Anaesthesia awareness: 3 years of progress

A. G. Hudetz1 and H. C. Hemmings Jr2,3*

1 Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI 53226, USA
2 Department of Anesthesiology and 3 Department of Pharmacology, Weill Cornell Medical College, New York, NY 10065, USA
* E-mail: hchemmi@med.cornell.edu

In June 2011, nearly 100 physicians and scientists gathered for a scientific meeting in Milwaukee, WI, USA to discuss the problem generally known as anaesthesia awareness. Anaesthesia awareness refers to the unintended intraoperative experience of awareness, which is often benign but occasionally is seriously distressful, accompanied by subsequent recall and psychological consequences. Continuing the tradition of the triennially organized symposia since 1989, the 8th International Symposium on Memory and Awareness in Anesthesia (MAA8) focused on understanding of the prevalence, causes, consequences, mechanisms, detection, prevention, and amelioration of anaesthesia awareness. The Abstracts from this meeting are published in this issue of the British Journal of Anaesthesia.1

Similar to past MAA conferences, the Milwaukee meeting was characterized by its interdisciplinary nature. Physiologists, neuroscientists, physicists, and biomedical engineers joined anaesthetists and psychologists to explore the mechanisms of awareness, memory, cognitive changes after anaesthesia, and to explore novel techniques for measuring the depth of anaesthesia from brain activity. The 2.5 day symposium featured 30 lectures and 22 poster presentations. Keynote presentations were mainly reviews of current state of knowledge in specific fields or extensive overviews of ongoing investigations. Most of the poster presentations complemented or augmented main topics of discussion. Anaesthesia awareness is currently defined as consciousness under general anaesthesia with subsequent recall of the experienced events (American Society of Anesthesiologists Task Force 2006).2 This definition conflates intraoperative awareness (i.e. consciousness) and postoperative recall (i.e. memory). One of the themes of the meeting was development of a more appropriate and mechanistic dissection of awareness and memory based on precise definitions and systematic quantitative assessment.

The first and most traditional topic discussed was clinical presentation of anaesthesia awareness, including its incidence, aetiology, prevention, and cognitive/psychological consequences. An update on the Anaesthesia Awareness Registry (Domino and colleagues, page 338P)1 revealed new insights regarding anaesthetized patients’ distress during their awareness. How intraoperative experience might be stored sometimes in distorted form with severe psychological consequences was explored (Bennett, pages 336–7P).1 Because psychological distress can be brought about by implicit memories indicating inadequate anaesthesia, the dissociation of explicit from implicit memory of intraoperative events continues to be essential (Wang, page 366P; Wang and colleagues, pages 366–7P).1 The isolated forearm technique remains the exclusive gold standard to detect consciousness during general anaesthesia (Russell, page 358P).1 It can reveal responsiveness without wakefulness as dreaming often occurs under anaesthesia (Sanders and colleagues, page 358–9P).1 Going deeper into the cognitive aspects of anaesthesia awareness, ‘unconscious synaesthesia’ was proposed, from a unique first-person professional account (Freeman, page 339P),1 as an interesting aspect of sensory processing. It is suggested that different sensory streams crossover and mix in postoperative memory, and this is not fully revealed by standard methods of testing and interview.

Obviously, the prevention of anaesthesia awareness is a primary task of the anaesthetist and, thus, requires a number of strategies before operation, intraoperatively, and after operation (Munte, pages 352–3P).1 A Cochrane review of 51 yr of data revealed that wakefulness was significantly more frequent than awareness; however, the incidence of the latter was higher with total i.v. anaesthesia than with inhalation agents (Messina, page 352P).1 The distinction between explicit and implicit memories continues to be essential to better understand just what type of information the brain can store under general anaesthesia and how potentially hidden memories might alter subsequent behaviour without explicit recollection (Veselis, page 365P).1 The role of hippocampal–cortical interactions in the anaesthetic modulation of distinct types of memory is also currently being examined (Perouansky, page 354P).1

Each previous MAA meeting had its own flavour and points of emphasis, and the MAA8 was no exception. Of the many presentations directed at scientific questions, an area that was extensively discussed was the neurobiological mechanisms of loss of and return of consciousness. Arguably,
the mechanisms of consciousness and of general anaesthesia represent two intertwined mysteries (Hameroff and colleagues, pages 341–2P). Likewise, the mechanistic basis for anaesthesia awareness cannot be fully understood without an understanding of the neurobiological bases of consciousness and memory. The same can be stated with respect to anaesthesia depth monitoring (see below). Several lectures at MAA8 were devoted to the consciousness and its suppression. Over the past decades, significant progress has been made towards a better understanding of the influence of anaesthetic agents on specific proteins, particularly ligand-gated ion channels. The emerging direction of research is now to understand the consequences of these molecular actions at cellular, network, cognitive, and behavioural levels (Hemmings, page 342P). To date, theories that attempt to bridge the key events in anaesthetic action from molecular to cognitive psychological levels are rare, and the postulated mechanisms might be rooted in the quantum physical properties of neuronal microtubules (Hameroff and colleagues, page pages 341–2P).

In a more ‘top-down’ approach, neuroimaging has contributed significantly to a data-driven exploration of how anaesthetics affect regional brain metabolism, blood flow, and functional connectivity. This has spawned several new ideas on how anaesthetics lead to unconsciousness at a systems level (Alkire, page 334P). Insights into the mechanisms of unconsciousness can also be gained by comparing similarities and differences with other unconscious states such as coma, persistent vegetative state, and dreamless sleep. A novel and exciting work in functional brain imaging of patients with disorders of consciousness has progressed rapidly during the last few years, and has revealed functional connectivity in the brain as a putative correlate of consciousness (Boly, pages 337–8P). Intracranial EEG recordings in select brain regions in neurological patients provide complementary information to imaging at high temporal and spatial resolution (Plourde, pages 355–6P).

Although anaesthesia and deep sleep might look similar superficially, the electrophysiological and biochemical traits of these states turn out to be substantially different (Lazar and colleagues, page 348P; Baghdoyan and colleagues, pages 335–6P). In addition, anaesthetic agents differ in their manner they modulate sleep homeostasis and in the degree they can substitute for sleep (Mashour, page 351P). In most aspects, anaesthesia is more akin to coma than to sleep, although the possibility of dreaming in anaesthesia could challenge this analogy. Identifying the neural correlates of anaesthetic unconsciousness is complicated by the distinct neuronal changes that mediate loss of consciousness compared with regaining consciousness, leading to a hysteresis in anaesthetic dose–response relationship that cannot be accounted for by pharmacokinetics alone (Kelz, pages 345–6P).

A novel topic at MAA8 was postoperative cognitive decline. It was hypothesized that even in the absence of an explicit and implicit memory, episodes of intraoperative awareness can result in subsequent cognitive impairment, particularly in memory and executive functions. Postoperative cognitive dysfunction has been recognized as a potential consequence of surgery under general anaesthesia. This has been generally related to neuronal injury, especially in high-risk populations (age, reduced cognitive reserve), and high-risk procedures (cardiac surgery with cardiopulmonary bypass). Highly stressful events might also contribute to postoperative cognitive decline. In this context, the neuroinflammatory response to surgery and postoperative sleep deprivation might be significant factors in postoperative delirium and cognitive decline, with tumour necrosis factor-α as an early indicator of neuroinflammation, and therefore a potential therapeutic target (Maze, pages 351–2P; Terrando and colleagues, pages 363–4P).

As in the past, numerous presentations were directed to quantitative EEG analysis as applied to the monitoring of depth of anaesthesia and to preventing anaesthesia awareness. The BIS remains the leading monitor in popularity, although recent cousins such as the Sedline® and Entropy provide nearly equivalent information and reliability. All commercially available monitors could benefit from improvements in handling patient-dependent variability in the EEG, anaesthetic agent-specific differences in EEG effects, and improved artifact rejection (Rampil, pages 356–7P).

Further desired improvements include better discrimination between aware and unaware states, adjusting to individual differences in anaesthetic sensitivity, increasing response time, and accuracy with agent combinations (Avidan and Whitlock, pages 334–5P). Some of these improvements might require extension of current EEG montages to multisite measurements and estimation of coherence and functional connectivity (as already attempted in the early models of the Patient State Analyzer, a forerunner of the Sedline® monitor), or statistical approaches that evaluate the temporal and spatial regularity or irregularity of EEG signals in the time domain (Schneider, pages 360–1P). Obviously, there is a need for novel approaches to monitor depth of anaesthesia based on fundamental neurophysiological principles of brain activity. Mathematical modelling of cortical neural population activity has been applied to better understand anaesthetic modulation of the hypnotic state and peripheral input relevant to analgesia (Liley, pages 348–9P). Thalamocortical oscillations, especially α-frequency sleep spindles, have received particular attention as they might play a role in gating corticofugal sensory input under anaesthesia (Sleigh and Schieb, page 362P), a mechanism with specific EEG features that might be exploited in anaesthesia depth monitoring (Scheib, pages 359–60P).

Such suppression of thalamic function might be mediated by a local increase in the inhibitory neurotransmitter γ-aminobutyric acid (GABA) (Romani and colleagues, page 356P). The task of finding a unitary EEG correlate of hypnosis is nevertheless complicated by the emerging realization that a large variety of EEG patterns can be present at almost any depth of anaesthesia and in other comparable states of disturbed consciousness, including sleep, epilepsy, and cerebral ischaemia (Jäntti, pages 342–3P). Sensory-evoked responses that...
measure reactivity of complex neuronal circuits hold promise for detecting the residual capacity of the brain for potentially conscious information processing (Ozgoren and colleagues, page 353P).\textsuperscript{1} A novel attempt to separate the affective and conscious components of pain by electromagnetic tomography performed in volunteers highlighted involvement of the cingulate gyrus and frontal cortex using ketamine and sevoflurane as prototypic affective modulatory or hypnotic agents, respectively (Untergehrer and colleagues, pages 364–5P).\textsuperscript{1}

Several presentations considered the emerging theme of cortical integration as a correlate of the conscious state, and its loss in anaesthesia. Network analysis has taken centre stage in this research (Shin and colleagues, pages 361–2P).\textsuperscript{1} Using functional magnetic resonance imaging and EEG methods, a selective decrease in higher-order thalamocortical systems (Liu, Ward and colleagues, pages 349–50P)\textsuperscript{1} and in frontoparietal cortical connectivity (Jordan and colleagues, pages 344–5P)\textsuperscript{1} in propofol-induced unconsciousness was reported. The long-latency auditory-evoked response, an index of higher cortical integration, was reduced in parallel with a reduction in BIS (Gokmen and colleagues, pages 340–1P).\textsuperscript{1} Cortico-cortical-evoked potential measurement in epileptic surgical patients might be a novel investigating tool for a direct assessment of anaesthetic modulation of cortical functional connectivity (Kurata, pages 346–7P).\textsuperscript{1}

At the local neuronal level, anaesthetics suppress the connectivity of excitatory and inhibitory cortical units (Vizuete and colleagues, pages 365–6P).\textsuperscript{1} At the network level, they suppress cross-modal auditory-visual modulation of cortical-evoked responses while primary reactivity is preserved (Banks and Grady, page 336P).\textsuperscript{1} A novel EEG analysis of local field potentials using bivariate permutation entropy revealed that propofol altered functional interactions in the hippocampus more than in the cortex (Kreuzer and colleagues, page 346P),\textsuperscript{1} a finding consistent with the known anaesthetic disruption of memory before that of consciousness. Memory circuits, including the amygdala involved in the mediation of aversive memories, are affected differently by different anaesthetic agents (Kahana and colleagues, page 345P).\textsuperscript{1} Taken together, investigations seem to confirm the hypothesis that anaesthetics do not suppress the modality-specific cortical responses to sensory stimuli, but instead they disrupt long-latency recurrent processing and higher-order integration during loss of consciousness.

The subcortical modulation of consciousness has also been of interest for some time. In this respect, electrical stimulation of the pontine nucleus oralis in propofol-anaesthetized animals augmented cortico-limbic functional connectivity (Liu, Pillay and colleagues, pages 350–1P),\textsuperscript{1} which perhaps is relevant to episodic memory formation during surgical stress. Another important subcortical control site appears to be the nucleus basalis of Meynert, whose pharmacological stimulation was shown to transiently reverse the anaesthetic state in desflurane-anaesthetized rats (Pillay and colleagues, pages 354–5P).\textsuperscript{1}

Additional experimental investigations explored the dependence of minimum alveolar concentration on metabolic syndrome as a rodent model of obesity (Pal and colleagues, pages 353–4P)\textsuperscript{1} and the neurophysiological mechanism of altered MAC in advanced age (El Beheiry and Carlen, pages 338–9P).\textsuperscript{1} A key molecular mechanism of amnesia by etomidate was identified in the modulation of β2 subunit containing GABA\textsubscript{A} receptors (Rodgers and colleagues, pages 357–8P).\textsuperscript{1}

In all, the MAA8 Symposium represents another milestone in the progress towards a better understanding of the true incidence, causes, and mechanisms underlying anaesthesia awareness. Experimental and clinical research directed towards an understanding of the cellular, molecular, and integrative mechanisms of the anaesthetic modulation of consciousness and memory continues to evolve, with continued progress expected until the next meeting in 2014. Likewise, novel methods for anaesthesia depth monitoring based on fundamental neurophysiological responses are evolving, and strategies to prevent anaesthesia awareness are improving such that hopefully soon we shall be unaware of awareness.

Declaration of interest
A.G.H. has no conflicting interests to declare. H.C.H. is an Editor of the British Journal of Anaesthesia.

References