50 Hz) oscillations modulated by ultraslow (~0.3 Hz) oscillations within and between M1 and the GPe. The phase distribution was centred around zero within the structures (−3.5° [SD 31.8°] and −0.4° [SD 6.0°] for M1 and GPe pairs, respectively) and skewed, with a mean of −18.4° [SD 20.9°], between the structures. The γ oscillations lasted longer than the ultraslow modulation and continued even after the monkey regained consciousness, suggesting two independent mechanisms. The spiking activity was phase locked to the local field potential oscillations in both structures, but with different phase relations.

Conclusions: The phase distribution suggests that these oscillations are propagating through the corticobasal ganglia–thalamic network. We suggest that the ultraslow (0.3 Hz) modulation of the γ oscillations plays a role in the loss of consciousness, whereas the γ oscillations are important to other effects of ketamine. Depth of consciousness monitors should include these effects in their algorithm, in order to measure anaesthetic depth reliably when using ketamine.

Role of brain noradrenergic neurones in mechanism of anaesthesia: a proposal focused on its relevance to endogenous sleep-related substances

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Background: Brain noradrenergic (NA) neuronal activity is responsible for sleep–wakefulness and pain, which are elements of general anaesthesia. Several endogenous sleep-related substances also affect the NA activity. Recent studies showed that sleep and anaesthesia share, in part, the mechanism of loss of consciousness.[1] We hypothesized that brain NA activity would be involved in the mechanism.

Methods: With approval of the institutional committee on animal research of Hirosaki University Graduate School of Medicine, we studied the effect of changes in brain NA activity on anaesthesia time and analgesia provided by various anaesthetics. We used α_2 agonist, α_2 antagonist, DSP-4 (a specific NA toxin), and orexin to modify the NA activity in rats.

Results: We classified anaesthetics into two types based on their effect on brain NA modulation. One enhanced NA activity (ketamine, Xe, and N_2O) and the other reduced it (propofol, midazolam, and barbiturates). Brain noradrenergic neuronal activity (200% to baseline) decreased anaesthesia time of both types of anaesthetics (Fig. 2). Pharmacological counteraction of anaesthetic-induced changes in NA activity reduced anaesthesia time and the analgesic effect of both type of anaesthetics.[2]

Conclusions: Brain noradrenergic neuronal activity is involved in the mechanism of anaesthesia. Moreover, the

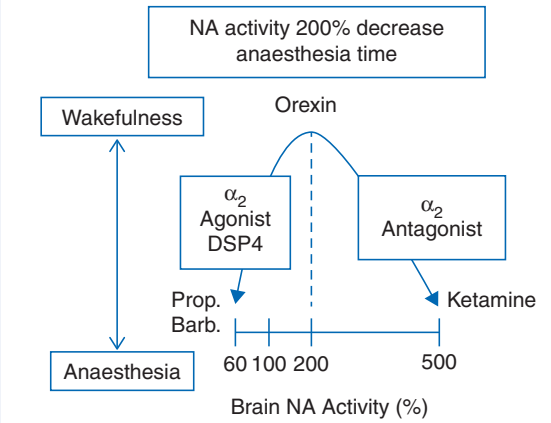

Fig 2 Brain noradrenergic neuronal activity is involved in mechanism of anaesthesia. Degree of the noradrenergic activity level is crucial to determine anaesthesia status. Two hundred % of basal activity may promote wakefulness; while 60 or 500% of basal activity may produce anesthetic status.

degree of the activity level is crucial to determining the anaesthesia status.

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Bispectral index: yesterday, today, and tomorrow

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Until recently, anaesthetists lacked the ability to monitor the effects of anaesthetics on the brain, so-called 'depth' or 'adequacy' of anaesthesia. Typically, surrogate measures of autonomic activity, such as changes in blood pressure and heart rate, were used to assess the adequacy or inadequacy of anaesthesia. Given that we believe that general anaesthetics block consciousness by depressing the central nervous system and we can measure electrical activity of the cerebral cortex via the EEG, it is intuitive that some component of the EEG should relate to the adequacy of anaesthesia. Such a relationship was first suggested in 1937. With the advent of microcomputer technology, it became possible to reduce the amount of data obtained from an EEG to various processed derivatives. Derivatives, such as the power spectral edge, median frequency, and zero-crossing frequency, were described as potential measures of anaesthetic effect on the central nervous system. In that these measures were found to depend on specific drug combinations and were not monotonically related to drug effect or clinical response, no 'gold standard' for measuring the entire spectrum of anaesthetic effect was accepted widely.

The first technology approved by the US Food and Drug Administration, in October 1996, for marketing as an EEG-based monitor of anaesthetic effect is the bispectral analysis derivative known as bispectral index (BIS; Aspect Medical Systems, Natick, MA, USA). Bispectral analysis provides an alternative description to a continuous pseudo-randomly varying signal (such as EEG) than other conventional power spectral analysis techniques derived from fast Fourier transformation.

A series of clinical studies established the relationship of BIS to effect site concentrations of anaesthetic drugs, and subsequent clinical utility studies established BIS as an effective measure of anaesthetic effect on the central nervous system. It has now become established as a common monitor in many operating theatres throughout the world. Since the introduction of BIS, several other EEG derivatives have been proposed as alternative measures, but comparative randomized studies of the different technologies are lacking. Unfortunately, the technology is now viewed as a mature technology, and little research and development is currently in progress.

With a reduced research and development programme, the future of EEG monitoring in the operating theatre is uncertain. Clinical benefits need to be established clearly, and the possible effect of EEG monitoring on outcome after surgery is a likely area of fruitful study.

Monitoring and prevention of awareness during general anaesthesia: towards mechanism-based monitoring of anaesthesia

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Currently, indices of the hypnotic level of anaesthesia follow a probabilistic approach. For the construction of such an index, the occurrence of particular EEG characteristics, such as frequency, power, or specific patterns (e.g. grapho elements), is observed during defined levels of anaesthesia. This probabilistic approach of current EEG-based indices allows a first insight into reactions of the brain to general anaesthesia, and may already reduce the incidence of awareness with recall.[1] It has been shown that the combination of EEG-based parameters and standard monitoring parameters provides a more precise description of the level of anaesthesia than either EEG parameters or standard parameters alone.[2]

Nonetheless, a probabilistic EEG-based index value reflects probability of awareness (i.e. awareness may still occur while such an index is within the target range of general anaesthesia).[3 4]

Recently, studies using functional magnetic resonance imaging have suggested a common mechanism of anaesthesia-induced unconsciousness.[5 6] On the basis of EEG analysis, the change in functional connectivity has been verified and specified; loss of consciousness is attributable to loss of corticocortical feedback connectivity, while feedforward connectivity is maintained.[7] This has been shown not only for propofol, but also for sevoflurane and ketamine.[8 9] This allows the construction of an index that is based on the main mechanism of anaesthesia, loss of feedback connectivity. Future studies are required to verify this approach to EEG analysis. Mechanism-based monitoring may then provide more specific information about the brain during anaesthesia and may therefore prevent awareness by monitoring the mechanism of awareness.

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Changes of EEG during anaesthesia and their physiological background

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An EEG monitor is now commonly used to assess the level of hypnosis during anaesthesia. However, most anaesthetists only watch the indices calculated by the EEG monitors, such as bispectral index (BIS), and do not observe the raw EEG. However, such EEG-derived parameters show only some aspects of EEG features. To understand the usability and reliability of EEG-derived indices, we should know how the raw EEG changes during anaesthesia. We also should know its physiological aspects during anaesthesia.

To make the matter simple, here I handled the EEGs when a GABAergic anaesthetic agent (i.e. volatile anaesthetic or propofol) was used, and I mainly handled the EEG obtained from the hemi-frontal lead, as for the BIS monitor.

Generally speaking, the dominant frequency of the EEG became slower and the amplitude of the EEG became larger when the concentration of anaesthetic was increased. However, detailed changes of the EEG were more complicated. When the concentration of anaesthetic agent was gradually increased, the power in the β range was transiently increased. At an anaesthetic concentration, the spindle wave (α range) became dominant, and at a deeper level the activity of the spindle wave then became smaller and the power of θ and δ waves became dominant. At an even deeper state, the EEG waveform changed into a burst and suppression pattern, and finally, it became flat.

Steriade and colleagues[1 2] extensively investigated the mechanism of generation of spindle waves. They clarified that the rhythm of the spindle wave is generated in the thalamic reticular nuclei and thalamocorticothalamic reverbing circuit, and the EEG rhythm is determined by the membrane potential of the thalamocortical projection neurone. When the membrane potential of the thalamocortical neurone was between −55 and −65 mV, the rhythm became that of the spindle wave, and when it was below −65 mV it changed into that of the δ wave. Considering that thalamic reticular nuclei send a GABAergic projection to thalamocortical neurones and volatile anaesthetic or propofol potentiates GABAergic inputs, I speculated that the activity of the spindle wave would become the key to assess the effect of anaesthetics among patients.

The spindle wave was also sensitive to noxious stimuli. The EEG waveform showed variable changes when noxious stimuli were added. However, the spindle wave disappeared after noxious stimuli were added, and it reappeared when adequate analgesia was obtained.

I now speculate that it will be important to maintain the level at which spindle wave becomes most dominant to prevent awareness during anaesthesia.

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The response of bispectral index to neuromuscular block in awake volunteers

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Background: In 2003, Messner and colleagues[1] reported that the bispectral index (BIS) decreased after neuromuscular block in the fully awake patient, to levels which incorrectly suggested anaesthesia. This was concerning, because it implied that the BIS monitor relied upon muscle activity (electromyogram: EMG) to detect awareness rather than brain activity (EEG). This finding has been neither replicated nor refuted, although studies have shown that EMG will increase BIS in the anaesthetized patient.[2 3] Because this device is used clinically to detect unintended awareness in patients given a neuromuscular blocking agent, it is of great importance that we understand how it responds to the effects of neuromuscular block.

Methods: Ten volunteers, who were all practising anaesthetists in our department, underwent a period of awake paralysis on two separate occasions, once with

suxamethonium and once with rocuronium. An isolated forearm technique was used to confirm awareness. The subjects were ventilated by facemask until return of muscle function. In the rocuronium arm, sugammadex, 200 mg, was administered to antagonize rocuronium after at least 15 min. Two BIS monitors, a 2003 model A2000 and a 2013 model BIS-Vista, were used to examine whether there was any significant difference in response attributable to software upgrades over the last 10 yr.

Results: The BIS in all subjects decreased after administration of either suxamethonium or rocuronium.[4] In some subjects, it reported values less than 60 for minutes at a time, with transient decreases to values as low as 44. All subjects had full recollection and were able to answer simple arithmetic questions throughout the experiment using hand signals. The BIS did not return to levels above 80 until after recovery of muscle function, which occurred within 60 s of administration of sugammadex. The two BIS monitors showed a broadly similar response to neuromuscular block.

Conclusions: The BIS monitor consistently generates index values suggesting deep sedation and anaesthesia in awake subjects who have been given neuromuscular blocking drugs. It would appear that the BIS relies upon muscle activity to generate values that predict awareness.

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Isolated forearm technique

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Given that response to commands is the accepted indication of consciousness, the isolated forearm technique (IFT) is the only direct method of detecting consciousness during general anaesthesia in the presence of neuromuscular blocking agents.[1–3]

Despite the use of the IFT for more than three decades, and studies where its use has clearly demonstrated the fallibility of anaesthesia brain monitors,[4 5] there continue to be published inaccurate and unfounded criticisms. This presentation will look at the history of the IFT, its practicalities and uses, and how the myths about limitations of the technique have arisen. These myths are often uncritically reproduced from review to review.[6–8] More recent articles have been published in attempts to correct these fallacies.[9]

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A multimodal indicator combining EEG and standard monitoring parameters provides reliable detection of depth of anaesthesia with different anaesthetic drugs

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Background: Electroencephalographic depth of anaesthesia monitoring has been suggested, supplementing standard monitoring to reduce over-/underdosage-related side-effects. However, the benefit of available monitors has been critically discussed. To improve present monitoring techniques, the anaesthesia multimodal indicator of consciousness (AMIC) integrates EEG parameters, vital signs, and individual information (patient data and drug protocol).[1] The present investigation evaluates whether the AMIC reliably indicates hypnotic states from wakefulness to deep anaesthesia in different anaesthetic combinations.

Methods: Approved by the ethics committee and after written informed consent, 263 adult patients undergoing surgery under general anaesthesia were included in a study conducted in six European centres.[1] Patients were assigned to one of 10 anaesthetic groups, consisting of opioid analgesics (remifentanil, fentanyl, and sufentanil), hypnotic drugs for induction [thiopental (T), propofol (P), and etomidate (E)] and maintenance [P, isoflurane (I), sevoflurane (S), and desflurane

Table 1 Prediction probability (P_K) and 95% bootstrap confidence intervals of AMIC and BIS to separate consciousness, unconsciousness, clinical practice and burst suppression in the specific anaesthetic groups. *P_K of AMIC significantly higher than P_K of BIS ($P<0.05$)

Induction/ maintenance	No. of patients	AMIC	BIS
T/I, opioid	40	0.96* (0.94–0.99)	0.85 (0.76–0.89)
E/I, opioid	35	0.94* (0.92–0.98)	0.79 (0.69–0.85)
P/P, remifentanil	37	0.96* (0.94–0.99)	0.80 (0.79–0.92)
P/P, sufentanil	20	0.97* (0.92–0.99)	0.87 (0.78–0.94)
P/D, opioid	40	0.98* (0.96–0.99)	0.77 (0.66–0.83)
P/S, opioid	21	0.96* (0.92–0.99)	0.79 (0.66–0.86)
P/I, opioid	30	0.96* (0.92–0.99)	0.74 (0.62–0.84)
E/P, sufentanil	14	0.91 (0.74–0.96)	0.65 (0.54–0.92)
E/P-S, sufentanil	20	0.95* (0.90–0.99)	0.68 (0.58–0.86)
E/P-I, opioid	6	0.90 (0.69–0.98)	0.90 (0.65–0.94)

(D)]. Standard parameters and EEG were continuously recorded. During induction of anaesthesia, patients were asked twice every 15 s to squeeze the investigator's hand to detect loss of consciousness (LOC). After skin incision, anaesthetic doses were increased until EEG burst suppression occurred. Subsequently, anaesthesia was performed according to standard clinical practice. At the end of surgery, drugs were discontinued and commands to squeeze the hand were given until return of consciousness (ROC). The AMIC was developed through a data-driven adaptive neuro fuzzy inference system, which maps EEG parameters (weighted spectral median frequency,[2] approximate entropy,[3] permutation entropy,[3] and burst suppression ratio), standard parameters (heart rate, blood pressure, inspiratory and expiratory gas concentrations, pulmonary peak pressure, MAC equivalent, and plasma concentration), patient data (age, sex, and BMI) and drug protocol (induction and maintenance drug) onto an output indicator (three-fold cross-validation). Both AMIC and BIS (calculated offline)[4] were analysed during consciousness (before LOC and after ROC), unconsciousness (after LOC and before ROC), clinical practice, and burst suppression. Prediction probability (P_K), including 95% percentile bootstrap confidence intervals (CI), indicates the ability of the indicators to separate anaesthetic levels.

Results: Anaesthesia multimodal indicator of consciousness detects anaesthetic levels at significantly higher P_K than BIS (Table 1). Values of P_K for AMIC remain stable through the anaesthetic combinations.

Conclusions: A multimodal integration of EEG and standard monitoring parameters together with individual information exceeds the performance of the current standard EEG monitoring to indicate depth of anaesthesia and may lead to a more reliable detection of awareness.

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A comparative study of the EEG-return plot with bispectral index monitoring

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Background: The return plot (Poincaré plot) is a type of state-space approach described in a two-dimensional plane, where a timed signal is plotted against itself after a time delay.[1] The plot pattern depends on the randomness and variability of the signal, and the quantification of a return plot of the EEG was found to reveal sevoflurane-dependent EEG changes.[2] In the present study, we compared a quantification index of the return plot with bispectral index monitor-derived parameters during sevoflurane, desflurane, and propofol anaesthesia.

Methods: Frontal EEG signals in 51 patients anaesthetized with sevoflurane, desflurane, or propofol were continuously monitored. Return plots were sequentially constructed using EEG signals 10 s in duration acquired with 128 Hz sampling. The scattered pattern of the plots was quantified as the SD of the voltage dispersion perpendicular to the line of identity (SD1), the standard deviation along the line of identity (SD2), and their ratio (SD1/SD2). The average of the two SD1/SD2 values, obtained from EEG signals 5 s in duration, were compared with simultaneously recorded bispectral index and spectral edge frequency 95 (SEF95), by regression analysis.

Results: Regression analysis between return plot (SD1/SD2) and SEF95 showed a tight linear regression equation (Fig. 3; n=32 351, SEF95=SD1/SD2 × 61.9 + 1.3, root mean square of errors=0.8989, $P<0.0001$), with a coefficient of determination (r^2) value of 0.904.

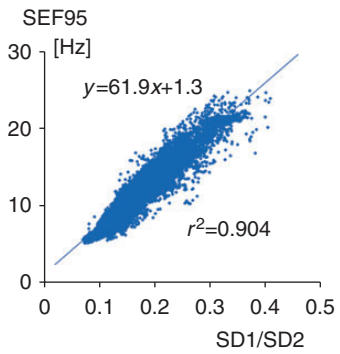

Fig 3 The relationships between simultaneously obtained pairs of SD1/SD2 and SEF95 were plotted in all the cases.

Conclusions: Quantification of the return plot (SD1/SD2) of the EEG is tightly correlated with SEF95, reflecting anaesthesia-dependent spectral changes in EEG oscillation.

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Aging delays emergence from general anaesthesia in rats

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Background: Aging decreases the dose requirement for immobility induced by general anaesthetics.[1] However, the effects of aging on emergence from general anaesthesia are not known. In this study young and aged rats were used to test whether aging delays emergence from general anaesthesia with isoflurane and propofol. We also tested whether aging decreases the dose requirements for isoflurane-induced loss of righting and burst suppression in electroencephalogram (EEG).

Methods: Return of the righting reflex was used to define emergence from general anaesthesia. Male Fischer 344 rats aged 6–8 months (*young*, *n*=6) and 24–26 months (*aged*, *n*=6) were anaesthetized with isoflurane (1.5% for 45 min) and time to emergence was recorded in room air. In a separate experiment at least 3 days later, a 24-gauge IV catheter was placed in a lateral tail vein under isoflurane anaesthesia. After full recovery from isoflurane, propofol (8 mg/kg IV) was administered and time to emergence was recorded. In order to test the minimum dose of isoflurane required for loss of righting refles, rats were placed supine in an anaesthetizing chamber and the dose of isoflurane was decreased by 0.1% every 40 min until the animal exhibited purposeful movement (i.e., any movement other than a spontaneous

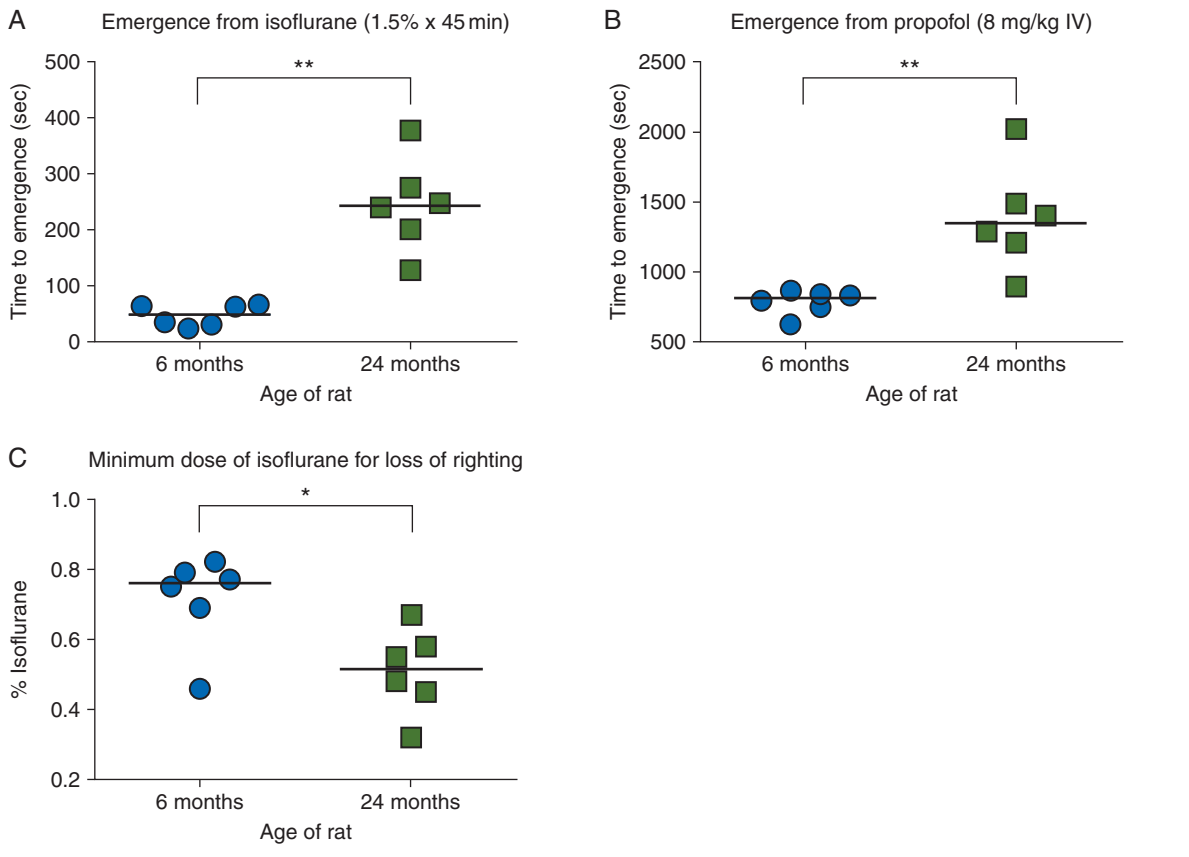

Fig 4 (A) Scatter plot of time to emergence after isoflurane anaesthesia (1.5% inhaled for 45 min) in young adult (6–8 months old, blue circles) and aged (24–26 months old, blue circles) F344 rats. Return of righting was used to define emergence. (B) Scatter plot of time to emergence from propofol anaesthesia (8 mg kg^{-1} IV) in young adult (green squares) and aged (green squares) F344 rats. (C) Scatter plot of minimum isoflurane dose necessary to maintain LOR in young adult (blue circles) and aged (blue circles) F344 rats.

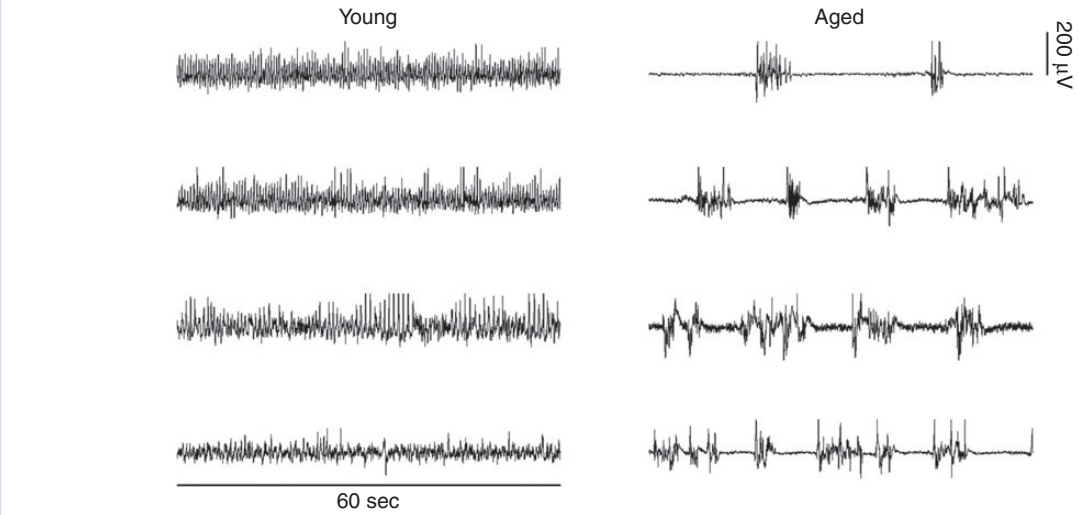

Fig 5 (A) Representative 60 s EEG recordings from 4 young adult rats inhaling 2.0% isoflurane. None of the animals are in burst suppression. (B) Representative 60 s EEG recordings from 4 aged rats inhaling 2.0% isoflurane. All of the animals are in burst suppression, indicating a deeper depth of anaesthesia.

muscle twitch). The dose of isoflurane was then increased by 0.1% until the animal did not exhibit any spontaneous movement for 40 consecutive minutes. At the final dose, a Riken FI-21 anaesthesia agent analyzer was used to confirm the inhaled isoflurane concentration. In a separate group of young (n=4) and aged (n=4) rats with implanted skull electrodes, the EEG was recorded at 2% isoflurane after a minimum of 40 min to reach steady-state.

Results: The median time to righting reflex after isoflurane anaesthesia was 49 s in young rats vs. 242 s in aged rats (Fig 4A). The median time to righting reflex after propofol was 813 s in young rats vs. 1344 s in aged rats (Fig 4B). In both instances, the differences were statistically significant (P=0.0022 for both, Mann-Whitney test). The median dose of isoflurane required to maintain loss of righting reflex with no spontaneous movement was 0.76% for young rats vs. 0.52% for aged rats (Fig 4C). The difference was statistically significant (P=0.026, Mann-Whitney test). As shown in the representative 60 s EEG epochs from individual rats (Fig 5), 0/4 young rats were in burst suppression while inhaling isoflurane 2.0%, whereas 4/4 aged rats were in burst suppression, indicating a greater depth of general anaesthesia.

Conclusions: Aging prolongs emergence from general anaesthesia with isoflurane and propofol, suggesting that delayed emergence is not a unique feature of a particular general anaesthetic. The dose requirement for isoflurane-induced loss of righting reflex decreases with age, suggesting that the aged brain is more sensitive to anaesthetic-induced unconsciousness. This notion is further supported by neurophysiological data showing that the same dose of isoflurane induces a greater depth of general anaesthesia in older rats. The results of this study encourage further work to elucidate the neural mechanisms underlying aging-related changes in sensitivity to general anaesthesia.

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SmartPilot View™: a navigation aid for safer balanced anaesthesia

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Accidental awareness during general anaesthesia may result in serious postoperative psychiatric disorders, sometimes lasting for months or even years. Therefore, intraoperative awareness is one of the anaesthetic complications that must be prevented at any cost.

In aviation, navigation aids, such as the ground proximity warning system, play a crucial role in preventing fatal aeroplane crashes. A pilot controls the aircraft with all vital information, such as airspeed, altitude, and heading, displayed in the cockpit panels from take-off to landing. The practice of anaesthesia is often compared to controlling a commercial flight, but do we have similar and efficient pharmacological navigation aids at hand in the operating theatre?

Short-acting drugs, such as desflurane, sevoflurane, propofol, and remifentanil, are most widely used nowadays. These drugs are distributed from the plasma to the periphery or broken down quickly to inactive metabolites by enzymes in blood, tissues, or both. Their unique pharmacokinetic profiles make it possible to attain and maintain stable concentrations easily or to titrate when necessary. However, the effect-site concentrations will rapidly decrease if delivery

is interrupted. In other words, modern balanced anaesthesia carries an inherent risk of unintentional awareness, particularly in paralysed patients.

Pharmacokinetics (PK) explains the time course of drug concentration in the body after injection of a bolus dose or continuous infusion. Pharmacodynamics (PD) deals with the relationship between drug concentration and clinical effects. Both PK and PD are essential knowledge for anaesthesia, but in reality very few trainees are keen to read through textbooks full of intimidating equations, and many regard these as boring subjects with no relevance to their clinical practice. Is there any innovative way to make PK/PD friendlier to novices and consultants without an interest in mathematics?

Dräger Medical GmbH (Lübeck, Germany) has developed a software program, SmartPilot View™, which calculates concentrations of i.v. and volatile inhalation agents based on the 'history' of drug administration by an infusion pump or a vaporizer. Starting from the origin on a two-dimensional plane, SmartPilot View™ depicts a 'flight path' of balanced anaesthesia as the path of a dot, with concentrations of opioid analgesics and hypnotics shown on *x*- and *y*-coordinates, respectively. Several isobolograms reflecting the probability of somatic and sympathetic responses to various noxious stimuli (calling the patient's name, laryngoscopy, and surgical incision) are superimposed. This allows easy visualization of synergistic interactions between opioids and hypnotics and appreciation of the temporal changes of their pharmacodynamic effects. For example, if an anaesthetist forgot to restart an infusion pump after changing a syringe of propofol, SmartPilot View™ would predict a decrease in propofol concentration in the next 15 min, thus warning the anaesthetist against impending awareness. The potential value of SmartPilot View™ as an educational tool is discussed, with particular emphasis on prevention of intraoperative awareness.

Unconscious memory formation during anaesthesia

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As opposed to conscious, explicit memories that we can recall and which are personally relevant in a context of time and place, implicit memories are prototypical of 'hidden' memory; memories that exist, but that we do not know we possess.[1 2] Nevertheless, our behaviour is affected by these memories; in fact, these memories allow us to function seamlessly in an ever-changing world. What happens to these memories during anaesthesia? More to the point, is it possible to create implicit memories during anaesthesia? Memory is a behaviour, and thus, difficult to pin down precisely. Conscious memory has multiple manifestations, and thus, end points of anaesthetic effect can be considered 'fuzzy'. These considerations are multiplied several-fold in the study of unconscious memories. It is difficult to quantify with any reliability the presence or absence of unconscious memory.[3] A brief review of the difficulties in interpreting the literature for implicit memory formation during anaesthesia will be done.[4 5]

A relevant question is whether implicit memory formation is a realistic possibility during anaesthesia. A potential neurobiological basis for implicit memory formation will be presented. A review of subliminal information processing will be presented, again in the context of brain function as embodied in network interactions.[6–9] The role of sensory and perisensory cortices, in particular the auditory cortex, in support of memory function will be discussed.[10–16] A different conceptualization of memory taxonomy will be presented, which focuses on dynamic information processing with interactions among different memory systems rather than static classification of different types of memory.[17] Directions for future research in this area will be presented.

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Indirect memory during anaesthesia

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Memory can be divided into direct (recall for events with orientation as to time and place) and indirect (a change in

task performance without direct recall of the priming stimulus). There is evidence, for instance, that profoundly amnesic Korsakoff patients will prefer abstract art to which they have previously been exposed, even without remembering the initial exposure.

Research on the assessment of indirect memory during anaesthesia has concentrated on word performance tasks; for instance, the presentation of familiar words during anaesthesia and then a postoperative task involving the completion of word stems. Completing the stem with a word presented during anaesthesia more frequently than might be expected by chance is evidence that auditory perception occurred during anaesthesia and that memory of that stimulus has been encoded.

The literature on whether indirect memory exists during anaesthesia is confusing and contradictory. There are studies with poor experimental design and failure to replicate positive findings in well-controlled studies. There is some suggestion that emotionally relevant material (i.e. you will feel well after surgery) is processed more effectively than emotionally neutral material. Generally, the studies in the literature have not controlled for depth of anaesthesia.

In summary, the literature suggests that indirect memory is a fragile phenomenon that can occur during anaesthesia and that its occurrence is related to inadequate depth of anaesthesia.

Implicit memory during surgical anaesthesia

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The term 'implicit memory' was primarily used by Schacter[1] to describe the type of memory that is not accessible to the conscious mind but may be evident in its subsequent influence on behaviour. In contrast to explicit memory, which requires specific attention at the time of learning, implicit learning is essentially an automatic process, which does not need any attention on the part of the subject. The implicit and explicit memory distinction is supported by many studies of amnesic and healthy persons. Those with anterograde amnesia, who fail completely in standard tests of explicit memory, such as recall and recognition, can have unimpaired implicit memory. A similar dissociation between explicit and implicit memory functions can be caused by general anaesthesia. Most research methods used to test implicit memory in anaesthetized patients come from experimental research on patients with amnesic syndromes.

Many of the implicit memory tests methods are based on the phenomenon of 'priming', which means that previous presentation of words facilitates the performance in the following memory test. For example, in the word stem completion (WSC) tasks, patients are presented with words during general anaesthesia. Later, they are asked to complete stems of words (e.g. BAN-) with the first word that comes to mind (e.g. BANANA). Some of these stems are the first letters of previously presented (study) words, and others are not. If the critical stems are more often completed using study words than would be expected by chance alone, this indicates implicit memory of those words.

Studies of implicit memory function during anaesthesia have yielded mixed results. Investigators are trying to establish the precise influence of experimental variables, such as depth of anaesthesia, anaesthetic regimen, type of memory test, acoustic stimuli, and time of postoperative testing, that determine the outcome of studies. Current literature suggests that implicit memory function may remain intact during light anaesthesia levels and is impaired when anaesthesia is deepened. Also, the surgical stimulus may play a role, because more implicit memory formation has been reported during surgery than in volunteer studies without surgical stimulus.

If patients are able to process acoustic information during the surgery, they may also have subconscious experiences of other intraoperative events. It is at least possible that these experiences might influence the patients' well-being and postoperative course also outside of an experimental context. Better understanding of implicit memory might allow us to optimize the anaesthesia techniques used for surgical patients.

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Intraoperative paralysis and existentialist fear of death: is there a link?

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Background: Traumatized anaesthetic awareness patients commonly describe intraoperative distress and postoperative flashbacks and nightmares around themes of existential death and burial.[1] We set out to analyse systematically awareness reports from the recent NAP5[2] project in terms of intraoperative experience and subsequent psychological sequelae.

Methods: The UK audit project NAP5[2] collected reports of accidental awareness under general anaesthesia from the whole of the UK and Ireland throughout a 1 yr period from all hospital anaesthesia departments. These reports were carefully analysed by an expert panel of anaesthetists, psychologists, and a patient representative.

Results: NAP5 received 141 reports that were judged as valid by the expert panel. Of these, 93% were from patients in receipt of a neuromuscular blocking agent, which is in contrast to a baseline anaesthesia activity survey[3] that identified neuromuscular block in only 46% of general anaesthetics in the UK and Ireland. Moreover, at least half of these patients experienced intraoperative distress, and for the majority of these (67%), distress was caused by neuromuscular block and dyspnoea (and not so much by pain). Some patients feared they were about to die, and two

patients thought they were already dead as a direct result of the unanticipated experience of intraoperative paralysis. Most (79%) of those with intraoperative distress developed postoperative psychological sequelae, such as post-traumatic stress disorder.

Conclusions: Fear of death is the most pervasive specific anxiety in children aged 7–10 yr.[4] Preschool children commonly report believing that dead relatives and pets 'now live underground', perhaps in cemeteries. Nightmare content and themes reported by traumatized awareness patients with explicit recall often involve being buried alive. This raises the possibility that experience of intraoperative paralysis reawakens primitive childhood fears of death involving some form of disembodied consciousness.

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Dynamic brain states and consciousness

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The quest to elucidate the unitary neural correlates of loss and return of consciousness during anaesthesia continues. Previous investigations aimed at finding the critical brain centres, pathways, regions, and networks whose modification by anaesthetic agents may be responsible for modulation of the state of consciousness. Recently, attention has turned to the temporal aspects of neuronal activity as modified by anaesthetic agents during, or when approaching, the loss of consciousness.[1 2] During wakefulness, spontaneous activity of cortical neurones is nearly continuous, whereas under anaesthesia the activity becomes intermittent, typically characterized by an alternation between UP and DOWN.[3] It is hypothesized that fragmentation of neuronal activity is incompatible with the ongoing stream of consciousness. However, it remains to be determined whether the transition in the dynamics of neuronal firing is correlated with the transition in the state of consciousness.

I investigated the dynamics of brain activity at different spatial and temporal scales using electrophysiological and functional magnetic resonance imaging (fMRI) techniques in rats anaesthetized at levels near the loss and return of consciousness. In electrophysiological experiments,[4] the dynamics of spontaneous ongoing activity of a mesoscopic cortical neuronal population was studied during graded emergence from desflurane anaesthesia at 8, 6, 4, 2, and 0% inhaled concentration. Unit activity and local field potentials were recorded simultaneously at 64 sites from the primary visual cortex using chronically implanted multielectrode arrays. During unconsciousness, unit activity was intermittent, broken up by silent gaps between firing periods that exceeded 200 ms. During the graded withdrawal of the anaesthetic, unit activity was defragmented and transformed to a continuous pattern. The information entropy of local field potentials increased abruptly upon regaining consciousness.

Using fMRI, I studied the effect of propofol on the dynamics of large-scale brain networks.[5] Task-free 'resting' state functional connectivity patterns of the brain change dynamically on the time scale of seconds. None of the patterns ever repeats in exactly the same form because each of them is affected by the brain's history, leading to an inexhaustible repertoire of states the brain accesses over time. According to the information integration theory,[6] the latter property is critical to conscious experience. To sample the repertoire of dynamic brain states, I acquired fMRI in rats from 30 min resting-state whole-brain scans during conscious sedation and unconsciousness (propofol 20 and 40 mg kg^{-1} h^{-1} i.v.). Intrinsic brain states were identified by regional homogeneity analysis using 200 s sliding windows and by the point process method of coincident blood oxygenation level-dependent (BOLD) threshold crossings. Both analyses revealed substantially different temporal dynamics as a function of anaesthetic depth. The temporal variance of correlated BOLD activity was reduced by nearly 80% in unconsciousness relative to sedation, suggesting a dramatic reduction in the dynamic repertoire of brain states associated with loss of consciousness.

In summary, the results show that anaesthetics interfere with dynamic brain activity in two different ways. During anaesthesia, ongoing neuronal activity is temporally fragmented, presumably preventing the temporal contiguity of experiential events. Comparing the stream of consciousness to a movie, dropping frames (brain states) or slowing down the 'projection speed' below the visual fusion frequency prevents the perception of continuous change. This may be equivalent to losing the ability to bind the immediate past with the present, preventing coherence of perception. In addition, anaesthesia degrades the neural information encoded in the dynamic patterns of cortical local field potentials and reduces the repertoire of global brain states that is critical for conscious experience.

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Connectivity changes in functional magnetic resonance imaging and electroencephalogram during sevoflurane anaesthesia

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Background: In a recent combined electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) study, a decreased cortical and thalamocortical functional connectivity (FC) during propofol-induced loss of consciousness was reported.[1 2] In particular, graph-theoretical fMRI analyses indicated affected long-range connections,[1] and correspondingly, EEG-directed connectivity (EC) based on symbolic transfer entropy (STEn) showed a breakdown of frontoposterior feedback interaction.[2] In a follow-up EEG and fMRI study, effects of sevoflurane anaesthesia on fMRI FC and EEG EC were investigated.

Methods: Twenty-two healthy male volunteers were enrolled in the study. Blood oxygenation level-dependent 3T-fMRI and 63-channel EEG were simultaneously recorded in relaxed wakefulness (AW) and different concentrations of sevoflurane-induced unconsciousness from light to deep anaesthesia. In the present evaluation, systemic effects of sevoflurane on fMRI FC and EEG EC were analysed between AW and sevoflurane 3 vol% concentration. Independent components (ICs) of fMRI resting state networks were identified using independent component analysis based on a standard processing pipeline in GIFT/SPM8. Symbolic transfer entropy quantifies the directed interaction between two signals[3] and was computed over all EEG channel pair combinations (0.5–30 Hz total bandwidth, transfer delay 35–75 ms, embedding dimension m=5, time lag l=5) to reflect cortical EC. Effects of sevoflurane on FC and EC were analysed at corrected threshold $P<0.05$ (FC, two-sample t-test; EC, non-parametric test, bootstrap).

Results: Functional connectivity between AW and sevoflurane 3 vol% decreased within the frontoparietal default and attention networks ($P<0.05$). The EEG STEn showed a decreased feedback EC between frontal and posterior (parietal, temporal, and occipital) brain regions ($P<0.05$) as shown in Fig. 6. Values of STEn around zero indicate balanced interaction (white), STEn>0 feedback EC (red), and STEn<0 feedforward EC (blue).

Conclusions: The fMRI and EEG connectivity analyses reveal affected long-range pathways according to higher cortical networks during sevoflurane anaesthesia. Different anaesthetics (propofol and sevoflurane) show similar effects on connectivity, suggesting that coherence of corticocortical network structures might be a key feature for conscious perception beyond haemodynamic properties of specific anaesthetics.[4 5] Further analyses of the study data are needed to assess whether deepening of anaesthesia causes a gradual decoupling of specific brain areas.

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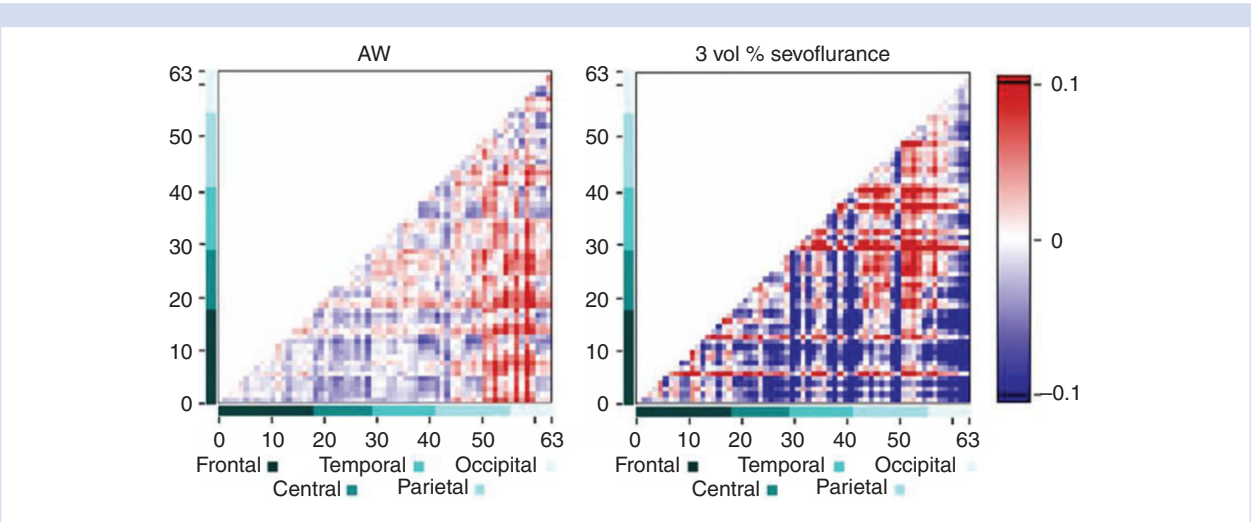

Fig 6 Symbolic transfer entropy (STEn) at wakefulness (AW) and sevoflurane 3vol% concentration. The maps show average values of STEn for each electrode combination in all 22 subjects: STEn>0 (color coded in red) indicates that electroencephalogram from the electrodes on the vertical axis drives electroencephalogram from electrodes on the horizontal axis (feedback); STEn<0 (blue) indicates that electroencephalogram from the electrodes on the vertical axis is driven by the electroencephalogram from electrodes on the horizontal axis (feedforward); STEn=0 indicate a balanced interaction (white).

Brain network theories of chronic pain: bottom-up meets top-down

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Electrophysiological, functional, and anatomical data support a growing consensus that chronic pain is supported by a distinct pattern of neural activity across a broad network of brain regions and not the overactivity of a single or restricted number of brain regions. This naturally leads to two different approaches to try to understand how such network-level activity gives rise to the sustained conscious perception of pain: bottom-up approaches and top-down approaches.

A bottom-up approach seeks to build a network-level account of chronic pain by piecing together component parts built of small functional circuits, each of which is thought to support a specific function that is in some way involved in pain. Such a constructionist approach might consider, for example, the physiological role of pain in achieving a behavioural system of defence against harm. In this example, such behaviour is known to be supported by a combination of learning and action systems, typically evaluated in the controlled experimental paradigms of Pavlovian and instrumental learning (mediating escape and avoidance behaviour). Computational neuroimaging studies have shown that these functions are supported by a small network of regions, including striatal subregions and orbitofrontal, insular, and medial prefrontal circuits. In contrast, perceptual pain functions that support functions such as discrimination of pain are mediated by thalamic, insular, and sensory regions. It can be seen that putting these different functions together allows quite mature circuit-level theories of pain, which can then, in principle, support dynamic simulation and modelling approaches to make predictions about what might go wrong in chronic pain. The advantage of this approach is that it supports quantitatively precise mechanistic theories of chronic pain that can be directly mapped to neurobiological substrates. The disadvantage is that it can be very difficult to predict exactly how these subcircuits should be expected to be different to produce emergent properties that should underlie the state of chronic pain.

A top-down approach is based on trying to decipher exactly what aspects of brain networks are different in chronic pain using techniques such as functional and anatomical connectomics. Then, adopting a reductionist approach, one tries to identify the most important characteristics and understand their biology; this might be some sort of global network characteristic, a problem in key network 'hub' regions, of a specific identifiable subcircuit (module). The advantage of this is that it is driven by the data and is not dependent on generating specific hypotheses. The disadvantage is that it can be very difficult to distinguish cause from effect; if one identifies a key network difference, how do we know whether it causes the chronic pain state or simply represents a downstream physiologically adaptive change as a consequence of the changed sensory and affective landscape caused by chronic pain?

We argue that both approaches should ideally proceed in parallel. Top-down approaches should try to map specific changes to an understanding of basic pain-based neurophysiology; this can then lead to new, computationally precise predictions to be made about potentially subtle behavioural differences in chronic pain. Bottom-up approaches should make use of opportunities to identify how sensitivity to parameters (e.g. impaired avoidance learning and excessive fear responding) might manifest at the level of brain network analysis. Ultimately, it is the fusion of these two approaches that will show the most promise for understanding the puzzle of chronic pain.

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Mysteries of memory: anaesthestic amnesia amnesia

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Memory is a behavioural end point with multiple variations depending on the testing paradigm.[1] As opposed to consciousness and unconsciousness, anaesthetic effects on memory are more difficult to quantify. However, brain processes supporting memory and consciousness share many similarities, and the mechanisms of anaesthetic effects on one may be relevant to the other. It is likely that there are multiple memory systems, which interact with each other to affect behaviour.[2] Memory can 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.[3] Explicit memories consist of general knowledge about the world (semantic memories) and episodic memory (i.e. personal memories that occurred in a particular place and time).[4] A brief review of different forms of conscious memory, namely familiarity and recollection, will be done, and the importance of oscillatory rhythms and network activity in memory function will be highlighted.[5–8] The importance of hippocampal–neocortical interactions in support of memory function will be discussed.[9] Anaesthetic drugs disrupt episodic memory function by two major mechanisms, sedation and a specific amnesic effect. A review of the possible neurobiological targets that may explain sedation and 'amnesic' amnesia for anaesthetic drugs on episodic memory will be presented.[10–19]

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The significance of a positive isolated forearm technique response: consciousness or 'dysanaesthesia'?

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Introduction: Since Tunstall[1] first described the isolated forearm technique (IFT; subsequently modified by Russell[2] for more general use), it has been apparent that positive isolated forearm responding does not correlate with 'clinical signs' or postoperative recall. This has led some to question the validity of the IFT. However, for those with clinical experience of the IFT, it is the gold standard for determining intraoperative consciousness,[3] and indeed, it is clear that levels of intraoperative consciousness are not necessarily correlated with postoperative recall because of the amnesic effect of many anaesthetic drugs.[4] However, recent reviews have questioned whether positive isolated forearm responding indicates true consciousness or some third state in which the patient is not fully aware of their circumstances; this has been variously described as a lack of 'connectedness'[5] or a state of 'dysanaesthesia'.[6]

Symposium/debate: We propose that this symposium begins with a video demonstration of positive isolated forearm responses in a patient undergoing a Wertheim's hysterectomy. The audience will at this point be asked to vote as to their opinion whether this constitutes consciousness or some other state. Subsequently Pandit, Wang, and Russell will present formal arguments for and against the propositions that this represents full consciousness or 'dysanaesthesia'. There will then be a second audience vote to see whether there has been any shift in opinion as a result of the debate.

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Intraoperative awareness and post-traumatic stress disorder

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Post-traumatic stress disorder (PTSD) is a debilitating mental illness after exposure to one or more overwhelming events (psychological trauma) with the development of the following characteristic symptoms: intrusion; persistent avoidance; negative alteration in cognition and mood; and marked alteration in arousal and reactivity. The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition,[1] explicitly includes intraoperative awareness with recall as one of the traumatic events that can be followed by PTSD. According to a large-scale multisite prospective study in the USA, the incidence of confirmed intraoperative awareness was 0.09–0.21%; one or two among 1000 surgeries.[2] The most striking fact was that PTSD was not uncommon in the long-term consequences after intraoperative awareness even though their acute traumatic responses seemed to ameliorate within 3 weeks after surgery.[3 4] Another recent study using a well-validated structured clinical diagnostic interview also found that PTSD was common and persistent in the confirmed-awareness patients.[5] These facts justify strategies to provide psychological intervention for intraoperative awareness with recall.

Recent treatment guidelines of PTSD strongly recommend trauma-focused psychotherapies as the first-line treatment; these include trauma-focused cognitive behavioural treatment, such as prolonged exposure therapy or eye movement desensitization and reprocessing. These psychotherapies facilitate habituation and processing of traumatic memories and cognitive coping. Recommendations in practice are as follows. Patients

sometimes avoid talking about their awareness after anaesthesia. Therefore, clinical routines for identifying patients with intraoperative awareness should be implemented to provide postoperative counselling and psychological support. Later on, follow-up psychiatric assessments are needed to refer patients who need trauma-focused psychotherapies for PTSD. In this presentation, how to conduct psychological first aid for identified patients within weeks after surgery will be mentioned.

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The difference of nucleus accumbens activation between chronic low back pain with or without psychiatric problems

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Background: Regional grey matter atrophy, cognitive changes, and unique patterns of brain activity have been demonstrated in patients with chronic low back pain (cLBP). In addition, dysfunction of the nucleus accumbens (NAc) is found in the patients with cLBP. Furthermore, psychological factors are associated with chronicity of pain. However, a comparison of brain activation in cLBP with or without psychiatric problems has not yet been completed. The aim of this study was to investigate how NAc activation of cLBP patients with psychiatric problems compared with that of cLBP patients without psychiatric problems.
Methods: The subjects were 22 cLBP patients who had suffered from persistent LBP for more than 3 months. The Brief Scale for Psychiatric Problems in Orthopaedic Patients (BS-POP), which is a questionnaire to assess psychiatric problems, was conducted. The subjects were classified into two groups by BS-POP scores, ≥17 (high score; HiS group) and <16 (non-high score; Non-HiS group). Each subject was placed in the prone position on a 3 T magnetic resonance imaging scanner and stimulated by manual pressure with the tail of an air-filled, 20 ml syringe at 5 cm left of the fourth–fifth lumbar spinal interspace. Three blocks of 30 s painful stimulus, calibrated at five on the numeric rating scale (NRS), were applied with intervening 30 s rest periods during whole-brain echo-planar imaging. The numeric rating scale of unpleasantness was evaluated after each session. Functional imaging was analysed using a multisubject general linear model with Bonferroni multiple comparisons at $P<0.05$.
Results: Activation was observed at the NAc, the prefrontal, insular, and supplementary motor cortex. The subjects in the HiS group showed a smaller activation cluster in the NAc than those in the Non-HiS group. There were no differences of activation clusters in other area.
Conclusions: The cLBP patients with psychiatric problems showed reduction of activation in the NAc in cluster size than those without psychiatric problems. This result suggests that cLBP in patients without psychiatric problems might not be related to NAc dysfunction.

Brain complexity quantification to assess the level of consciousness

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Background: A fundamental shortcoming of current clinical practice is the lack of a reliable method to assess the level of consciousness objectively. Theoretical considerations suggest that consciousness depends on the ability of neural elements to engage in complex activity patterns that are both distributed within a system of interacting cortical areas (integrated) and differentiated in space and time (information rich). The aim of the study was to test a novel measure of complexity, the perturbational complexity index (PCI), based on transcranial magnetic stimulation combined with electroencephalography (TMS–EEG) measurements to assess the level of consciousness in single individuals across different conditions.
Methods: We used TMS–EEG in healthy subjects during wakefulness, dreaming, non-rapid eye movement sleep, and different levels of sedation induced by different anaesthetic agents (midazolam, xenon, and propofol), and in severely brain-injured patients (vegetative/unresponsive, minimally conscious, and locked-in syndrome). In total, 208 sessions were performed in 52 subjects. The PCI was used to calculate the amount of information contained in the integrated response of the corticothalamic system to a direct perturbation using algorithmic complexity measures, such as the Lempel–Ziv complexity index.
Results: The PCI allowed discrimination between conscious and unconscious states in single individuals across the different physiological, pharmacological, and pathological conditions. The PCI was sensitive to graded changes in the level of consciousness and was stable across stimulation parameters such as intensity or site. For patients with severe brain injury, stimulation of brain-damaged areas induced no response (in comparison to stimulation of the preserved brain region).
Conclusions: This theoretically motivated quantification of brain complexity allows establishment of an objective, graded measurement scale along the consciousness–unconsciousness spectrum and provides a principled

approach for estimating objectively the level of consciousness at the bedside. The use of a neuronavigation system is strongly advised to assess the level of consciousness in patients recovering from coma.

Subconscious processing and chronification of pain

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Pain is a multidimensional, subjective experience that is perceived only when one is aware of oneself. Even during unconsciousness under propofol anaesthesia, however, noxious sensory information does reach the brain and activate pain-related cerebral substrates collectively called the 'pain matrix'. Those subconscious pain-related brain areas include the secondary somatosensory and insular cortices and the cerebellum,[1] which usually convey sensory-discriminative, affective-motivational, and motor components of pain perception, respectively; that is, pain does reach the brain but is not consciously perceived as sensation.

However, surgery usually forces the body to receive continuous, intense nociception under general anaesthesia, which might not necessarily be blocked by local or regional anaesthesia or by systemic opioid drugs. An anaesthetized, immobile patient cannot get away from such an extraordinary surge of nociception that does reach the brain 'subconsciously'. It should be no wonder if subconscious pain cause some plastic changes in the brain that result in persistent postoperative pain, cognitive dysfunction, or distress.

Here, I will discuss this possibility of 'memorized pain' during anaesthesia in analogies with the mechanisms of pain chronification that have recently been revealed by many functional neuroimaging studies.

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Integrated information theory of consciousness: theory and practice

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Assessing the level of consciousness based on the activity of the brain is an important issue, yet it is one of the most challenging problems in neuroscience. Brain-based measures of the level of consciousness are most required for assessing the conscious state of those who cannot speak or move (e.g. under anaesthesia or in the vegetative state), where behavioural unresponsiveness tends to be confused with unconsciousness.[1 2] The integrated information theory (IIT) of consciousness has potential importance for this purpose.[3–5] The IIT is an attempt to characterize consciousness mathematically both in quality and in quantity by analysing informational relationships between elements in a system. Regarding the quantitative aspect of consciousness, the IIT predicts that the amount of integrated information, which measures how much information is integrated in a system, corresponds to the level of consciousness. According to the IIT, the brain significantly loses the ability to integrate information when consciousness is lost. If the prediction of the IIT is correct, the level of consciousness could be measured by quantifying the amount of integrated information in brain activities. There is some supportive evidence for this prediction of the IIT.[6 7] However, there has not been yet direct evidence because it is computationally intractable to compute exactly the integrated information in real neural data.

In this talk, I briefly review the essence of the IIT and propose a practical method to quantify integrated information in real neural data. As a proof of concept, I apply the proposed method to the electrocorticogram data recorded in monkeys before and after anaesthesia. I discuss the implications of this study and future prospects for consciousness studies.

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Recovery from anaesthesia: bootstrapping into consciousness

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It is not clear how, after a large perturbation, the brain explores the vast space of potential neuronal activity states to recover those compatible with consciousness. I analyse recovery from deep anaesthesia to show that neuronal activity en route to consciousness is confined to a low-dimensional subspace. In this subspace, neuronal activity forms discrete metastable states persistent on the scale of minutes. The network of transitions that links these metastable states is structured such that some states form hubs that connect groups of otherwise disconnected states.

Although many paths through the network are possible, ultimately to enter the activity state compatible with consciousness, the brain must first pass through these hubs in an orderly fashion. This organization of metastable states, along with dramatic dimensionality reduction, significantly simplifies the task of sampling the parameter space to recover the state consistent with wakefulness on a physiologically relevant time scale.

Functional magnetic resonance imaging of memory and consciousness

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This talk will cover the functional magnetic resonance imaging (fMRI) of loss of consciousness (LOC) and memory as induced by low-dose sevoflurane and propofol in healthy ASA I volunteers. Functional MRI is a technology that has been constantly evolving over the years. In the 1990s, specific activation-induced response was being studied. In the last 10 yr, functional connectivity, which measures temporal correlation in low-frequency blood oxygenation level-dependent (BOLD) contrast; a qualitative measure of neuronal activity) signals between functionally related regions of the brain, has become the more commonly accepted fMRI technique.

With sevoflurane 0.25 MAC, a reduction in activation-induced response in higher-order association cortices, such as the hippocampus, thalamus, and visual cortices, was observed. With sevoflurane 0.5 MAC, there is LOC and memory, with a decrease in memory activation-induced BOLD response in the auditory cortex, amygdala, and thalamus, no change in the hippocampus, and increase in activation in the prefrontal cortex. With sevoflurane-induced LOC and memory, seed-based connectivity was altered only in the higher-order regions, such as the insula, hippocampus, and thalamus (as against the primary cortical regions).

A more recent technique in connectivity measurement is independent component analysis, which has no *a priori* assumption, with a focus on the 10 standard resting state networks (which cover more than 80% of the cortex and have been quoted in many studies).

With the independent component analysis technique, propofol-induced loss of consciousness decreased the neuronality of the higher mental function networks, such as the default mode network, the executive control network (bilateral), and the salience network. These three networks are linked to LOC and memory and are of great importance to anaesthetists. However, sevoflurane-induced LOC decreased the neuronality only in the executive control network and salience. This suggests that with LOC the executive control network and salience neuronality decrease first, followed by the default mode network.

Conclusions: The effects of fMRI on LOC and memory have been measured, with regional cerebral blood flow changes, activation-induced change in BOLD and alteration in functional connectivity. In all these measures, higher-order regions and networks are more sensitive to anaesthesia compared with lower-order regions.

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