Anaesthesia 2014, 69, 801–815

Editorial

Monitoring (un)consciousness: the implications of a new definition of 'anaesthesia'

What should we properly monitor, when we monitor the brain for 'anaesthesia'? Any answer is likely to depend on what we mean by 'anaesthesia'. The article by Escallier et al. in this issue of *Anaesthesia* is an important review of the status of processed EEG (pEEG) monitoring in anaesthesia [1]. Central to the role of pEEG (or any other type) of 'depth of anaesthesia' monitors is their putative ability to detect when a paralysed patient is suitably anaesthetised or not; apparently a simple binary decision-making process. Yet, this article contains a profound sentence whose implications, if widely accepted, are likely to change our entire view of 'anaesthesia', for reasons I will explain in this editorial. The apparently innocuous sentence is: "*There is a growing consensus that intra-operative awareness is a spectrum of brain states*" [my emphasis]. The following questions immediately come to mind: what is the basis for this new consensus? What does this consensus imply for mechanisms of anaesthesia? And what does it imply for monitoring of the anaesthetic state?

The emerging consensus that intra-operative awareness is a spectrum of brain states

Traditionally, anaesthesia has been regarded as an all-or-nothing, binary phenomenon. This view was most clearly proposed by Prys-Roberts when he wrote: "*There cannot be degrees of anaesthesia nor for that matter can there be variable depths of anaesthesia*" [2], a statement that was unsupported by other references but a sentiment that became nevertheless widely repeated in standard texts [3]. Superficially, this makes sense: either you are anaesthetised or you are not. Once you are anaesthetised, it is difficult to conceive then how you can be 'more' anaesthetised. It is not (to borrow Sleigh's phrase [4]) as if 'the patient is a submarine'!

Yet, things are never really so simple and this traditional view is now challenged in several ways. Assuming that anaesthetic drugs act at protein channel receptor targets, we know that dose-response pharmacology is not binary or all-or-nothing. Rather, the drug-dose-response relationship is characteristically continuous, described by relatively simple models in which the drug effect is non-linearly proportional to drug concentration, up to some maximum receptor effect. At some concentration of drug lower than this maximum, the active drug-receptor combination reaches a threshold that triggers the intended response (in this case, 'anaesthesia'). If there were no variability in individual organism sensitivity or receptor state, then all animals of a species would become anaesthetised at exactly the same anaesthetic concentration. We know that this is not true: at a given clinically relevant concentration, there will always be some proportion of animals not anaesthetised (this proportion dependent upon the steepness of the population 'dose-response' relationship for the drug) [5]. In this way, Dilger has elegantly summarised how continuous dose-response relationships at molecular level can translate into near (but not quite) binary relationships at population level [6] (Fig. 1).

Figure 1 also raises another question. Even if anaesthesia is

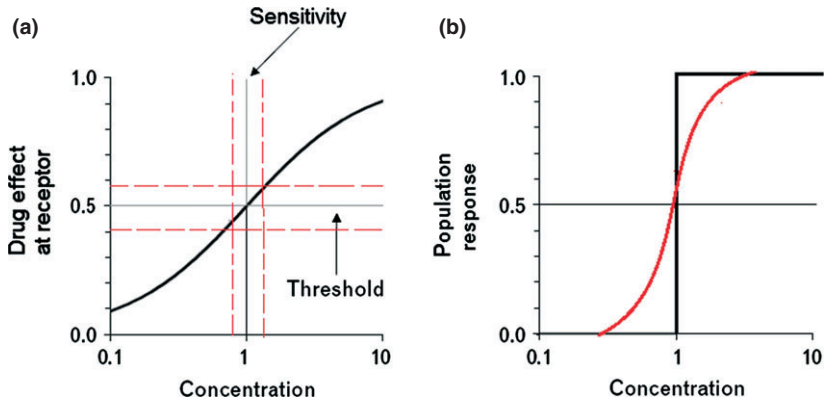

Figure 1 (a) Putative dose-response relationship (black curve) for a hypothetical anaesthetic at a candidate channel receptor. Anaesthesia is attained when the drug-receptor combination reaches the threshold concentration (50% receptor activation; horizontal grey line). If all animals are alike and reach this receptor threshold at the same drug concentration (~1 arbitrary unit, indicated by the vertical grey line), then they will all become anaesthetised at exactly the same concentration, as indicated by the black line in (b). However, within the population there is variability in the thresholds to be attained (horizontal red dashed lines in (a)), and in the sensitivity of the receptor(s) to the drug (vertical dashed lines in (a)). This results in a less steep population response relationship (for example, red curve in (b)). The relationships shown are intended to be illustrative and not quantitative; re-drawn from Dilger [5].

attained at the threshold concentration (in this example of Fig. 1, ~1 arbitrary dose unit), but further drug is administered to the organism, the panel on the left indicates that there is continued drug-receptor binding and a greater effect at the receptor. In other words, from the perspective of the receptor, maximal effect has yet not been reached and the drug must presumably be achieving something. What is an anaesthetic drug doing to the brain, if given in a concentration greater than that required to achieve anaesthesia? Let us return to this question later.

A binary view of anaesthesia implies that, just as 'being anaesthetised' is regarded as a singular brain state, then being 'not anaesthetised' is also a singular (opposite) state. Accidental awareness during anaesthesia is one situation in which anaesthesia is intended, but fails, and the patient is 'not anaesthetised'. The full results are awaited of the 5th National Audit Project (NAP5) of the Association of Anaesthetists of Great Britain & Ireland and of the Royal College of Anaesthetists [7]: this will present detailed reports of what patients experienced and the manner in which they were 'not anaesthetised'. However, the results of the NAP5 Baseline Survey [8, 9] already clearly indicate that, instead of being a singular state, there is in fact a spectrum of experiences when 'not anaesthetised', with the majority being apparently neutral and only a third involving pain or distress.

I have argued elsewhere that the brain state of a patient undergoing the isolated forearm technique, who responds both spontaneously to the surgery and to the verbal command to move their forearm (i.e. likely to be fully awake) cannot be the same as that of a patient who responds only to the command (who, I have proposed, is in a state of 'dysanaesthesia' [10–14]). These two patients are 'not anaesthetised' in very different ways, and the latter appears an acceptable state for surgery to continue. Shafer and Stanski have argued that anaesthetic depth can be regarded as the *probability* of separately attaining several different endpoints relevant to anaesthesia [15]. Sleigh has alluded to the analogy of anaesthesia's being the process of switching off a set of switches that are related to different functions such as 'pain', 'memory', 'autonomic response', etc [4]. This idea is not necessarily new, since Hopkin in the 1960s used a similar analogy of anaesthesia's being the switching off of different lights: the challenge he proposed was to work out 'which stayed flashing and which were off' during clinical anaesthesia [16]. Thus all these authors challenge the view that anaesthesia is binary, and there is indeed an emerging consensus that anaesthesia as a spectrum of brain states.

The implications of anaesthesia's being a spectrum of brain states

A single brain state is characterised by its own, singular pattern of neuronal activity (the 'neural signature'), which can be identified by

electrophysiology or brain imaging technologies [17, 18]. However, if as discussed above, several different brain states are compatible with 'anaesthesia' (including some that involve degrees of awareness), then it follows that all anaesthetic drugs do not necessarily produce the same pattern of neuronal activity, but potentially induce their own, distinct patterns. In other words, the drugs used to achieve the distinct brain states compatible with anaesthesia must be acting by different fundamental mechanisms.

Table 1 shows the crude spectrum of channel activities for a range of agents. Although it is generally the case that the GABA-A receptor is activated by all agents and generally the case that the nACh receptor is inhibited, other candidate receptors show a very heterogenous activity profile across the agents. It may be tempting to conclude, therefore, that this indicates that these other receptors are not really candidate receptors at all for general anaesthesia. However, this conclusion is only valid if we are restricting ourselves to considering a unitary mechanism of action. If we broaden our horizons and accept the possibility (as implied by Escallier et al.'s statement [1]) that there are several distinct forms of anaesthesia, then immediately it becomes clear that Table 1 is illustrating the different ways that each agent can induce anaesthesia via its own unique spectrum of receptor activities. Thus, the anaesthesia induced by etomidate cannot be an identical brain state to the anaesthesia induced by propofol or thiopental, etc. Furthermore, given the gaps in knowledge displayed within Table 1, it is conceivable that even each volatile agent is subtly unique in its actions (e.g. isoflurane vs sevoflurane). Moreover, the coupling of intravenous induction with volatile maintenance (with supplementary nitrous oxide) may result in some interesting interactions, some of which may even be potentially antagonistic at certain receptors, each resulting in their own unique anaesthetic state.

I asked earlier: what does additional anaesthetic dosing do after the state of anaesthesia has been achieved? The information discussed above helps address this question, at least in part. Additional dosing increases the degree or type of loss of brain function. Thus if, say, propofol acting on a GABA-A receptor achieves the threshold drug-receptor concentration to produce the endpoint of loss of consciousness or loss of response to verbal stimulation, then additional propofol might produce loss of response to a different endpoint of, say, nociceptive stimulus [18]. Or, at higher doses, propofol interacts with nACh receptors in the brain, where at conventional doses it is only weakly active (Table 1), and hence at high dose produces a wider loss of function of those activities mediated by these receptors (e.g. interference of sleep or of

Table 1 Crude overview of anaesthetic actions on the main putative candidate receptors/channels (red, strongly activating; orange, weakly activating; dark blue, strongly inhibiting; pale blue, weakly inhibiting; 0, no effect; n/a, data unavailable). Adapted from Rudolph and Antkowiak [19] using their broad definitions of strong/weak activation/inhibition (with TASK results added from data of Putzke et al. [20] and Pandit et al. [21, 22]. Results taken for sevoflurane and AMPA from [23], NMDA from [24] and HCN1 from [25]. The table is not comprehensive either for channel types or for agents, and agents with novel actions such as dexmedetomidine [26] are not represented.

	$GABA_A$	Glycine	nACh (muscle)	nACh (neuronal)	$5HT_3$	AMPA	Kainate	NMDA	TASK1	HCN1
Etomidate					0	n/a	n/a	n/a		0
Propofol					0		0		0	
Barbiturates								0	n/a	n/a
Ketamine		0				0	0		n/a	
Isoflurane										
Sevoflurane					n/a	0	n/a			n/a
Nitrous oxide									n/a	n/a

GABA-A, γ-amino butyric acid type A; nACh, nicotinic acetylcholine; $5HT_3$, 5-hydroxytryptamine (serotonin) type 3; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartate; TASK-1, TWIK (two-pore domain weakly inwardly rectifying potassium)-related, acid sensitive potassium channel type 1; HCN1, hyperpolarisation-activated cation channel type 1.

learning and memory) [27]. Thus, dosing produces quantitative effects related to a single receptor, as well as qualitative effects related to activation of multiple receptors [28].

Implications for monitoring

This all makes our approach to unconsciousness resemble more closely our approach to other physiological systems, such as the cardiovascular, respiratory or renal.

We readily accept that the cardiovascular system is composed of several more basic elements such as blood pressure, cardiac output, cardiac filling/venous return, etc, each of which requires its own separate measurement. In turn, we acknowledge that antihypertensives, for example, are not a single class of drug, but work in unique ways on one or more of these fundamental elements of the cardiovascular system (e.g. cardiac output or peripheral resistance, etc) to produce the common effect of 'lower blood pressure'. It is not sufficiently informative to say that a drug has reduced the blood pressure; in anaesthesia and critical care we need to know the mechanism(s) by which it has done so [29]. We view bronchodilators in the respiratory system, or diuretics in the kidney, in similar ways. Table 1 suggests that 'anaesthetics' may be a very crude term for a group of drugs that produce a superficially similar neurophysiological state, but that (like the antihypertensives) have highly specific actions [29].

The implications of this train of logic for monitoring the brain state are important. A brain monitor that yields as its output a single numerical value to reflect the state of the system is, at best, only providing a general estimate about the probability of the system (its 'capacity') to generate consciousness [30, 31]. It is not telling us which specific elemental functions contributing to consciousness are lost and which are retained. A single number is therefore of little or no use if, in fact, there are several different brain states induced by anaesthetic drugs, and if anaesthesia can be achieved with a spectrum of brain states, in some of which the capacity for consciousness is retained.

Even high-quality studies simply grasp for correlations between EEG/brain activity signatures with the moment of loss of/return to consciousness, and they often only study single agents, in the absence of surgery [32]. While correlations are indeed discovered by such experimental paradigms, it remains unclear if these really do signify sufficient loss of brain functions as to allow surgery to proceed acceptably, or if the same signatures pertain with different agents or mixtures of agents. Other methodologies indicate that brain responses are highly agent-specific [33, 34]. Recent work using functional magnetic resonance imaging (fMRI) has suggested that with very slow propofol induction, a state is reached where the thalamocortical region of the brain becomes an 'island' of activity, apparently separated from sensory input, and that this is associated with loss of this region's response to auditory and nociceptive inputs [18]. However, other parts of the brain retained their response to these stimuli. The suggestion was that, perhaps akin to the state of dysanaesthesia [10], these subjects were technically aware of the sensory stimulation but disinclined to be interested in it. It is not known if the same fMRI results are seen with other agents, or if this brain state is compatible with surgery.

The fact that many pEEG monitors such as the bispectral index (BIS) yield a different value when patients appear equally well anaesthetised with some agents (e.g. propofol) vs others (e.g. ketamine or xenon) has been argued to show that the monitors are very poor at detecting the state of 'anaesthesia' [35]. However, this interpretation is valid only if it is assumed there is a single brain state for anaesthesia. If, in fact, there are multiple brain states compatible with anaesthesia, then these results are telling us that the monitors are possibly very good at detecting some of these states (e.g. those achieved by propofol) but very poor at detecting others (e.g. those achieved by ketamine). If the technology only accommodates a single monitor to detect just the one brain function, then it follows that multiple monitors, where each focuses on a separate brain function, are more likely to be beneficial than just one. This is then akin to all other body systems, such as the cardiovascular, where we readily accept the need for separate monitors to provide information about the electrical activity of the heart, the blood pressure, cardiac output, etc. Sleigh reaches a broadly similar conclusion, focusing on the need for separate monitors calibrated for specific endpoints such as memory

loss, nociceptive arousal systems, inflammatory responses, etc [4].

The anaesthetic literature is surprisingly sparse on the properties of the 'ideal' depth of anaesthesia monitor(s), although Avidan and colleagues have cogently approached the problem, focusing on EEG-based monitoring [36, 37]. Whyte and Booker suggested some ideal properties in an educational publication [38], as did Gelb in unpublished material accessible on the internet [39]. Table 2 summarises these proposals, with the last column indicating what might be considered ideal, based on the discussions in this article.

Conclusion: a new meaning of 'anaesthesia'

Each anaesthetic agent appears to act via its own unique spectrum of affinity/efficacy for different channel receptors [19]. The resulting effect is not just related to effect of dose on one receptor system, but also to the spectrum of receptors on which the agents act at a given dose. Since these receptors are unevenly distributed in different parts of the brain, this suggests that each agent acts on its own unique set of brain regions [28]. And since brain function is localised by region, this suggests in turn that each anaesthetic drug may induce anaesthesia by its own unique mechanism involving different, specific brain functions. These conclusions are in

Table 2 Summary of proposed properties of an 'ideal' depth of anaesthesia monitor proposed by various authors (my interpretation). A '✓' indicates that the authors require the ideal to have this property; a 'x' indicates that this property is the opposite of what is desired; a blank indicates that the authors do not discuss this aspect. There are areas for further debate: *this property implies more than one monitor is needed (Jagadeesan et al. [37] do not explicitly argue this); **hysteresis: it is well established that the concentration of anaesthetic at which the patient wakens is less than that required for induction – the question is whether the monitor should reflect this or not; †these requirements are mutually exclusive; ‡this requirement raises complex questions as to the role of incentivisation in innovation and does not seem to be essential for the proper functioning of a monitor.

	Palanca et al. [32]	Gelb [35]	Whyte & Booker [34]	Jagadeesan et al. [33]	Pandit
Consistent with conceptual models of anesthesia/consciousness				✓	✓
Informs clinician about specific neuronal process (e.g. pain, memory formation, etc)*				✓	✓
Spatial resolution (i.e. identify activity from different, specific brain regions)				✓	✓
Similar output across all anesthetic agents at equipotent (i.e. equi-MAC) concentrations	✓	✓	✓	✓	x
Reliable (i.e. appropriate sensitivity, specificity, and positive/negative predictive values	✓	✓	✓	✓	✓
Predicts that awareness will happen before it does so (i.e. also implies rapid response time)	✓		✓	✓	✓
Fluctuates with changing noxious stimulation		✓	✓		✓
No hysteresis (same output on losing as on regaining consciousness)**			✓		✓
Uninfluenced by physiological changes such as blood pressure		✓			✓
Minimal inter-patient variability†	✓			x	x
Reflects inter-patient variability†	x			✓	✓
Uninfluenced by non-anesthetic agents and influences (e.g. surgical cautery)		✓		✓	✓
Cheap, portable, practical to use	✓		✓		✓
Technology of monitoring should be open-source‡	✓			✓	

contrast to the previous, widely-held view that there must a singular, binary mechanism by which all anaesthetics induce anaesthesia. Furthermore, there is an emerging consensus that accidental awareness during anaesthesia is also a spectrum of brain states, some of which are in fact broadly acceptable to patients (even though they involve a degree of awareness of surroundings, which may be surprising or unanticipated at the time) [10].

In this way, the train of logic arising from Escallier et al.'s innocuous statement has led us to a redefinition of 'anaesthesia'. In a highly restricted sense, anaesthesia is purely the brain state of complete mental oblivion with no sensory-perceptual experience, thoughts or recall of events. In a pragmatic sense, however, 'anaesthesia' is *any drug-induced mental state that makes surgery acceptable at the time, and later*, whether or not that includes some awareness and recall of events. In one (extreme) sense, this concept is not new to us: a technique employing regional anaesthesia (spinal or epidural) with light sedation is an entirely acceptable form of 'anaesthesia' wherein the patient is likely to be aware of events but unconcerned by them. The new notion presented here is that a rather similar state might arise, unanticipated, where the original intention was to induce complete mental oblivion.

This wider meaning and use of the word 'anaesthesia' might also yield strategic benefits for the specialty as a whole. First, it can act as an important driver for research, directed to linking the outputs of pEEG and other monitors to specific brain functions. Second, it can aid positive public engagement. Because hitherto, the professional and public understanding of what 'anaesthesia' is has been the narrow one, the involvement of an 'anaesthetist' in patient care has been assumed to imply that the input will solely be to induce a state of complete mental oblivion, and little else [40, 41]. Indeed, anecdotally there can be surprise and even disappointment that mental oblivion is not always the proposed solution to the presenting clinical problem. By redefining 'anaesthesia' to mean the more subtle manipulation of sensory-perceptual modalities to create a range of possible acceptable mental states for surgery, this might in turn broaden the public view of anaesthetists' skills and knowledge in contributing to patient care [41].

Conflicts of Interest

JJP is Clinical Lead of NAP5; the views expressed here are his own and not those of NAP5, the Royal College of Anaesthetists or the Association of Anaesthetists of Great Birtain and Ireland. No funding or other competing interests declared.

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doi:10.1111/anae.12668

Editorial

Learning from Semmelweis: engaging in sensible infection control

Healthcare-acquired infection is considered an adverse event and anaesthetic practitioners share a professional responsibility to ensure that high standards of infection control are maintained. However, there are

Review Article

CPD available at http://www.learnaagbi.org

Monitoring the brain: processed electroencephalogram and peri-operative outcomes

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Summary

Although the brain is the target organ of general anaesthesia, the utility of intra-operative brain monitoring remains controversial. Ideally, the incorporation of brain monitoring into routine practice would promote the maintenance of an optimal depth of anaesthesia, with an ultimate goal of avoiding the negative outcomes that have been associated with inadequate or excessive anaesthesia. A variety of processed electroencephalogram devices exist, of which the bispectral index is the most widely used, particularly in the research setting. Whether such devices prove to be useful will depend not only on their ability to influence anaesthetic management but also on whether the changes they promote can actually affect clinically important outcomes. This review highlights the evidence for the role of bispectral index monitoring, in particular, in guiding anaesthetic management and influencing clinical outcomes, specifically intra-operative awareness, measures of early recovery, mortality and neurocognitive outcomes.

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Accepted: 31 March 2014
This article is accompanied by an editorial titled "Monitoring (un)consciousness: the implications of a new definition of 'anaesthesia'" by Pandit. Anaesthesia 2014; **69**: 801–910.

Introduction

It is hypothesised that incorporating a brain monitor into routine anaesthetic practice can improve both anaesthetic management and patient outcomes by optimising the depth of anaesthesia. Both inadequate, or 'too light', and excessive, or 'too deep', anaesthesia have been linked to negative outcomes. Some of these associations are well established, while others are controversial.

Brain monitoring is heuristically appealing as the brain is the target organ of general anaesthesia, and since 1937 the incorporation of electroencephalogram (EEG)-based monitoring into routine anaesthesia practice has been advocated [1]. However, anaesthetists remain divided as to the usefulness of such monitoring. Recently, guidelines were published by the National Institute for Health and Care Excellence (NICE) in the UK recommending the use of EEG-based brain monitoring, especially in 'vulnerable' patients [2, 3]. Implementation of these guidelines has been controversial due to the lack of definitive evidence for the benefit of such monitors and insufficient information on what constitutes 'vulnerability'. Thus, most anaesthetists in the UK currently do not follow the NICE guidelines, and either through choice or unavailability of the devices, do not use brain monitors [4].

Most clinicians who do use a brain monitor opt for a processed electroencephalogram (pEEG) device, and the bispectral index (BIS) monitor® (Covidien, Boulder,

CO, USA) is currently the most widely used pEEG device. The concept of pEEG monitoring and the development of the BIS algorithm have been described elsewhere [5, 6]. Briefly, the BIS monitor uses a proprietary algorithm to process frontal EEG signals and produces a number between 0 and 98, with values in the 90s reflecting a preponderance of higher frequency beta waves, suggesting wakefulness, and values approaching 0 occurring with progressive EEG suppression. On the one hand, it has been recommended to target BIS values < 60 in order to avoid inadequate anaesthetic depth with resultant intra-operative awareness [7]. On the other hand, it is advocated to avoid EEG suppression and lower BIS values (i.e. attempt to maintain BIS values > 40) to prevent unnecessarily deep anaesthesia with its hypothesised adverse consequences [8–10].

Whether BIS monitoring, or guidance by any form of pEEG, can have a meaningful impact on particular patient outcomes is inextricably linked to whether general anaesthesia itself impacts these outcomes. While anaesthetic depth clearly impacts the occurrence of intra-operative awareness, its contribution to other outcomes is less well established. In defining the appropriate role of brain monitoring during general anaesthesia, we must seek to answer two main questions. First, does the particular monitor actually influence anaesthetic management? Second, to what extent are changes in depth of anaesthesia management likely to affect a variety of patient outcomes? In this review, we seek to highlight some of the key evidence and controversies surrounding these important questions.

Does pEEG or BIS guidance influence anaesthetic management?

The utility of pEEG monitors in general, or the BIS in particular, for guiding anaesthetic management depends on (1) the accuracy of the monitor of interest in reflecting depth of anaesthesia and (2) the ability of practitioners to titrate anaesthesia based on the monitor. Although this review focuses mainly on the BIS because of its widespread adoption, and as much of the relevant evidence has been obtained using the BIS, it is important to emphasise that the BIS is only one of many available candidate depth of anaesthesia monitors. While pEEG monitors have probably advanced practice in certain situations and have helped focus the attention of the anaesthesia community on the brain as the appropriate target organ, they all have important limitations that must be addressed with future technologies [11–16].

The difficulty in judging the accuracy of the BIS or any brain monitor in measuring anaesthetic depth is that there is no clinical or neurophysiological gold standard beyond loss of responsiveness with which the monitor can be calibrated or against which it can be tested. One of the approaches to this challenge has been to evaluate the BIS against exhaled concentration of a volatile anaesthetic agent [11]. Whitlock et al. found that while some patients show a steep concentration–response relationship between age-adjusted minimal alveolar concentration (MAC) and BIS values, others show minimal change in BIS over a clinically relevant range of age-adjusted MAC [11] (Fig. 1). This was consistent with other studies that have described a 'plateau phenomenon' in the concentration–response curve, with volatile anaesthetic as the independent variable and the depth of anaesthesia indices as the dependent variables [17–20]. This finding could be interpreted as showing either that pEEG devices are not accurate in reflecting changes in anaesthetic depth or that over a clinically relevant range of volatile anaesthetic concentrations, depth of anaesthesia does not change in many patients. The key limitation with this approach is that volatile anaesthetic concentration is the input function (i.e. administered drug concentration), and as such is not a measure of drug effect, or the output function [21]. Therefore, volatile anaesthetic concentration is arguably a less reflective surrogate of brain states than EEG-based monitors, which provide at least potentially some measure of drug effect, independent of administered dose. As the transition between responsiveness and unresponsiveness is clinically meaningful, and might provide an approximation of the switch between consciousness and unconsciousness, pEEG devices have also been tested for their ability to detect this transition with a variety of anaesthetic agents [22–24]. Unfortunately, with all pEEG devices, there is no specific value of the index, or even a relatively narrow range, that reliably predicts when this transition occurs, both within and between individuals [23–25]. Nonetheless, even if pEEG monitors do not precisely track anaesthetic depth or dis-

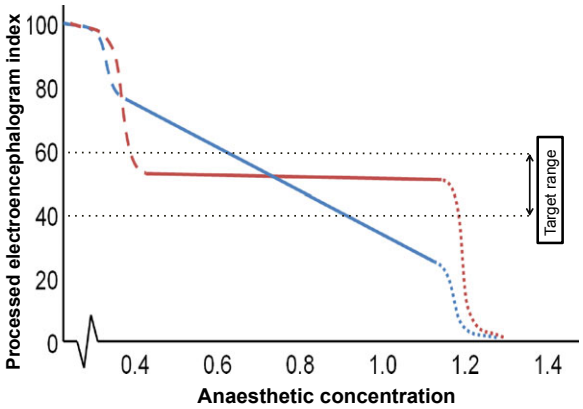

Figure 1 Inter-patient variability in the concentration–response relationship between anaesthetic concentration and a processed electroencephalogram (EEG) index. This figure illustrates the concentration–response relationships for two hypothetical patients, with anaesthetic concentration as the independent variable and processed EEG (pEEG) index as the dependent variable. The dashed portion of the line (on the left of the x-axis) represents responsiveness. The dotted portion of the line (on the right of the x-axis) represents 'excessive' EEG suppression. The solid portion of the line represents a hypothetical optimal plane of anaesthesia, where the patient is no longer responsive but does not demonstrate excessive EEG suppression. This corresponds to a 'plateau' of the concentration–response curve, where the slope of the curve is often relatively flat. As described by Whitlock et al., the slope of this plateau phase varies from patient to patient, with some showing a steep concentration–response relationship between anaesthetic concentration and a pEEG index (blue line) and many others showing minimal change in pEEG index over a clinically relevant range of anaesthetic concentrations (red line) [11].

criminate consciousness from unconsciousness, it does not mean that they are not useful in broadly guiding anaesthetic management. For example, they might help provide a minimum level of anaesthesia to minimise the risk of awareness and they might help limit unnecessarily excessive anaesthetic administration (Fig. 2).

To date, studies that have attempted to clarify whether pEEG monitors can be used as anaesthetic titration aids and can change the way anaesthesia is administered have yielded conflicting results. Small efficacy trials have found that pEEG devices could be used to guide anaesthetic management, with the goal being to limit safely the patient's exposure to general

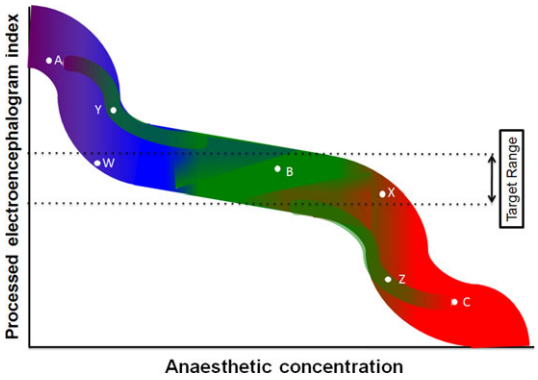

Figure 2 Guiding anaesthetic administration with a processed electroencephalogram index. The figure shows a stylised population plot for anaesthetic effect site concentration (independent variable) on the x-axis plotted against a candidate depth of anaesthesia processed electroencephalogram index (dependent variable) on the y-axis. The colours reflect clinical states from awake (dark purple) to very deep anaesthesia (intense red). In this figure, the purple zone represents increasing sedation, the blue zone represents a theoretical transition between sedation and general anaesthesia during which loss of responsiveness to command occurs, the green zones represent a hypothetical optimal plane of general anaesthesia, and the red zone depicts excessive depth of general anaesthesia. The band designated 'Target Range' is the recommended range of the processed electroencephalogram index for general anaesthesia (e.g. bispectral index 40–60). The points A, B and C are examples of concordance between the index readings and an individual patient's clinical state. At point A, an individual patient is responsive, and the index is reading high. At point B, an individual patient is 'optimally anaesthetised' and the index is within the target range. At point C, an individual patient is 'excessively anaesthetised' and the index is reading very low. The points W and X designate discordance. At point W, a particular patient would be responsive despite the index suggesting that anaesthetic depth was optimal. At point X, a particular patient would be 'too deeply' anaesthetised despite the index suggesting that anaesthetic depth was optimal. This figure also illustrates that both the index and anaesthetic concentration, as surrogates, can be discordant with the clinical state even when they are concordant with each other. At point Y, both the low anaesthetic concentration and the high index value would suggest that the patient is 'too lightly' anaesthetised, but the patient is actually optimally anaesthetised. At point Z, both the high anaesthetic concentration and the low index value would suggest that the patient is 'too deeply' anaesthetised, but the patient is actually optimally anaesthetised.

anaesthesia. These trials showed reductions in both cumulative intravenous and inhalational anaesthetic doses. A study by Lindholm et al. challenged the notion that pEEG guidance could markedly alter anaesthetic administration. In this study, certified registered nurse anaesthetists (CRNAs) were trained in the use of BIS monitors [25]. Despite increasing experience with the BIS and subjective appreciation of its value, the average doses of anaesthesia administered by them were not altered when they used the BIS nor were there any differences in BIS values when the BIS was applied but they were blinded to the index [25]. Large randomised controlled trials including > 30 000 patients have appeared to corroborate these findings [7, 26–28]. In the B-Aware, B-Unaware, and BAG-RECALL trials and the Michigan Awareness Control Study, there has been no meaningful difference between the volatile anaesthetic concentrations in patients randomly assigned to BIS guidance or to the control arm [7, 26–28]. For propofol, studies have been more compelling in showing that BIS guidance could discriminately decrease propofol administration [7, 29]. But this may reflect the current inability in clinical practice to monitor propofol concentration directly in contrast to the universal availability of end-tidal anaesthetic agent monitors. The randomised, controlled, CODA trial in 921 non-cardiac surgical patients has provided evidence from a large clinical trial that BIS guidance can in fact markedly decrease both volatile and intravenous anaesthetic administration [8]. If these results are replicated, this could have a major impact on the field and would probably lead to much more widespread adoption of pEEG monitoring into routine anaesthetic practice. However, just because a monitor can work (is efficacious) in achieving a desired outcome (e.g. targeted reduction in anaesthetic administration), it does not necessarily follow that this outcome will be achieved when the monitor is incorporated into routine practice (i.e. is effective) or that it is worthwhile to incorporate the monitor into routine practice (i.e. is cost-effective).

Do changes in anaesthetic management affect outcomes?

If we assume that pEEG guidance can effectively guide the titration of anaesthetic administration by targeting the desired depth of anaesthesia, the question remains whether subtle changes in anaesthetic management can influence clinically important outcomes. Distressing, unintended intra-operative awareness is a rare but potentially devastating complication. Avoiding inadequate anaesthesia should theoretically eradicate this complication, and a pEEG monitor might be helpful in achieving this. Conversely, there is strong evidence that administering higher doses of anaesthetics, particularly volatile anaesthetics, adversely influences a variety of measures of early postoperative recovery, such as postoperative nausea and vomiting (PONV) and time to discharge from the postoperative recovery area. Below, we will review the evidence regarding the impact of pEEG-guided anaesthesia on these peri-operative outcomes. We will also address the controversy surrounding the impact of pEEG-guided anaesthetic management on outcomes beyond the immediate peri-operative period, including death, delirium and cognitive decline.

Awareness

The evidence regarding approaches to prevent intra-operative awareness, including the use of pEEG devices such as the BIS, has been recently reviewed [30]. Despite the completion of high-quality randomised controlled studies, awareness remains a controversial topic for the field for important reasons. Most fundamentally, the definition of intra-operative awareness is disputed, which is unsurprising given the gaps in our knowledge of the scientific underpinnings of general anaesthesia. There is a growing consensus that intra-operative awareness is a spectrum of brain states. Perhaps the most egregious awareness experiences are those when patients have relatively lengthy or repeated periods of lucid wakefulness during surgery with full comprehension of their situation, where they are unable to move, are in severe pain, are extremely distressed, and have explicit postoperative recall of the experience. Mashour et al. classified intra-operative awareness experiences with the Michigan Awareness Classification Instrument [31] (Table 1). Intuitively, it would seem far more important to prevent a Class-5D awareness experience (pain, paralysis plus distress) than to prevent a Class-1 experience (isolated sensory perception such as auditory without pain or distress). It is likely that awareness experiences associated with

Table 1 Michigan awareness classification instrument.

Class 0: No awareness
Class 1: Isolated auditory perceptions
Class 2: Tactile perceptions (e.g. surgical manipulation or tracheal tube)
Class 3: Pain
Class 4: Paralysis (e.g. feeling one cannot move, speak or breathe)
Class 5: Paralysis and pain

An additional designation of 'D' for distress can also be included for patients' reports of fear, anxiety, suffocations, sense of doom, sense of impending death, etc. Reproduced from ref. [31].

inability to move or distress are more likely than other awareness experiences to have adverse consequences, such as symptoms of post-traumatic stress disorder [32]. It is possible that the majority of awareness events are Class-1 experiences, which might not be associated with negative sequelae. Pandit has proposed a state termed 'dysanaesthesia', which implies a degree of environmental awareness but is not associated with cognitive appraisal of distressing aspects of surgery (e.g. pain, inability to move), and may or may not be explicitly remembered [33]. He suggests that dysanaesthesia probably occurs relatively commonly and itself might not have negative consequences.

Apart from the challenges with definitions, there is debate regarding the incidence of intra-operative awareness, with reports from studies ranging from a high of 1 in 100 [34, 35] (e.g. when repeated postoperative questioning is used) to a low of 1 in 15 000 [36] (e.g. when relying on patients' self-reporting, as in the 5th National Audit Project in the UK, NAP5 [4, 36]). We might expect that patient self-reports are more likely to detect distressing awareness experiences, unlike studies where awareness is elicited through questioning [37]. However, in the B-Unaware and BAG-RECALL trials, where all patients were repeatedly contacted and questioned explicitly about whether or not they experienced intra-operative awareness, about a third (13 of 37) of patients with definite or possible awareness reported pain or distress associated with their awareness experience [27, 28]. This is a similar proportion to those reporting pain or distress in the NAP5 Baseline Survey [4]. The value of pEEG devices in preventing awareness rests on their ability to detect distressing awareness experiences, but it is unknown whether pEEG devices have increased sensitivity (i.e. are better able to rule out) for distressing awareness experiences (e.g. cognitive appraisal of pain) or for experiences that are encoded as explicit memories. Experiments with the isolated forearm technique suggest that current pEEG devices are unreliable in detecting when patients are able to respond appropriately to a verbal command such as, 'squeeze your right hand twice' [38, 39]. However, this endpoint may not relate to a later distressing experience (especially if, as argued by Pandit, this response is indicative of another brain state, dysanaesthesia). If, based on the preliminary findings of NAP5 [4], the incidence of awareness was much lower than the currently accepted estimate of 1–2 in 1000 [26, 40, 41], the number needed to treat to benefit from pEEG monitoring (i.e. to prevent one patient from preventing a distressing awareness experience) would be extremely high.

Notwithstanding the hypothetical limitations of current pEEG devices regarding the prevention of intra-operative awareness – defined as both consciousness *and* explicit recall of intra-operative events [42] – there is a growing body of evidence suggesting that in specific situations, pEEG devices are effective in this regard. Evidence from several large trials suggests that a BIS-based protocol during the administration of total intravenous anaesthesia with pharmacological paralysis decreases intra-operative awareness with postoperative recall [7, 27, 30]. Yet, when anaesthesia is based on a potent volatile agent, a BIS-based protocol has not been shown to be superior to a protocol based on exhaled anaesthetic concentration (ETAC) in preventing awareness with recall [26–28, 30]. When general anaesthesia is administered *without* neuromuscular blocking agents, movement might be the best indicator of awareness. Figure 3, adapted from a recent review by Avidan and Mashour, presents a proposed evidence-based decision tree for selecting the appropriate protocol to prevent awareness during intended general anaesthesia [30].

Early recovery

Deep anaesthesia is commonly thought to prolong and impair the quality of recovery [43]. This is almost certainly true in the short term with the use of volatile agents. Inhalational anaesthetics are known emetogenics

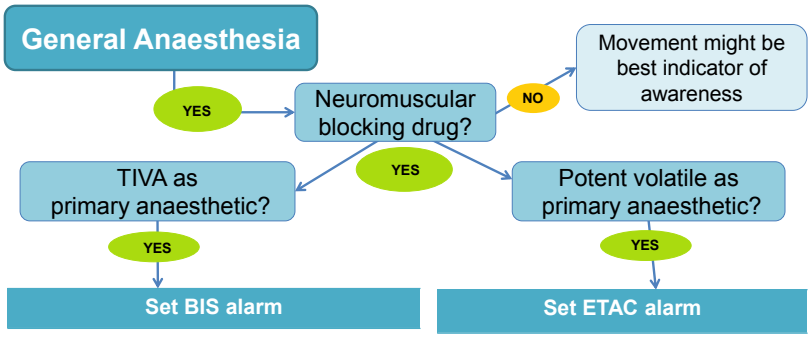

Figure 3 Evidence-based decision tree for protocol to prevent awareness with recall. Movement is likely to be the best indicator of awareness for patients undergoing general anaesthesia without the use of neuromuscular blocking drugs. However, for those in whom motor activity is pharmacologically blocked, other approaches might aid in the prevention of unintended intra-operative awareness with recall (AWR). The results from the B-Aware and TIVA trials offer support for the use of a BIS monitor with alerts for preventing AWR in patients undergoing total intravenous anaesthesia (TIVA). In the B-Aware trial, a BIS protocol prevented AWR compared with routine care in high-risk patients [7]. More than 40% of patients in this study underwent TIVA. The TIVA trial showed that a BIS protocol prevented AWR compared with routine care for patients undergoing TIVA [29]. For patients undergoing general anaesthesia with a potent volatile agent, the current evidence endorses the use of an end-tidal anaesthetic concentration (ETAC) alarm to prevent AWR. The BAG-RECALL (BIS or Anaesthetic Gas to Reduce Explicit Recall) [27] and B-Unaware trials showed that a BIS protocol was not superior to an ETAC protocol in preventing AWR in high-risk patients [28], and the Michigan Awareness Control Study found that a BIS protocol was not superior to an ETAC protocol in preventing AWR in an unselected surgical population [26]. Modified from ref. [30].

that increase the risk for PONV, which is the most common side-effect in the hours following emergence from general anaesthesia [44, 45]. The incidence of early vomiting exhibits a strong dose-dependent relationship with the degree of exposure to inhalational anaesthesia [46]. Not only does PONV cause significant patient discomfort and morbidity, such as dehydration and suture dehiscence [47], but it can also delay discharge from the postoperative recovery area [48].

The role of pEEG guidance in improving early recovery outcomes is unclear. Presumably, a reduction in anaesthetic exposure could lessen the risk of PONV and other anaesthesia-associated outcomes. However, as discussed, the effectiveness of pEEG guidance in decreasing anaesthetic administration is controversial. Not surprisingly, clinical trials have yielded mixed results when examining whether BIS guidance improves measures of early recovery. Some trials and meta-analyses have supported associations between a BIS-based protocol and decreased anaesthetic administration or improved early outcomes, compared with routine care or alternative protocols [8, 43, 49]. Several clinical studies demonstrated associations between BIS guidance and shorter time to extubation, increased orientation in the postoperative recovery area, and faster discharge from the postoperative recovery area [6, 50–52]. A Cochrane meta-analysis found that BIS monitoring significantly reduced propofol and volatile anaesthetic consumption, early recovery times, and length of PACU stay [43]. However, Pavlin et al. reported in a large, randomised clinical trial that although BIS monitoring was associated with a slight decrease in sevoflurane administration, it did not lead to faster emergence or a shorter stay in the postoperative recovery area [53]. Similarly, analyses from the BAG-RECALL and B-Unaware trial populations and the Michigan Awareness Control Study demonstrated no difference in anaesthetic administration, time to discharge from the postoperative recovery area, or incidence of PONV with the use of BIS guidance compared with controls [26, 54].

Mortality

During the past decade, several studies have addressed the question of whether deep general anaesthesia might be a contributor to intermediate-term (e.g. one year) postoperative mortality. One observational study found that cumulative duration in hours of

BIS < 45 was an independent predictor of one-year mortality (relative risk 1.244 per hour of cumulative deep hypnotic time, 95% CI 1.062–1.441) [55]. Cancer was the leading cause of death in this study. Lindholm et al. reported a similar finding; however, when pre-existing malignancy was added as a covariate, cumulative duration of low BIS fell out of the model as an independent predictor of death [56]. In a secondary analysis from the B-Aware trial, Leslie et al. [57] found that the risk of death was not significantly different between those randomily assigned to the BIS-guided group or to the standard care (i.e. no BIS) group. They did find within the BIS group that patients with deep anaesthesia (defined as BIS < 40 for > 5 min) had an increased rate of intermediate-term mortality over a median of four years compared with propensity matched patients (i.e. patients with a similar risk profile) who did not meet this definition of deep anaesthesia [57]. That same year, in a secondary analysis of patients undergoing cardiac surgery in the B-Unaware trial, Kertai et al. also found a significant association between cumulative duration of BIS < 45 and intermediate-term mortality (hazard ratio of 1.30 per hour of cumulative duration of BIS < 45, 95% CI 1.13–1.49) [58]. Interestingly, in a follow-up study of non-cardiac surgery patients in the B-Unaware trial, Kertai et al. reported no significant association between cumulative duration of BIS < 45 (or BIS < 40) and postoperative mortality (hazard ratio of 1.06 per hour of cumulative duration of BIS < 45, 95% CI 0.99–1.13) [59]. In this study, neither higher mean concentrations of volatile anaesthetics nor increasing cumulative exposure to volatile anaesthetics was associated with increased postoperative mortality [59].

There are several challenges in interpreting the association between low BIS values and all-cause mortality. If deep anaesthesia were really indiscriminately increasing mortality, a variety of mechanisms would have to be implicated such as myocardial damage, neurotoxicity, nephrotoxicity, immunosuppression and promotion of tumour growth. The variations in results when factoring malignancy status or considering type of surgery necessitate more nuanced interpretations of the relationship between low BIS and mortality. For example, deep anaesthesia could mediate increased mortality only in vulnerable patients by exacerbating an underlying pathology. Another possible explanation is that low BIS could sometimes reflect deep anaesthesia, but it might also occur in patients with underlying frailty, possibly even with light anaesthesia (Fig. 4). This possibility was reinforced by Whitlock et al., who reported that the average relationship between volatile anaesthetic concentration and BIS was affected by factors such as age, ASA physical status and postoperative vital status [11] (Fig. 5). In 2012, Sessler et al. reported findings from a large observational study of the possible influence of low mean arterial pressure (MAP), low BIS and low MAC on 30-day postoperative mortality [60]. Surprisingly, this study found that low BIS (< 45) in isolation was actually associated with a *decreased* risk of 30-day mortality [60]. Only when low BIS occurred concurrently with low MAC, low MAP, or both low MAC and low MAP (a condition termed 'triple low' by the investigators) was there an increased adjusted risk of 30-day mortality [60]. Moreover, supporting the credibility of the relationship, longer cumulative durations of 'triple low' were associated with progressively increasing 30-day mortality [60], which is conceptually similar to a dose–response phenomenon. However, even though the association between 'triple low' and mortality is likely to be robust, causality cannot easily be established from observational trials, and 'triple low' could simply be a marker of patient frailty.

Indeed, if deep anaesthesia or 'triple low' were really potent contributors to postoperative mortality, we would have expected that studies in which patients were randomly assigned to general or regional anaesthesia would have had markedly increased mortality among patients allocated to general anaesthesia arms. In recent years, there have been large randomised trials in both major cardiac (e.g. coronary artery bypass grafting) [61, 62] and non-cardiac (e.g. carotid endarterectomy) [63] surgery where patients have received either regional vs general anaesthesia or surgical intervention vs non-surgical intervention. Interestingly, intermediate-term mortality has not been significantly higher in the general anaesthesia (or surgical intervention) groups in these trials. This suggests that the causal contribution of general anaesthesia, let alone deep general anaesthesia, to postoperative mortality is likely to be either minor or non-existent. Currently,

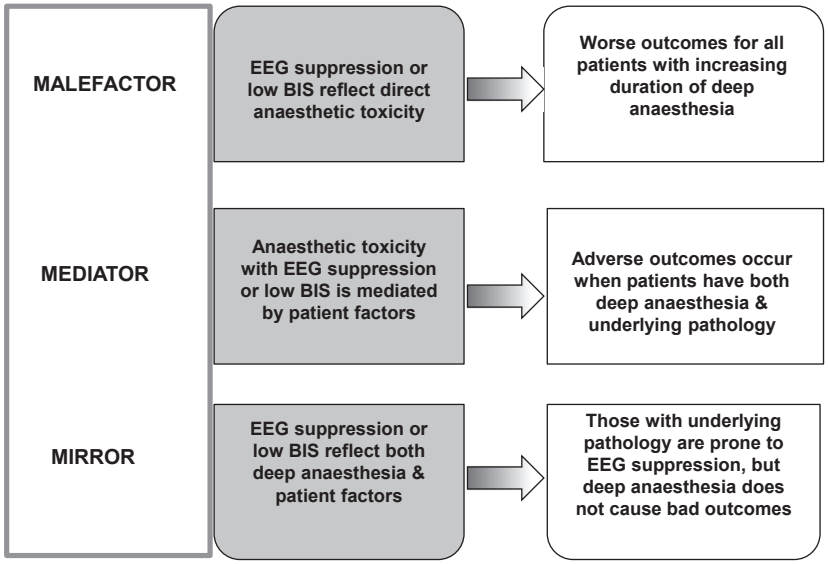

Figure 4 Electroencephalogram (EEG) suppression, low bispectral index (BIS) and adverse outcomes. There are several possible explanations for the observed relationship between EEG suppression or low BIS values and adverse outcomes, like death, stroke and myocardial infarction. It is possible that this association has revealed a directly toxic effect of deep general anaesthesia on the brain or other organs, a 'malefactor' effect. Alternatively, it is possible that deep anaesthesia mediates harm in patients who are concurrently vulnerable (e.g. have low blood pressure) or those who have specific frailties or co-morbidities (e.g. early dementia); this is the 'mediator' effect. A third possibility is that the association between EEG suppression or low BIS values and adverse outcomes represents an epiphenomenon (simply a mirror to something else). According to the 'mirror' hypothesis, EEG suppression or low BIS values would readily occur during general anaesthesia in patients with specific frailties or co-morbidities. These patients are, unsurprisingly, more likely to have adverse outcomes after surgery, but the relatively deep anaesthesia is not a contributing factor to the adverse outcomes.

large clinical trials are underway to determine whether triple low or deep anaesthesia (e.g. low BIS) do indeed contribute to negative postoperative outcomes.

Neurocognitive outcomes

Delirium is defined in the *Diagnostic and Statistical Manual of Mental Disorders* as an acute and fluctuating neurologic disorder that reflects a change from baseline cognition and is characterised by inattention and disorganised thinking [64, 65]. Delirium is a common postoperative complication, affecting between 10% and 70% of patients older than 60 years who undergo major surgical procedures. It is a clinically important complication, is distressing to patients and their families, and is linked to increased costs and worse outcomes including mortality [66–71]. There is mounting evidence from several randomised, controlled trials that a BIS-based protocol can decrease postoperative delirium, possibly by decreasing anaesthetic administration [8–10]. A meta-analysis of four randomised studies comparing BIS-guided anaesthesia with an alternative protocol strongly suggests that BIS-guided anaesthesia decreases postoperative delirium (Fig. 6) [8–10, 72]. Although the finding is compelling, the mechanism for decreased delirium is unclear because, as discussed, most large studies have not demonstrated that BIS guidance alters anaesthetic administration on average [9, 27]. It might be that the protection afforded by a pEEG monitor is to guide practitioners to decrease anaesthesia in a targeted way only in the most vulnerable patients. Before pEEG guidance can be recommended to prevent delirium, a large pragmatic trial is needed to confirm or refute these findings.

Unlike delirium, postoperative cognitive decline (POCD) is a controversial diagnosis, which is not described in the *Diagnostic and Statistical Manual of Mental Disorders*. Conceptually, POCD is a subtle and frequently transient cognitive decline that is often only

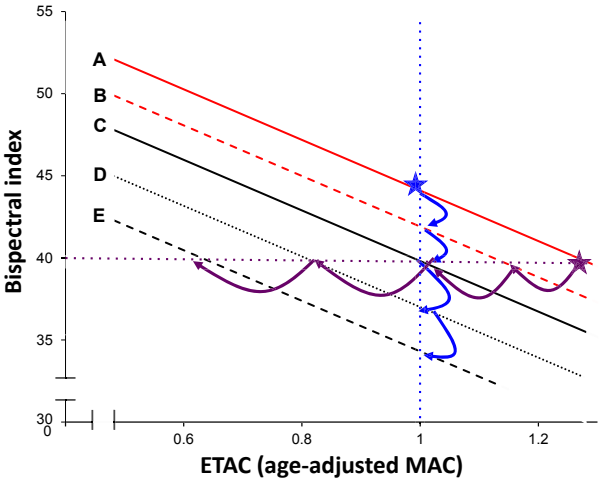

Figure 5 Hypothetical influence of select patient factors on the relationship between bispectral index (BIS) vs end-tidal anaesthetic concentration (ETAC). This figure illustrates the approximate contributions of various factors to inter-patient variability seen during the linear portion of the BIS-ETAC relationship as described by Whitlock et al. [11] (refer to Fig. 1, above). In their model, female sex, age < 60 years, and ASA physical status > 3 were each factors that significantly influenced the BIS-ETAC relationship. They also found that the BIS-ETAC relationship was linked to one-year mortality. This might reflect that patients who died by one year postoperatively were more likely to have been particularly frail at the time of their surgery. This potentially unknown frailty could have influenced the BIS-ETAC relationship. The figure shows idealised BIS-ETAC relationships for five different hypothetical patients. Patient A (solid red line) represents an average male who is > 60 years old, relatively healthy, and who will be alive at one year after surgery. Patient B (dashed red line) has the same characteristics, but is < 60 years old. Patient C (solid black line) has the same characteristics as B, but is female. Patient D (dotted black line) has the same characteristics as C but is relatively sick. Patient E (dashed black line) has the same characteristics as D, but (albeit unknown to anyone now) will be dead at one year after surgery. In this way, as shown, each factor is associated with decreases in the BIS value corresponding to a given ETAC value (these estimated declines are shown by the blue arrows, for each factor that changes). This can also be viewed as each factor's being associated with an estimated decrease in the amount of anaesthetic needed to achieve a given BIS value (these reductions are shown by the purple arrows). Importantly, this model was derived from a single high-risk surgical population and might not be generalisable.

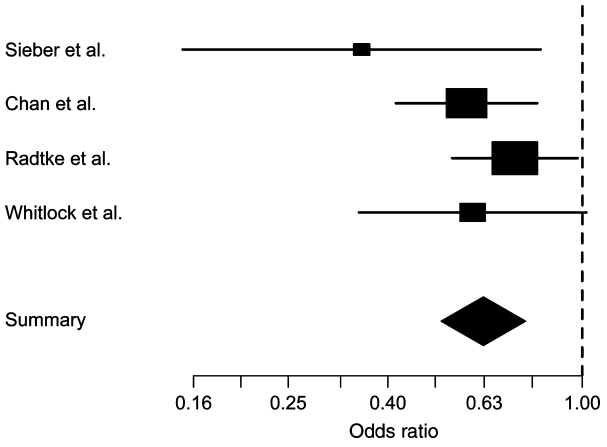

Figure 6 Meta-analysis of randomised controlled trials with bispectral index (BIS) guidance for delirium prevention. This figure summarises four randomised clinical trials (Sieber et al. [10], Chan et al. [8], Radtke et al. [9] and Whitlock et al. [72]) meta-analytically, and suggests that BIS-guided anaesthesia is associated with an estimated odds ratio of 0.63 for postoperative delirium (i.e. is protective) against not using BIS-guided anaesthesia. Given that delirium is common, this would translate into a clinically meaningful reduction in delirium. Reproduced with permission [72].

detectable with appropriate neuropsychological tests and a comparison with pre-operative cognition [73]. Most studies that have included matched, non-surgical control groups suggest that cognitive decline attributable to surgery resolves within a few months of surgery [74–76]. Nonetheless, early POCD is clinically important because it can interfere with postoperative rehabilitation, and is associated with increased mortality and long-term likelihood of leaving the workplace [77, 78]. Studies that have randomly assigned patients to pEEG guidance or control have found conflicting results regarding the impact of pEEG guidance on early POCD [8, 79, 80]. One small nested randomised controlled trial found that a combination of BIS and cerebral oximeter guidance decreased POCD up to one year postoperatively [81]. This is an interesting finding that warrants investigation in future studies.

Conclusion

There are still considerable limitations to the use of pEEG devices for intra-operative brain monitoring. Further refinements, based on neurophysiological

insights and discoveries, will be needed to improve their reliability and utility in measuring of anaesthetic depth. Regardless of the utility of pEEG devices, clinicians can glean important information from the unprocessed EEG waveform [82, 83]. Efforts to educate anaesthetists about the EEG and its underlying neurobiology should proceed in tandem with advances in pEEG technology [42, 84, 85].

It does seem that pEEG monitors may already be useful for broadly guiding anaesthetic management. This is particularly true in the case of decreasing intra-operative awareness events with the use of TIVA with neuromuscular blocking agents. The role of pEEG guidance in the improvement of other clinical outcomes remains less clear. Despite an intuitive role for anaesthetic dosing in measures of early recovery, the evidence from large trials does not consistently support the use of pEEG devices for improving these measures. Although initial results linking low BIS values with increased mortality were alarming, this relationship is possibly reflective of patients' co-morbidity, or harmful only when coupled with hypotension. Nonetheless, the question of whether we can prevent adverse outcomes such as delirium, stroke, myocardial infarction and death with pEEG guidance of anaesthesia deserves rigorous exploration. As our understanding of the specific molecular and functional effects of general anaesthesia on the brain and body continues to improve, intra-operative brain monitoring will become increasingly interesting and useful to biomedical science and to society.

Competing interests

No external funding and no competing interests declared.

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