



Review

Acceptably aware during general anaesthesia: 'Dysanaesthesia' – The uncoupling of perception from sensory inputs



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ABSTRACT

This review makes the case for 'dysanaesthesia', a term encompassing states of mind that can arise in the course of anaesthesia during surgery, characterised by an uncoupling of sensation and perceptual experience. This is reflected in a macroscopic, functional model of anaesthetically-relevant consciousness. Patients in this state can be aware of events but in a neutral way, not in pain, sometimes personally dissociated from the experiences. This makes events associated with surgery peripheral to their whole experience, such that recall is less likely and if it exists, makes any spontaneous report of awareness unlikely. This state of perception–sensation uncoupling is therefore broadly acceptable (a minimum requirement for acceptable anaesthesia) but since it is likely a dose-related phenomenon, may also represent a precursor for awareness with adverse recall. This hypothesis uniquely explains the often inconsistent responses seen during the experimental paradigm of the 'isolated forearm technique', wherein apparently anaesthetised patients exhibit a positive motor response to verbal command, but no spontaneous movement to surgery. The hypothesis can also explain the relatively high incidence of positive response to relatively direct questions for recall (e.g., using the Brice questionnaire; ~1:500; the vast majority of these being neutral reports) versus the very low incidence of spontaneous reports of awareness (~1:15,000; a higher proportion of these being adverse recollections). The hypothesis is consistent with relevant notions from philosophical discussions of consciousness, and neuroscientific evidence. Dysanaesthesia has important implications for research and also for the development of appropriate monitoring.

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1. Introduction

A recent authoritative review of anaesthetic mechanisms by Hameroff began with the summary statement: “...*both consciousness and actions of anaesthetic gases are mediated through extremely weak London forces (a type of van der Waals force) acting in hydrophobic pockets within dendritic proteins arrayed in synchronised brain systems*” (Hameroff, 2006). While this statement may be entirely correct, explaining the mechanism of anaesthesia in these molecular terms does not provide any insights at a functional, macroscopic level. The purpose of this current review is to offer a model of consciousness at functional level, as a basis for a pragmatic explanation of anaesthetic action. I will first outline the problem, then summarise some relevant concepts of consciousness from philosophy, neuroscience and psychology. I will show how these considerations lead to a functional model for consciousness, a key element of which is the distinction between sensory inputs (sensation) and perception (experience) of those. I argue that the minimum requirement for satisfactory general anaesthesia for surgery is an uncoupling of perception from the sensations, which leads to a condition I have termed ‘dysanaesthesia’ (Pandit, 2013). I will discuss how this hypothesis relates to alternative suggestions that have been made about the functional effects of anaesthesia (notably those of ‘unbinding’ or ‘disconnectedness’) and I will demonstrate the limitations of those alternatives.

2. The fundamentals of the problem being addressed

It is simple to state as a general goal that when administering general anaesthesia for a surgical procedure, anaesthetists wish to be satisfied that the patient is unconscious; that is, unaware of the surgical procedure such that the patient cannot adversely recall events later.

2.1. Detecting consciousness during paralysis: the ‘anaesthetist’s dilemma’

The presence of consciousness in another person is generally established through their responses to verbal or behavioural interrogation. However, these responses can be abolished by neuromuscular blocking drugs alone. The patient may be fully awake, but only paralysed and so appears unconscious. Unfortunately indirect autonomic or involuntary responses (such as an increase in heart rate, blood pressure or lacrimation) have all proved unreliable signs of consciousness, because they can also be influenced directly by the surgical process, or by other non-anaesthetic drugs (i.e., these reflexes can be activated by processes independent of consciousness; Schneider & Sebel, 1997).

The problem of how to detect consciousness in a paralysed patient (the ‘anaesthetist’s dilemma’) connects the disciplines of (a) the nature of consciousness (in terms of a philosophical, conceptual understanding), (b) the nature of anaesthesia (in terms of relevant neuroscientific mechanisms) and (c) the principles of monitoring (in terms of how to detect a given state). Within each of these disciplines are many issues of no relevance to the other disciplines, but it is within the overlap of these that the solution to the ‘anaesthetist’s dilemma’ is to be found (Fig. 1). In other words, a macroscopic model must be consistent with ideas from philosophy and neuroscience, and also help lead to a design of a suitable monitor, whose outputs can be interpreted within the model framework. An ideal monitor would be a technical solution to the ‘anaesthetist’s dilemma’. If it correctly distinguished patients who are suitably anaesthetised from those who are simply awake, but paralysed, it would also help solve some of the questions strictly confined to the philosophical domain of ‘the nature of consciousness’ (Fig. 1), as the monitor could also *pari passu* distinguish the conscious from the unconscious in a sense wider than that limited to anaesthesia. More generally, ‘monitoring’ represents the interface between the anaesthetist and the patient.

2.2. The need for a model of the system in question

In order for anaesthetists to interpret the output of any real or hypothetical monitor, they first need to have a suitable model for the process being monitored. For example, a sphygmomanometer reading of 140/90 mmHg can only be interpreted meaningfully within the context of a model for the cardiovascular system which incorporates the concept of ‘blood pressure’; the sphygmomanometer numbers have no independent meaning outside of the model. This is so, regardless of the

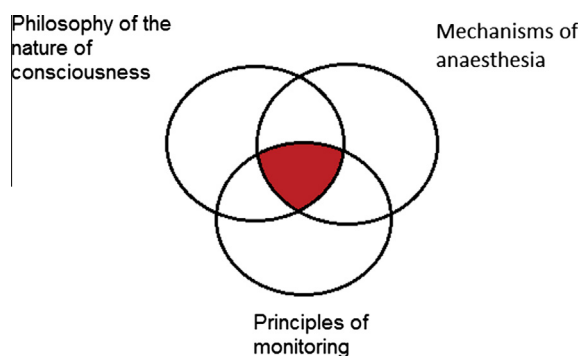


Fig. 1. Venn diagram of three fields of enquiry interlinked in relation to the question of how to detect awareness in a paralysed patient. Each of the fields has within it many issues of no relevance to the other(s), but there is a clear area of overlap which is germane to the problem, and hence the focus of this article.

technology employed – it is essential to know in advance in the design of any monitor what specific *process* the monitor is trying to measure. The process in question for us in this article is ‘consciousness’ and the aim is to present an anaesthetically-relevant model for it.

It is apposite to indicate what we mean by a ‘model’, and the cardiovascular analogy is useful. There are many aspects of cardiovascular function. The electrocardiogram (ECG) measures electrical activity (on the skin surface) reflecting cardiac electrical excitation, and is useless as a monitor for the volume of blood expelled by the heart. Monitors for the latter are in turn useless for assessing changes in cardiac excitability. The electrical signal might be regarded as reflecting the *activity* of the cells, while cardiac output is the resulting meaningful *process*. Furthermore, we regard the cardiovascular system functioning as an integrated system, where values for individual elements like peripheral resistance, venous pressure, etc. are highly relevant to knowing if the system as a whole is in an acceptable state. Outputs from separate monitors for each of these are combined using models for the system (e.g., Guyton’s models; [Dorrington & Pandit, 2009](#)) to ascertain if this is the case.

If our collective approach towards consciousness/unconsciousness in anaesthesia were consistent with this approach, then we would require that *first*, an acceptable model for the relevant processes involved in consciousness is developed, *before* the output of any monitor can be interpreted. Simply monitoring the *activity* of neurones of the brain (e.g., using an electro-encephalogram, EEG-based monitor) would be akin only to recording an ECG, without knowing what the purpose of this activity is. Purpose or function is the proper focus for a macroscopic model.

[Fix, Rougier, and Alexandre \(2007\)](#) have argued that neuronal models can be described on (at least) three levels: a *microscopic* (molecules, channels or neurotransmitters at cells/synapses); a *mesoscopic* (how different specialised brain regions communicate with each other); and a *macroscopic* (concerned with the tasks, behaviours or responses of interest). This paper is primarily concerned with a *macroscopic* model for anaesthetically-relevant (un)consciousness. Amongst other things, macroscopic models need to be simplifications of reality (nothing is gained by creating a model as complex as reality). Models also need to be consistent with experimental results at meso- and microscopic level, and they should lead to specific predictions of system behaviour that are testable by experiment ([Dym, 2004](#)).

3. The nature of the anaesthetically-relevant consciousness to be modelled

The nature of consciousness is one of the fundamental questions of biology and there is a huge literature base encompassing philosophy, psychology, neuroscience and anaesthesia. Extensive discussion of the field is outside the scope of this article, but it is useful to draw upon those specific aspects identified as relevant to our ‘anaesthetist’s dilemma’.

For a patient to report awareness after an operation requires an explicit memory. For that memory to have been ingrained required, at the time of surgery, some perception and attention to events. Thus, these three elements – attention, perception and memory – are closely related. These are the focus of a large literature base and the discussion below is perhaps biased towards certain interpretations of these more than others, and is far from being comprehensive, but the lack of completeness or detail may thereby be compensated by a more cohesive argument more specifically focussed on issues concerning anaesthesia.

3.1. Some relevant concepts from philosophy

To adapt a notion perhaps first suggested by Chalmers ([Chalmers, 1996 and 2000](#)), there is a distinction between (1) an overall brain state yielding a *capacity for consciousness* (e.g., alert, tired, drunk, comatose, sedated, etc.; also termed examples of ‘intransitive consciousness’ which is a form of consciousness with no object, simply a state) and (2) a *specific content of thought*, such as to think of a tree vs a bus, or to think “*I am aware*”. The brain states might assigned shorthand labels α_1 , α_2 , α_n , etc., while the specific thoughts might be termed β_1 , β_2 , β_n , etc.

Furthermore, Hacker and colleagues (Bennett & Hacker, 2001; Hacker & Bennett, 2003; Hacker, Bennett, Dennett, & Searle, 2007) argue that one can only be 'conscious of something' (transitive consciousness); it is not possible to be conscious of nothing. It makes perfect sense to say that one is conscious/aware of a chair, or of the ticking of a clock, devoting attention to these things. However, it makes no sense to say "I am conscious but my mind is empty; I have no thoughts and am aware of nothing", because the first three words contradict the others in the sentence. (As a logical corollary of this: a mind devoid of all thought is indeed truly unconscious).

In other words, there seems to be philosophical consensus that any given brain state ($\alpha_1, \alpha_2 \dots \alpha_n$) is always associated with one or more thoughts ($\beta_1, \beta_2 \dots \beta_n$), albeit not deterministically so (i.e., being drunk, α_2 , does not necessarily lead to thinking of a tree, β_3 , etc.). In this way the state of consciousness at any given time might be denoted shorthand by a combination of the overarching brain state and all the specific thoughts. This state by definition changes with each specific combination of brain states and thoughts (e.g., $\alpha_1 + [\beta_3 + \beta_4]$ is different from $\alpha_2 + [\beta_3 + \beta_6]$, etc.). Generally, it can be supposed that brain states associated with lower conscious levels (e.g., coma) are associated with a paucity of thoughts (consistent perhaps with an overall reduced level of neuronal activity in these states).

To return to Hacker et al.'s emphasis, transitive consciousness relates to the linking of 'self' to 'environment'. Except perhaps in a meditative way, we are not conscious in an abstract way but normally through our relation to the world around us. The sensory system provides information about the environment, but the role of *perception* in consciousness is important, as something different from *sensation* (Gazzaniga, Heatherton, Halpern, & Heine, 2010). Pocket (1999) has emphasised these differences between 'raw' sensation and the emotional or intellectual response to these (using the example that a hypothetical aboriginal with no previous contact with civilisation would *perceive* an engine differently from an engineer, although their *sensations* of it would be identical). Perceptions are broader than specific thoughts or individual sensory inputs, encapsulating a much wider array of notions, but they cannot always be articulated (even to oneself) in a complete way that captures the entire experience (Shanks & St John, 1994). To underline this distinction, philosophers have used the question "what is it like to...X..." (where X might be "be a bat", or "walk along a beach in sunshine" or "be a postman", etc.; Hacker, 2002; Nagel, 1974). The point is that while we can accept that there is an entity of 'being a postman', and a postman could describe certain aspects of 'being a postman' there is no extent of articulation that conveys the complete experience.

These notions are also reflected in the 'higher order thought' theory of consciousness, which argues that we are only conscious of our sensations if or when we have thoughts about them. It is argued that higher order thought defines what a perception is, and makes the distinction between perception and sensation (Lau & Rosenthal, 2011).

Other philosophers have given the term 'qualia' to the idea that sensory input is translated to have a certain quality to it (the 'feel' of the experience), that underlies perception, which is the hallmark of consciousness (Hacker, 2002; Hardin, 1987; Ramachandran & Hirstein, 1997; Wright, 2008). Chalmers has extended this idea to conceive of imaginary 'zombies' who are identical to us in every way, with the same sensory systems and respond in the same manner to stimuli, but they lack any capacity to experience or feel what they sense (i.e., they lack qualia; Chalmers, 1996; Chalmers, 2000; Harnad, 1995). For Chalmers, to be conscious (of something) is to have qualia (related to that thing). Noting that the zombie is a creature that behaves and responds as if conscious when in fact unconscious, Mashour & La Rock have noted that the inverse of this condition would be a being that appears unconscious but is in fact conscious: this would be an accidentally awake, but paralysed patient (Mashour & LaRock, 2008). Incidentally, they further argue (as I argued above in Section 2.1) that any hypothetical monitor that enabled us to identify *consciousness* in the latter would, logically, have properties that also enabled us to identify *unconsciousness* in the zombies.

To summarise the relevant ideas from philosophy about consciousness: (a) brain states yield a capacity for thought; (b) specific 'thoughts' are distinct from the brain state; (c) 'attention' is an important component of transitive consciousness; (d) 'sensation' is distinct from perception, with higher order thought (thoughts directed to sensations) putatively defining perception; (e) perceptions lead to qualia, the 'feel' of a sensation, regarded by some as the hallmark of what it is to be 'conscious'.

3.2. Relevant insights from neuroscience, concordant with philosophy

Some philosophers therefore argue that lacking qualia, or uncoupling perception from sensory input (akin to Chalmers' zombies), is synonymous with being unconscious. This important distinction between perception and sensation is also well recognised in neuroscience. Sensation is the transmission of sensory information to the brain; perception refers to how that information is interpreted. For example, the distinction between nociception (the sensory input) and pain (the perception) is well established (Lee & Tracey, 2013). Surgical lesions performed for intractable pain syndromes can reduce emotional or motivational aspects of 'pain' but leave 'nociception' intact (Wilkinson, Davidson, & Davidson, 1999). The notion is emerging that pain as a perception arises when nociceptive input is prioritised over other sensory inputs that are competing for attention for conscious awareness within the brain (Tallon-Baudry, 2011), a model which is consistent with the 'global workspace theory' (Baars, Ramsøy, & Laureys, 2003, discussed further below). Furthermore, treatment modalities are being developed based on modulating the perception of pain by teaching patients to reinterpret the significance of adverse events to reduce negative emotional responses (a phenomenon that involves the prefrontal cortex; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008; Wiech et al., 2006).

This approach has similarities with several ideas with origins in philosophy. One is (Hilgard's (1974), Hilgard's (1977) neodissociation theory that characterises the mind as a set of separate components that monitor, organise, and control

mental functioning in different domains. The 'executive ego' is a central cognitive structure which serves as the ultimate endpoint for all inputs and for the outputs, and is the basis for the 'experience of awareness'; when inputs reach the executive ego, the person becomes aware of them. In such a 'Cartesian theatre', perceptions and thoughts are as if presented to a 'conscious observer', the executive. This has been challenged by Dennett's (1991) 'multiple drafts' model, where mental content is produced in parallel, and consciousness is that content which has the biggest impact. However, Dennett (1978) has also explicitly discussed pain and proposed a model consisting of layers of increasing complexity, from nociceptors to a 'control' area that incorporates 'reasoning', 'belief' and 'desire'. Dennett argues that in this model, some analgesics might produce a state in which (his words) "*pain continues and continues to be pain, though [patients] no longer mind it*". Similarly, within the scheme of neodissociation, one potential analgesic mechanism is to uncouple the substructure that governs the processing of painful stimulation and what Hilgard terms the 'executive ego'. The intensity and location of the painful stimulus is still processed, and even reflex tachycardia or lacrimation, etc., might result, but because none of this reaches the executive ego, the person has no conscious awareness of pain (Kihlstrom, 1992).

Baars's Global Workspace Theory proposes that consciousness arises from highly co-ordinated, parallel (simultaneous) separate activities in the brain, each competing for prominence at any given time (Baars & Franklin, 2003; Baars et al., 2003). What we are conscious of at any moment is which of these processes predominates at that time, and our attention can switch from one to another. This has been likened to a competition on a stage, where the 'spotlight of consciousness' can fall upon different 'performers'; the winner is the one whose message is then momentarily broadcast to all others. In this scheme, pain can be modelled as the relevant pain centres taking over this communications infrastructure to send out alarm signals, which then override other information. The dissociation of pain might be modelled in this scheme as a weakening or failure of these pain centres' ability to do this.

Although these philosophical ideas compete as explanations of consciousness, they serve equally well in describing how pain and nociception can be dissociated in a way that is consistent with the neuroscience.

What applies to pain should logically apply to other sensory modalities (e.g., touch, auditory, etc.) and for each of these, sensation could also be uncoupled from perception. This is well established in the visual neurosciences, perhaps most entertainingly by the use and science of optical illusions. Fig. 2A shows the Necker cube, which as a *sensory input* always remains the same two-dimensional image, but which can be volitionally *perceived* as three-dimensional in two different ways (either with the lower left 'face' at the front, or the upper right 'face' at the front). This is reflected in specific neuronal activities that are recordable when perceiving the cube in one form vs another (Gaetz, Weinberg, Rzepoluck, & Jantzen, 1998). There are, however, some illusions where the sensory input is constant yet we have an experience that is unshakeable. Fig. 2B shows the Jastrow illusion. Here, the two figures are of identical size yet we always perceive the upper image to be smaller, *even when we know the truth* (Pick & Pierce, 1993). Dissociation of sensation and perception also arises during the phenomenon of binocular rivalry. When different images are presented to each eye, we do not see a blend of the two images; rather – not under our volitional control – the perception alternates from only one image to only the other (Blake & Logothetis, 2002).

If perception and sensation are distinct and can be separated in these ways, the question arises as to whether any associated neuronal activities could be separately recorded as a basis for monitoring. Theoretically, one monitor might be designed to detect the transmission of the relevant sensory information to the brain, another to detect its translation (or not) as a perceptual experience.

To describe normal consciousness more completely, a further step is necessary beyond considering the separate perceptual experiences of individual sensations. This involves the idea of a 'unity of consciousness'. At any given time, we have very many sensory inputs that each lead to perceptions and thoughts, yet we combine all of these into a single experience of 'consciousness'. As Revonsuo and Newman (1999) have observed, we are able to see a blue circle and a red square respectively as single entities, associating each colour with each shape, even though the neurones involved in detecting colour versus shape are different, and how these otherwise independent neuronal activities are combined create a single perception is not fully understood (David, McMahon, & Olson, 2009). Understanding the basis of our ability to combine apparently disparate sensations into a single experience has been termed in philosophy the 'cognitive binding problem'.

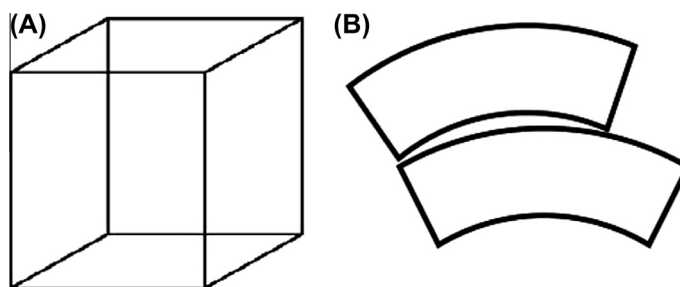


Fig. 2. Optical illusions. A: Necker cube. B: Jastrow illusion.

In summary neuroscience research (a) confirms the distinction, often made in several philosophical ideas, between sensation and perception; (b) reflects the appreciation that perceptions are bound into a coherent whole to create a single conscious experience.

Whereas much of this philosophical and neuroscientific research has been directed to help create a macroscopic understanding of *consciousness*, we are seeking in this paper an explanation for its reverse: *unconsciousness*. If the latter can be achieved by disrupting the processes that underpin the former, it follows that consciousness will be impaired by three mechanisms: namely, if

- (a) sensation is lost, and/or
- (b) perception is uncoupled from sensation, and/or
- (c) the binding of perceptions is impaired.

Perception therefore sits centrally between sensations and consequent processes such as binding.

3.3. *The relevant psychology of memory*

Explicit memory is the intentional recovery of previous experience and as to how the memory is formed, almost all models acknowledge that we cannot consciously attend to all of our sensory input at the same time (Broadbent, 1958; Musen & Treisman, 1990). Therefore, this limited capacity (bottleneck) for paying attention raises the problem of understanding how material is selected to pass through the bottleneck for later recall. Using experimental paradigms of dichotic listening, in which different messages are played to the two ears, Broadbent developed the concept of a sensory buffer, receiving all sensory inputs (Broadbent, 1958). At any given time, just one of these inputs appears selected on the basis of its 'physical' characteristics (e.g., for sound this might be its volume or tone) rather than on its content or meaning. One can only pay attention to the message played to one ear at a time, but it is possible to flip attention from one ear to another. This is also termed 'binaural rivalry' (rather like binocular rivalry) and argued also to provide insights into the importance of perception over sensation (Brancucci & Tommasi, 2011). Semantic processing or decoding the meaning of the information, appears to take place later in the putative pathway after the sensory buffer. The information that remains within or fails to pass the buffer decays rapidly or is attenuated (Treisman, 1964) and so lost/forgotten.

Explicit memory appears to involve four main processes (Atkinson & Shiffrin, 1968; Deutsch, 1969) encoding, storage, consolidation and recall. Encoding is the first step allowing the perceived item of interest to be converted into a form that can be stored (somewhere) within the brain. Incompletely understood, encoding can relate to the individual senses (e.g., visual, auditory, tactile encoding) but also importantly relate to the overall meaning of the information (semantic encoding). Memory thus can be 'associative' (i.e., information is remembered better if associated with previously acquired knowledge or if personally meaningful). Information that is difficult to understand is often poorly remembered, or recalled in distorted forms. A common test is to use a list of words like "thread", "sewing", "haystack", "sharp", "syringe", "pierce", "injection" and "knitting": most people incorrectly remember the word "needle" through this process of association.

Once encoded and stored, consolidation is a process of strengthening memory through repeated recall and reflection, perhaps prompted by repeated associations with new experiences. This can change the initial memory and sometimes, false memories can be created. These last are more likely when the cue contains negative emotional content, coupled with a weak true memory. Once integrated into a memory, false information can be readily perpetuated (Gallo, Foster, & Johnson, 2009; Schiller & Phelps, 2011; Simons & Spiers, 2003; Squire & Wixted, 2011).

The two main methods of later accessing memory are recognition and recall. Recognition is the relatively simple process of concluding whether the event or entity has been encountered before and involves rapid, unconscious association (e.g. recognising a face, or instant true/false recognitions relating to facts). Recall is a two-step process in which the search and retrieval of candidate items from memory is followed by a 'familiarity decision' where the correct candidate is chosen. Thus, recall involves actively reconstructing information. In 'free recall', a person is given a list of items to remember and then is asked to recall them in any order. A primacy effect may arise, wherein items presented at the beginning of the list are recalled earlier and more often. Alternatively, a recency effect may arise, when the items presented last are better recalled. The contiguity effect describes the tendency for items from neighbouring positions in the list to be recalled successively. In 'cued recall' a person is given a list of items to remember and then prompted with cues. This often prompts recall of items not freely recalled. 'Serial recall' concerns the memory of events in order, whether chronological events or the order of words in a sentence in a way that makes sense.

Franklin, Baars, Ramamurthy, and Ventura (2005) have illustrated this complex construct of human memory in diagrammatic form (Fig. 3). Their model reflects the generally accepted view that perceptions, rather than sensations per se, lead to explicit memories. They define *sensory memory* as that which holds incoming sensory data in relatively unprocessed form and propose that this has the fastest decay rate of all the memory types, measured in hundredths of milliseconds. By contrast they define *perceptual memory* as that for individuals, categories and their relationships enabling recognition and also the feel (qualia) of, say, food, faces or events.

Examples demonstrating the importance of perception (rather than sensation per se) to memory include the conditions of acquired cerebral achromatopsia and prosopagnosia. In the former, sufferers lose the ability to perceive colours (usually due to traumatic brain injury or tumour) and report also forgetting what colours 'look or feel like'; loss of qualia. Loss of

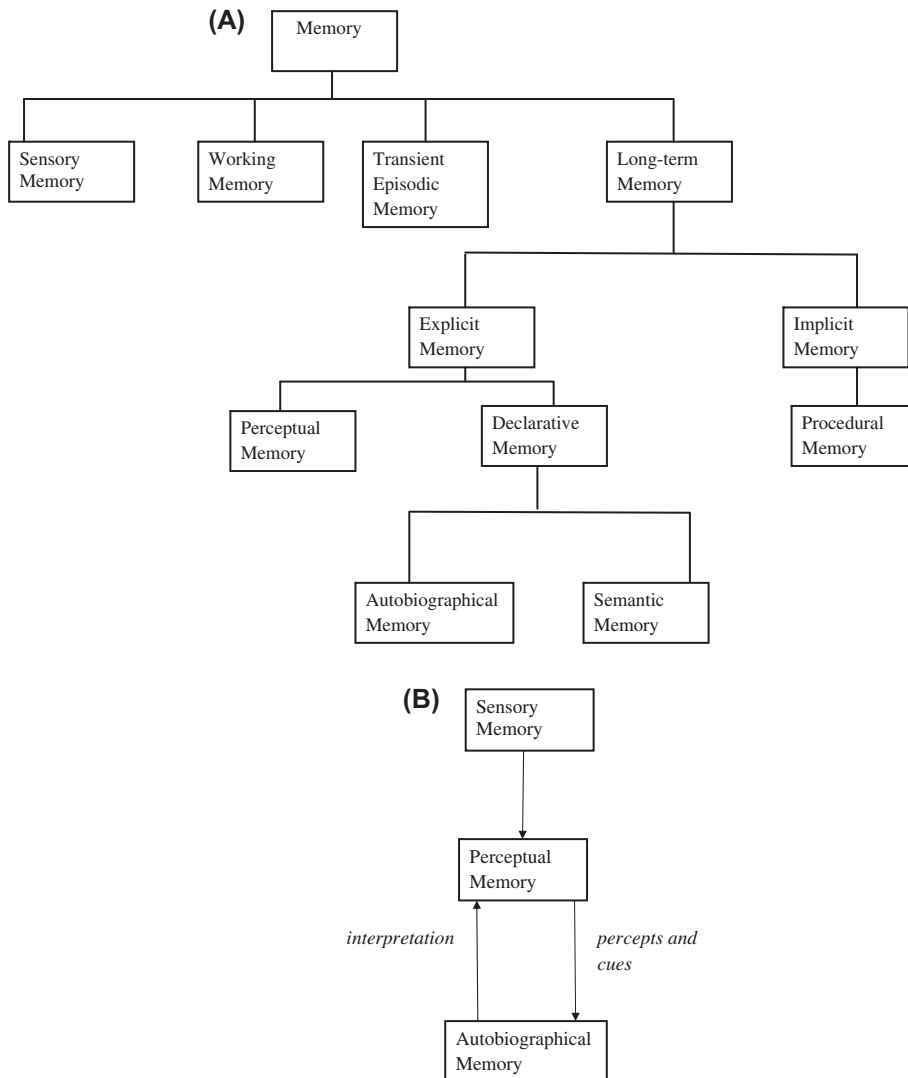


Fig. 3. (A) Subdivisions of memory (after Franklin et al., 2005). *Working memory* holds sensory data, both endogenous (e.g., visual images and inner speech) and exogenous (e.g., sensory) and has a decay rate of seconds. A conscious event is stored in *transient episodic memory* by a broadcast from a global workspace (Baars et al., 2003); conscious contents can only be encoded and consolidated in long-term declarative memory via transient episodic memory. *Explicit memories* are conscious and subdivided into *perceptual* (discussed in text) and *declarative* (memory for facts/events which decays slowly, and inversely with the strength of memory traces; the stronger the trace, the less the decay). It consists of *autobiographical memory* (for features of a particular time or place) and *semantic memories* (memories of fact or belief typically lacking a particular source with a time and place of acquisition). *Implicit memories* are unconscious and *procedural* (memory for motor skills). While (A) shows the hierarchical relationships (i.e., inter-relationships not shown), (B) illustrates the sequential relationships and interactions for one small part of the model. For example, sensory memory helps create perceptual memory, which via cues and percepts forms autobiographical memory, which in turn via interpretation shapes perceptual memory.

perception of colour appears to lead to loss of memory for colour, even though there is no defect in their sensory system for colour or overall memory impairment (Bouvier & Engel, 2006). In prosopagnosia, visual sensory input is normal as is the ability to perceive that a given image is, say, a face. What is specifically impaired is the ability to perceive whose face it is and hence no memory trace can be formed to link the name to the face (Mesulam, 1998). Ogden (1993) describes a patient with both achromatopsia and prosopagnosia in whom long term visual memory (but not memory in general) was also severely impaired.

Implicit memory, quite different from explicit memory, can help in the performance of tasks without any conscious awareness of previous experience. There may be the 'illusion of truth', wherein subjects are more likely to recognise statements that they have already heard, without conscious recognition. Implicit memories also include information learned by repetition subconsciously, such as riding a bicycle.

One of many controversies in the field of memory research is whether information about experience that is inaccessible for years can be later recovered (Patihis, Ho, Tingen, Lilienfeld, & Loftus, 2013). The argument is that information for

traumatic events is suppressed (and in this way ‘implicit’) but can be recovered and made explicit through various forms of therapy (Freyd, 1994; Loftus, 1993).

However, information that was trivial or peripheral to one’s attention at the time is also suppressed and less likely consolidated as a memory. A candidate at an important interview focussing at the time only on the interviewers, will unlikely recall a plant in the corner of the room. There do not seem to be any significant reports of the recoverability of such trivial information. This presents a problem for interpretation: a patient’s *failure* to recall an event does not help us identify whether that event was trivial or traumatic. However, making an event appear trivial makes it less likely to be recalled later and this is something which might be used for therapeutic advantage. Anaesthetics and related drugs do this and can influence memory *directly* through actions on the brain processes involved, such as actions on the limbic system (Evans & Viola-McCabe, 1996). Or *indirectly*, they might create a brain state in which an event normally commanding attention becomes no longer compelling.

Many questions remain unanswered. If a patient becomes accidentally aware and experiences surgery, but cannot later explicitly recall anything (e.g., because of direct amnesic effects of drugs), is this detrimental? Or is it detrimental if implicit memory for events is established by later experiment, if the patient at the time did not actually perceive the experience? Is there in fact any evidence for implicit memory during anaesthesia? Do we need to be ‘more aware’ to form an explicit memory than an implicit one? All these can be investigated using the paradigm of anaesthesia (Andrade & Deeprose, 2007; Cork, Heaton, Campbell, & Kihlstrom, 1996; Deeprose & Andrade, 2006; Lubke & Sebel, 2000; MacRae, Thorp, & Millar, 1998).

Emotion is also interlinked with attention and memory such that emotion at the time of an experience can influence memory of it (and *vice versa*; our memory can influence our emotions; Sharot, Delgado, & Phelps, 2004). The ‘affective primacy hypothesis’ suggests that emotional processing can persist even when the stimuli are so faint or brief that there is no cognitive perception of them (Kunst-Wilson & Zajonc, 1980). The theory has its critics (Rachman, 1981) and the relevance of this theory for anaesthesia may be limited as most experimental work uses repeated subliminal exposure to readily identifiable stimuli (which in fact can also yield a favourable, positive emotional reaction). In contrast, the surgical setting involves a single (one-time) exposure to stimuli which can be at the time difficult to interpret (e.g., the unrecognisable surroundings of a surgical operating room). More recently, it has been argued that the primacy of affect is only one possible outcome, and not inevitable (Lai, Hagoort, & Casasanto, 2012). Whether it occurs or not depends on the context in which the original sub-cognitive stimulus was presented. Studies of the affective primacy hypothesis employ experimental models where the stimulus is weak, rather than where cognition is impaired (e.g., by drugs). In the light of work suggesting that implicit memory is retained even during general anaesthesia or sedation (Andrade & Deeprose, 2007; Deeprose & Andrade, 2006), it would be important to assess the degree to which (if at all) primacy of affect occurs when cognitive processes are abolished or impaired by drugs.

After apparently adequate general anaesthesia, studies using the Brice questionnaire (which directly asks patients if they recalled anything between ‘going to sleep’ and ‘waking up’) consistently elicit a surprisingly high positive response of ~1:500, but the majority of experiences are neutral, almost trivial experiences (Avidan et al., 2008; Avidan et al., 2011; Myles, Leslie, McNeil, Forbes, & Chan, 2004; Sandin, Enlund, Samuelsson, & Lennmarken, 2000; Sebel et al., 2004). This appears to be an example of explicit memory of experiences, recalled by the cue of the questions, generally regarded by patients as unimportant. Some patients clearly regard the episode of awareness as so trivial that they volitionally delay reporting of it, even when educated to do so as part of clinical trials (Villafranca et al., 2013).

In summary: (a) perception is key to formation of explicit memory and (b) explicit and implicit memories need inclusion in any model of anaesthetically-relevant (un)consciousness in a way that reflects the experimental observations.

3.4. *The anaesthetic consequences of the idea of consciousness being composed of multiple elements*

An important, anaesthetically-relevant conclusion to draw from these philosophical and neuroscientific considerations is that consciousness should not generally be regarded as a single, indivisible, all-or-nothing entity, but rather composed of several contributory elements such as sensations, perceptions, thoughts, memories, and emotions.

This is relevant for anaesthesia, because we can then ask the pragmatic questions: Do *all* these components of consciousness need to be eliminated (i.e., complete mental oblivion) to achieve a state in which surgery can satisfactorily proceed? Or can we facilitate surgery by anaesthesia when only *some* of these are eliminated (i.e., a partial consciousness)? For all drugs it is better to achieve no more than the minimum effect required, to avoid dose-related side-effects. It is not necessarily clear what patients expect. Antognini and Carstens (2002) observed that historically before anaesthetics were discovered, patients could not have had any *a priori* expectation of drug-induced mental oblivion, but their hope was simply to experience painless surgery (i.e., they may have normally expected to experience *something*, so long as this was not pain). This question of prior expectation warrants formal cultural and historical research.

In addition to surgically-induced nociception/pain and touch, there are many other potential sensations arising during the perioperative period that are *desirable* to avoid, such as nausea (vomiting), cold (shivering), headache, thirst, dizziness, breathlessness, etc. As sensations these are all by definition potential contributors to a satisfactory (or not) outcome, but eliminating all of these completely would not necessarily be regarded as *essential* to what we conventionally understand by adequate general anaesthesia. Equally there are many higher-order aspects of consciousness discussed in philosophy such as ideas of self-confidence, a moral or ethical code, religious or non-religious beliefs, likes and dislikes, etc. None of these

would seem relevant to our discussions and could all remain theoretically intact in an abstract sense without diminishing the quality of anaesthesia.

Traditionally, the essential requirements of general anaesthesia have been defined as a triad – but perhaps more accurately as a quartet – of: *immobility* (which is required for surgery), *analgesia* (which can be achieved alone via regional or local anaesthesia without impairing the conscious level), *amnesia* (which in large part is an inevitable effect of most if not all anaesthetic agents) and *hypnosis* (this last word loosely used to denote unconsciousness and sometimes used synonymously with ‘narcosis’; Urban & Bleckwenn, 2002). The ‘anaesthetic quartet’ can be achieved using a single agent (perhaps a historical technique) but the high doses required mean it is advantageous to employ several drugs in a more targeted way (the concept of ‘balanced anaesthesia’).

Moreover, it is already widely accepted that adequate general anaesthesia may not require achieving the whole quartet in full measure. Sometimes analgesia might predominate, at other times amnesia, and so on. Therefore, manipulating each of these in different ways could potentially influence the (un)conscious state. Further, each of the elements of this quartet themselves consist of (not all as yet not fully elucidated) more basic components. The implication of the quartet that anaesthesia can result in different ways from different balances of several elemental components is consistent with the notions derived from philosophy, neuroscience and psychology (discussed above) that consciousness itself has several elemental components. To ask what is the minimally acceptable state for anaesthesia is therefore akin to asking which combination(s) of the quartet are acceptable and in what proportions.

4. Coupling perception and sensory input: a basis for an anaesthetically-relevant model of consciousness

It is clear from the discussion above that perception (distinct from sensation) is key to achieving a ‘feel’ for sensation (the qualia). In turn, qualia are central to emotional experience. Perception is required for explicit memory formation. The step between sensation and perception appears fundamental to creating a sense of ‘person’ in relation to the environment.

This central notion of sensation–perception coupling can be incorporated into a macroscopic, functional model of consciousness (Fig. 4A). This model does not presume that any particular brain structure is associated with the functions displayed; it is a macroscopic, not a mesoscopic model. The model incorporates the distinction between sensory input and perception; the central role of ‘thought’ (as either spontaneous or stimulus-evoked; Fig. 4B), the role of explicit memory, and also the four elements of the ‘anaesthetic quartet’. The model is of course highly restricted to explaining the minimal requirements for satisfactory anaesthesia, and has limited application in a wider philosophical or psychological context (but remains consistent with many philosophical and psychological ideas). The elements of the model are intentional simplifications and could themselves be subdivided. For example, element A refers strictly to *all* the stimuli during surgery (nociception, touch, noise, etc.), and element B includes *all* the sensory modalities for these stimuli. In a more complex version of the model, these could be separately represented. Element C, perceptual experience, represents *both* the perception of each individual sensation *and* the cognitive binding (if such process exists) of these into a single experience (i.e., in this context, the realisation ‘I am undergoing surgery’). Adjuvant drugs commonly used in anaesthesia are readily factored into the model (Fig. 4B).

The main hypothesis is that the *minimum* requirement for satisfactory general anaesthesia is an uncoupling of perceptual experience from sensory input. The two model elements requiring elimination for this minimally adequate state are at least: (1) the ‘perceptual experience’ (element C) and (2) ‘stimulus-evoked thoughts’ (element H; Fig. 4C). Eliminating these will (according to model) reduce attention to the surgical process and so the formation of explicit memories. With use of adjuvant drugs (Fig. 4B), a considerable proportion of the structures underpinning consciousness can be disrupted.

The intactness of remaining elements is proposed not to impair satisfactory anaesthesia. These include reflex movements (Wiech et al., 2006) and thoughts unrelated to the surgical process (i.e., element G and steps I → D in Fig. 4 are intact). If dreaming is regarded as a form of thought unrelated to the real world, then it is well established that dreaming can occur during anaesthesia (Mashour, 2011; Sanders, Tononi, Laureys, et al., 2012) and, although some agents such as ketamine appear to predispose to nightmares (Blagrove, Morgan, Curran, Bromley, & Brandner, 2009), dreaming per se does not impair the quality or experience of anaesthesia and indeed can enhance it (Leslie et al., 2009). The implicit memory pathway (perhaps incorporating primacy of affect) might persist in minimally adequate anaesthesia, as shown, but the degree to which this exists and if it is detrimental is still under debate (hence the consequences of these are modelled as an unknown; Fig. 4).

4.1. Dysanaesthesia: analogy and evidence

I use the term ‘dysanaesthesia’ to describe this hypothetical drug-induced state in which perception and sensory inputs are uncoupled (Pandit, 2013). It is naturally difficult to predict with precision how this uncoupling might be later described by a patient but perceptual loss might result in some or all of: (a) a loss of ‘qualia’ to the sensations; (b) an impaired ability to integrate information and ascribe it meaning; (c) impairment of explicit memory; (d) where there is recall, the memory for events may be neutral rather than adverse; (e) tendency to regard events as incidental or neutral that would otherwise normally be a focus for attention; (f) a personal detachment from events. These elements might occur to different degrees in different patients. For example, one patient might be aware of (and recall clearly) the operating room lights but not recognise them as part of the surgical environment. Another might recognise the lights, and even have felt tactile sensations during surgery, but feel detached from them all. Dysanaesthesia is therefore a term that encompasses a range of possible mental

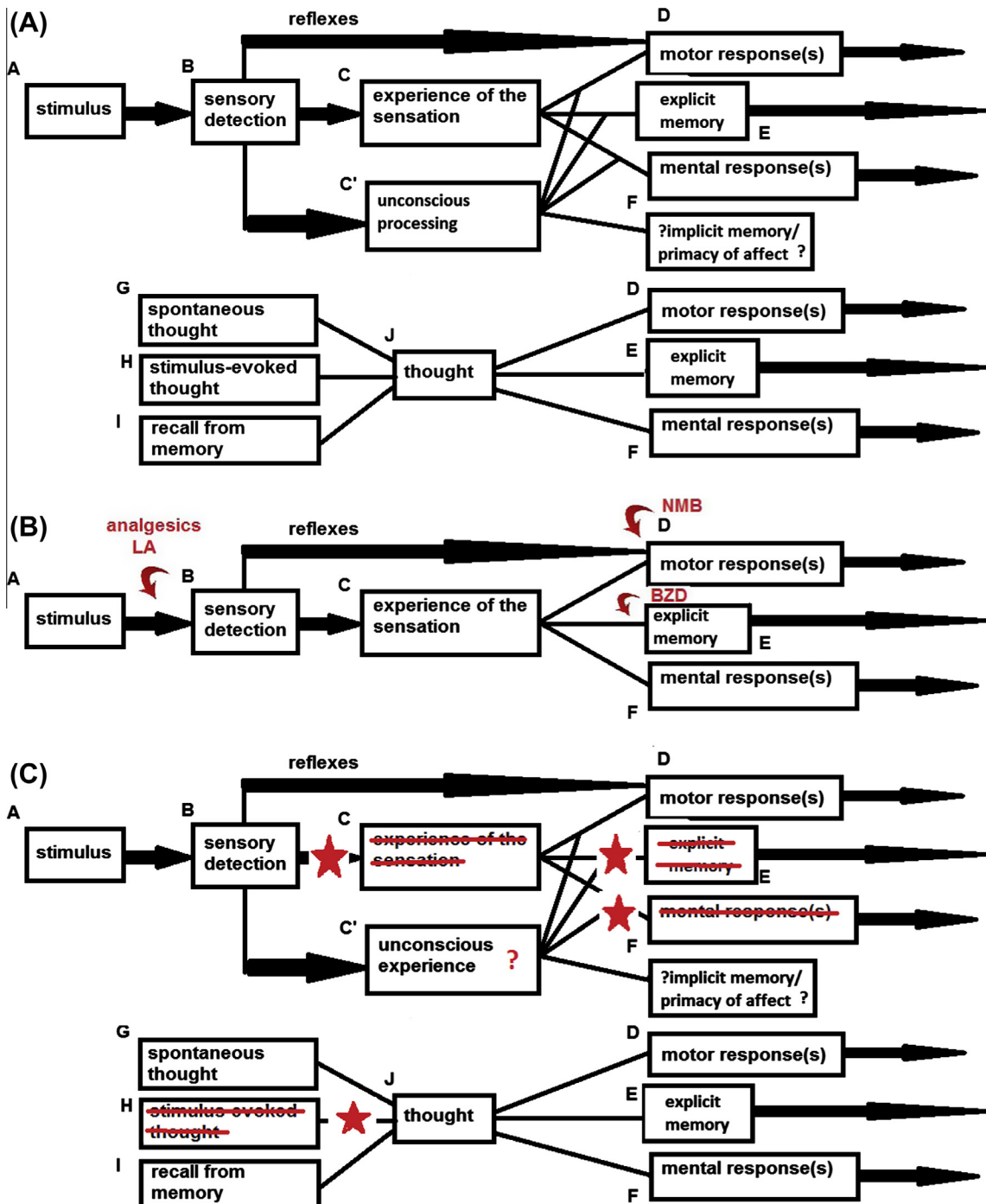


Fig. 4. (A) An anaesthetically-relevant model for consciousness. Each of the elements A–J represents an ingredient of the conscious process. The upper panel represents the sequence of events consequent upon a stimulus (in this context surgery). This would lead to reflex and/or volitional motor responses, and thoughts and explicit memories. The model does not imply that each element A–J is located in any specific brain region. Each of the elements A–J may be deconstructed into smaller parts, and the sequential nature represented in the diagram does not imply fixed or equivalent time-delays between the processes described. The central theme is the distinction of sensory input from perceptual experience. Unconscious processing is incorporated, but its role (e.g., in implicit memories or primacy of affect) is modelled as unclear. In the lower panel is displayed the general form for 'thought' as being spontaneous, stimulus- or memory-evoked, and leading to some of the responses described in the upper panel. (B) Example of the sites of actions of analgesics and local anaesthetics (LA), neuromuscular blockade (NMB) and benzodiazepines (BZD) in attenuating activity in elements B, D and E, respectively. (C) The minimum functions which need to be (reversibly) eliminated to achieve satisfactory general anaesthesia (the red star indicates uncoupling of the processes). It is not clear that unconscious processing also needs to be abolished, although it would seem desirable to do so.

states arising from the consequences of sensation–perception uncoupling. Within this continuous range the really important step, clinically, is the point at which emotional uncoupling occurs in the face of persistent sensation from the surgical site. This may not be at the same anaesthetic dose across all patients, because individual patients respond differently. In dysanaesthesia there is a greater degree of cognitive impairment than when awake, but also greater cognitive function than complete oblivion. This reflects the notion of loss of consciousness during anaesthesia being a graded phenomenon rather than all-or-nothing.

These discussions highlight the dual meaning of the term ‘anaesthesia’. In a restricted sense, ‘general anaesthesia’ is used to refer to the specific state of drug-induced, complete mental oblivion. In this usage, anything less is not anaesthesia: a case in which the patient unexpectedly recalls events during surgery, regardless of whether acceptable to the patient or not, must be regarded as ‘accidental awareness’. However in a pragmatic sense ‘anaesthesia’ refers to *any* perceptual state acceptable to the patient, which allows surgery to proceed. This might include cases where the patient became unexpectedly aware of surgery but was not troubled by it; this is ‘acceptable awareness’ and so still a form of ‘anaesthesia’ (i.e., dysanaesthesia). A very common technique to facilitate surgery consists of regional anaesthesia (e.g., spinal or epidural anaesthesia to eliminate pain). Without anxiolytic drugs this is closer to local anaesthesia as it is primarily abolishing sensation (i.e., any consequent lack of perception is because there is no sensation). Anxiolytics like midazolam or remifentanyl may be required if the regional anaesthesia is inadequate and there is partial sensory input. These can be regarded as modulating the link between sensation and perception, and so the differences between the brain state during this technique and dysanaesthesia are relatively small. The only differences are that the regional-sedation technique is intended by design and involves no direct muscular paralysis; dysanaesthesia is unintentional and often involves neuromuscular blocking drugs.

Importantly, the concept of dysanaesthesia uniquely explains certain observations during the isolated forearm technique (IFT). In IFT patients, one arm is vascularly-isolated using a cuff before administration of neuromuscular blockade to the contralateral arm. Therefore, patients retain capacity for movement in this unparalysed arm. Remarkably, during otherwise apparently adequate anaesthesia, about one-third of patients move their unparalysed arm/hand to command. Even more surprisingly, there are few reports of any spontaneous goal-directed movement to surgery during IFT (Russell, 2013a; Russell, 2013b). Some IFT patients may be fully awake (probably the minority), as their responses are consistent: they move *both* spontaneously in response to surgery, *and* they respond to verbal command. Therefore, the IFT is a useful monitor of intraoperative awareness. However, the behaviour of those patients (the majority) with *inconsistent* responses is much more difficult to interpret: these patients move only to verbal command, but not spontaneously to the surgery. Dysanaesthesia offers the explanation that these patients’ perceptions are uncoupled from many sensations relating to touch or pain of surgery, but remain coupled to other sensations such as vocal command (Pandit, 2013). Thus, Russell describes some IFT patients who *chose* not to respond to command as the anaesthetist’s voice was interrupting their thoughts: they knew perfectly well that they were undergoing surgery at the time but regarded this as trivial and were having unrelated thoughts (Russell, 2013c; Russell & Wang, 2014).

All analogies have shortcomings but one is to imagine that consciousness for events of surgery is the very ability to interpret the picture on a jigsaw puzzle. If you can interpret what the picture is, then you are (in simple, binary terms) ‘conscious’ but if you cannot then you are satisfactorily ‘unconscious’. Increasing the dose of anaesthetic (in practice an effect compounded by analgesics and local anaesthetics) progressively removes pieces from this puzzle. At first, the image is disrupted but the ability to recognise the picture (i.e., consciousness) is little impaired. But at some point, the picture is no longer recognisable. This is the critical point of uncoupling of perception from sensation. The remaining pieces are still seen (i.e., sensory inputs remain) but they carry little or no meaning (qualia lost; information integration critically impaired). From this point on, the jigsaw no longer compels attention (or, takes ever greater mental effort to interpret), and as thoughts wander to other unrelated matters, the information about the jigsaw may not be consolidated as an explicit memory. If it is later asked: “Were you aware of a picture (i.e., of surgery)?”, the technically correct answer (if the patient retains sufficient recall) is “yes”, because some jigsaw pieces remained. But it is unlikely that the individual would spontaneously report “I saw a picture of X”, as this idea never became sufficiently important to warrant spontaneous report. To refer back to the example of the interview candidate used above: even those candidates who recall it will unlikely spontaneously talk of the plant in the corner of the room, but they might acknowledge this if specifically asked.

If the cases of dysanaesthesia can be regarded as those patients responding positively to the Brice interview and/or those who respond to IFT, then the state is indeed broadly acceptable to patients. Aceto et al. (2013) have reported in a systematic review that overall rates of post-traumatic stress disorder after Brice-positive response are low (~15%; 28 of 189), which agrees with an estimate of ~13% by Mashour (2010). This appears comparable with post-traumatic stress disorder rates after major surgery (without awareness) of ~12% (Leslie, Chan, Myles, Forbes, & McCulloch, 2010).

In contrast to the relatively high rates of ‘awareness’ obtained with Brice interview (~1:500), there is a very low incidence of *spontaneous* reporting, of ~1:15,000, one-third of which are adverse experiences involving pain or distress (Pandit et al., 2013a and 2013b). Relatively fewer of these spontaneous reports are dysanaesthesia, but more commonly represent true awareness with recall, where perception remained coupled to sensory input and there was consequently a greater chance of memory for the event.

The idea that perception can be dissociated from sensation during anaesthesia is not new and has in part been long described for a technique known as ‘neuroleptic anaesthesia’ (Hopkin, 1963), which consists of a technique based on phenothiazines and opiates, with nitrous oxide (Morgan, Lumley, & Gillies, 1974). Collier (1972) reported many patients receiving subanaesthetic ketamine or nitrous oxide/oxygen described experiences (not dreams) of floating above their own bodies,

and altered visual, colour and auditory perception. It is not yet known if such experiences commonly arise when more mainstream anaesthetic drugs (e.g., halogenated ethers, propofol or barbiturates) are used, or if they are acceptable to patients. However, a large national audit of patient experiences is underway in the United Kingdom (the 5th National Audit Project, NAP5; http://www.nationalauditprojects.org.uk/NAP5_home; Cook & Pandit, 2012; Pandit, Cook, Jonker, & O'Sullivan, 2013a and b; Pandit & Cook, 2013). If NAP5 reveals patient reports of awareness consistent with the descriptions predicted for dyanaesthesia, this will lend considerable support to the uncoupling hypothesis and the model in Fig. 4.

5. Alternative notions of functional disintegration by anaesthesia

5.1. Cognitive unbinding

Philosophers have long sought solutions to the 'cognitive binding problem' and Mashour has elegantly summarised the main proposals as being (a) binding by synchrony, where activity of spatially separated cognitive processes in the brain are correlated in time, so as to unify the different features of an object into a single representation; (b) and binding by convergence, where sensory processing from diverse brain regions is synthesised by another, higher-order group of neurones which then generate the 'binding' (Mashour, 2004; Mashour & Alkire, 2013). Perhaps, the former underpins binding of sensory perceptions in *time*, while the latter assists their binding in a conceptual *space*. In both interpretations, a capacity to synthesise information from different brain regions by way of information integration is required for a system to be 'conscious'. In turn, this depends upon the degree of functional connections between neurones: the greater are the potential connections, the greater is the capacity for consciousness. This approach has similarities with the Integrated Information Theory (Tononi, 2004) and the Global Workspace Theory (Baars & Franklin, 2003; Baars et al., 2003; Dehaene & Naccache, 2001), both of which seek to explain how consciousness appears to us as a unified whole.

In this scheme, anaesthesia can induce unconsciousness by lessening the relevant connectivities and so 'unbinding' the cognitive processes. If this occurs, then independent cognitive processes should continue unabated during anaesthesia, but are not combined meaningfully to lead to a single conscious experience. This appears supported by several findings from neuroimaging studies showing that primary sensory networks are maintained during anaesthesia, but multimodal association areas and internetwork connectivity are differentially influenced by anaesthesia (especially, the anterior-to-posterior feedback connectivity is disrupted; Mashour & Alkire, 2013; Sanders et al., 2012). Mashour thus elegantly made a link between philosophy and neuroscience. His suggestion of anaesthesia being a process of unbinding might be interpreted as consistent with the notion of perception–sensation uncoupling (Fig. 4). There are two important distinctions, however.

The first is that Mashour's idea of unbinding seeks to explain the processes during *conventional general anaesthesia*; perception–sensation uncoupling seeks only to illustrate the conditions required for *minimally satisfactory anaesthesia* (dysanaesthesia).

The second is that whereas unbinding in Mashour's sense is a disruption of the process of unifying sensory inputs into single coherence, in Fig. 4 the relevant factor is the dissociation of perception from sensory inputs, even if what remains is coherent.

It would be relevant to analyse these difference in theories in terms of the modelling of Information Integration Theory (mentioned above). Tononi (2004) has created a mathematical model of the capacity for information integration (Φ), whose numerical value is increased in systems maintaining consciousness and decreased in those that do not. It would be important to assess how an uncoupling of perception and sensation might be predicted in a quantitative way to influence the capacity for information integration and, if possible, to compare with the quantitative predictions of an unbinding theory.

5.2. Disconnectedness

In a different approach, Sanders et al. (2012) made a distinction between three distinct elements: 'consciousness', 'responsiveness' and 'connectedness'. This last is a state in which the information obtained from sensations is interpreted by the brain in the context of (i.e., connected to) the external world. (Disconnectedness is the inability to do this). Explicitly, Sanders et al. regard dreaming as 'disconnected consciousness' (e.g., the 'sleep–wake cycle' in their understanding would be more accurately termed a 'disconnected–connected consciousness cycle'). General anaesthesia is the loss of all three, and different combinations of the three lead to specific brain states, summarised in the Venn diagram (my own interpretation; Fig. 5). One of their radical (and important) suggestions is that it is possible to be 'connected' yet 'unconscious' in the state of emergence delirium (Sanders & Maze, 2012; Sanders et al., 2012).

Notwithstanding any philosophical or neuroscientific criticisms of this approach, it is important to appreciate the difference in approach between Sanders et al. and that of the hypothesis of perception–sensation uncoupling presented in Fig. 4. Most importantly, Sanders et al. offer no macroscopic model for 'consciousness' itself (it is not their aim to do so). Rather, they propose a scheme in which the term 'consciousness' is not sufficient to describe the brain state we are in, say, when we read this article or play tennis or debate literature. They propose that this brain state requires an additional term (i.e., 'connectedness') to provide an accurate description. Consciousness alone is, in their terminology, minimally a state of only of dreaming or hallucination (indeed, they unambiguously describe rapid eye movement, REM, sleep as a state of 'vivid consciousness').

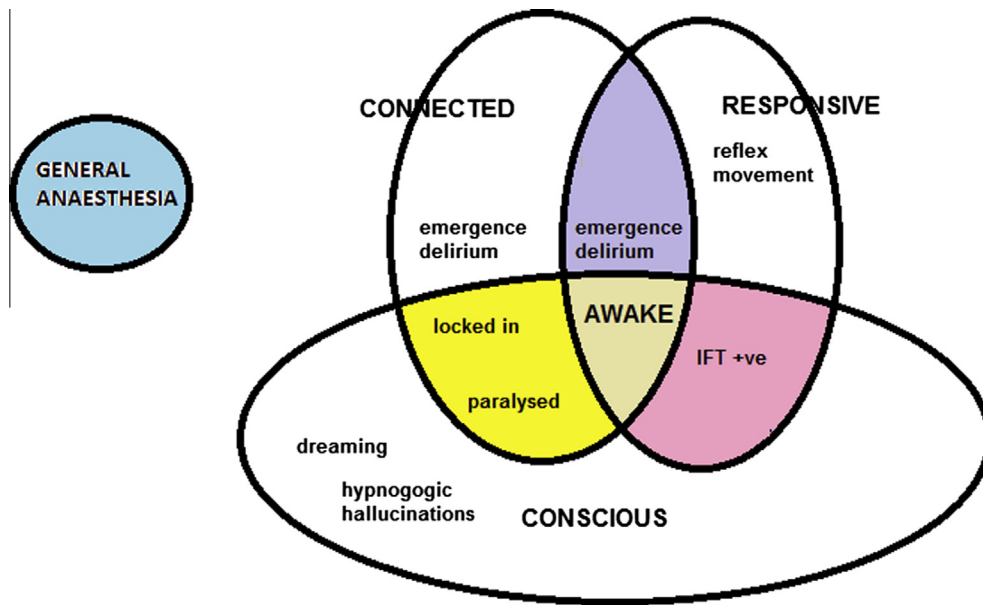


Fig. 5. A Venn diagram summarising the notion of Sanders et al. (2012), that consciousness, connectedness and responsiveness are separate entities. Being awake requires all of: consciousness, connectedness and responsiveness. General anaesthesia is loss of all of these (and nothing less). The interpretation of other combinations less than these are shown, as presented by Sanders et al. (2012). 'IFT +ve' indicates a positive motor response to verbal command during isolated forearm technique (further explanation in text).

Their proposal, therefore, is primarily one of fragmenting the overarching term 'consciousness' into three separate elements: 'consciousness' (which seems more discretely defined largely as the ability to create abstract thoughts, e.g., in relation to dreams), 'connectedness', and 'responsiveness'. Therefore, each of these three really requires its own macroscopic model and, while their proposal may be an important advance in the field, it still leaves open the question of what the macroscopic model for consciousness actually looks like. (Note that Fig. 4 presents a more explicit alternative).

Importantly, the Venn diagram in Fig. 5 shows a limitation. The proposal of Sanders et al. makes no allowance for coherent thoughts during anaesthesia that are *not* dreams: in their approach *all* thoughts disconnected from the environment (i.e., from surgery) are classed as dreams or hallucinations. This is in stark contrast to the model proposed in Fig. 4, which explicitly allows non-dream thoughts to arise. This is clearly testable by examining patient reports of accidental awareness: if these include coherent thoughts unrelated to surgery that are not dreams, then this favours Fig. 4 as opposed to the proposal of Sanders et al. The results of NAP5 (mentioned above) will therefore be very important in this regard, in terms of hypothesis selection.

The second important area where Sanders et al. differ from the approach in this article is in regard to their interpretation of isolated forearm technique (IFT) experiments. Sanders et al. (2012) describe an IFT-positive response in their terminology as 'environmentally-connected consciousness'. However, they restrict their definition of 'environment' strictly (and arbitrarily) to the verbal command and not to the stimulus of surgery. They ascribe the lack of spontaneous movement in response to surgery to anaesthetic-induced impairment basal ganglia function (implying that patients remain aware of the surgery but simply cannot respond).

There are at least two problems with this interpretation of the IFT results. First, if as also posited elsewhere (Russell & Wang, 2014) IFT patients are as aware of surgery as completely as an un-anaesthetised patient would be, then they should be likely to recall awareness. Yet this is rare or absent (Russell, 2013a; Russell, 2013b).

Second, completely non-paralysed patients (e.g., those who are spontaneously breathing in, say, a supraglottic airway-anaesthetic technique) also presumably suffer the same degree of putative basal ganglia impairment. Yet it requires no clinical trial to know that these patients often exhibit clear goal-directed spontaneous movements which are promptly abolished by deepening anaesthesia (happily rarely recalled). Furthermore, these patients do not exhibit any movement to command, in contrast to the IFT-responses that can be elicited in otherwise paralysed patients (Pandit, 2013; Russell, 2013a; Russell, 2013b). In the terminology of Sanders et al. (2012), these unparalysed patients exhibiting a goal-directed response to surgery but not to command would therefore seem difficult/impossible to classify. They are environmentally-connected to the surgery but not to verbal command; a combination that does not fall within their classification.

Yet, in contrast to the Sanders et al. approach, the model of Fig. 4 readily explains these apparent paradoxes. A patient who responds to any stimulus does so because perception is coupled to that relevant sensory input. This applies equally if the stimulus is 'surgery' and the response is spontaneous, and also separately if the stimulus is 'verbal' and the response is in consequence to this command. The model allows such distinct responses. If the patient responds to one stimulus but not

the other, it is simply because perception remains coupled to that stimulus. The existence of response to some stimuli may indicate a somewhat higher risk of awareness with recall, as opposed to a state where there is no response to any stimulus.

Furthermore, the model of Fig. 4 is not disrupted by a potential dynamic nature of a changing level of consciousness/dysanaesthesia. It is well established that IFT patients are not responsive throughout their anaesthesia but rather, episodically. The reasons for this are unknown but possibly relate to the changing level of stimulus during surgery that continually alters the balance between stimulus and hypnosis. Thus, the isolated forearm paradigm tests the conscious state of the patient at a given moment in time, which can later change within the same operation.

5.3. Dysanaesthesia, unbinding and disconnectedness: the common ground

It is important to stress that the approaches of Mashour (unbinding), of Sanders et al. (disconnectedness) and of the notion sensation–perception uncoupling (Fig. 4) may all be complementary. It would seem all these approaches likely agree upon a common sentiment (phrased using terminology borrowed from each of them):

“An understanding of consciousness which is anaesthetically-relevant rests on the ability to bind sensory inputs to perception, such that the patient is able to make sense of (i.e., connect to) the external environment. The minimum requirement for satisfactory general anaesthesia is therefore an uncoupling of perception from sensation, or a separation (disconnection) of ‘self’ from the environment”

Thus when Sanders et al. state that “consciousness during anaesthesia may not be a clinical problem if it is disconnected, or not associated with experience of surgery. . . achieving a depth of anaesthesia that produces unconsciousness may be unnecessary, provided the patient is disconnected from the environment” (Sanders et al., 2012), they are describing (albeit in a different way) a state identical to dysanaesthesia as the minimum requirement (Fig. 4).

6. Loss of consciousness during general anaesthesia: all-or-nothing or a graded phenomenon?

Important to our discussion is whether the loss of consciousness induced by general anaesthesia is a binary, all-or-nothing state or if it is a graded, dose-dependent phenomenon. Although not fully resolved, Fig. 4 and the proposals of Mashour and Sanders et al. all explicitly regard the process of losing consciousness as highly graded.

This idea is not new. Hopkin (1963) quoted earlier neuroscientific literature and noted that the brain effects of different agents were likely to be highly specific. Evoking Sherrington's (1951) allusion to the active brain being akin to “myriad of flashing lights” (representing synaptic activity), Hopkin described the problem as knowing which lights go out during anaesthesia and which stay flashing. He concluded poetically that “it is becoming apparent that fewer lights become extinguished than many of us supposed in the past”.

Perhaps it was Prys-Roberts (1987) who appeared to adopt the contrary view most robustly, when he wrote: “There cannot be degrees of anaesthesia nor for that matter can there be variable depths of anaesthesia.”. Prys-Roberts' terminology appears unambiguous and he did not quote any evidence to support this view, although the assertion has been often repeated in several anaesthesia texts (Miller, 2010).

However, the two approaches may not be as irreconcilable as they first seem, when attention is paid to the subtleties of terminology. Prys-Roberts was probably correct to regard ‘anaesthesia’ (if viewed as synonymous with the single end-point of complete non-responsiveness) as something which, in this restricted way, is indeed all-or-nothing. Once the patient is

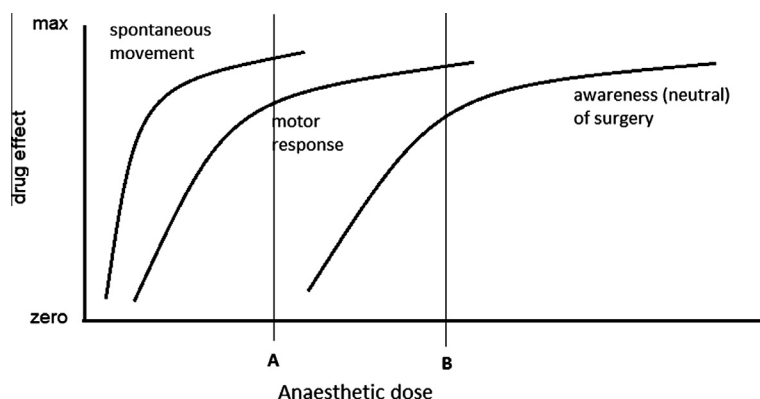


Fig. 6. Putative responses in a population to an increasing dose of anaesthetic. The y-axis is drug effect, from zero patients affected to the maximum, with the respective functions shown progressively lost. At hypothetical dose A, spontaneous movement is lost in almost all patients, but very many retain the capacity to move to stimulus. At dose B, these responses are lost but a significant proportion (hypothetically) retain capacity to form thoughts about the surgery (albeit in a neutral way). Thus with increasing dose, anaesthetic drugs can continue to influence aspects of consciousness despite some end-points being reached at lower dose.

unresponsive to noxious stimulus, this end-point has been reached. Yet if dose is increased nonetheless, then the additional drug must be doing something to the brain in a pharmacological sense (i.e., dose–response relationships may be continuous at molecular level and not all-or-nothing).

In contrast to the Prys-Roberts sense, the satisfactory end-point of Fig. 4 is reached when sensation is uncoupled from perception; further drug dose from then on has an effect on an ever-increasing number of model elements contributing to the conscious state. Put simply, the patient is certainly spontaneously unresponsive ('unconscious' in the Prys-Roberts sense) at, say, 1.5% isoflurane but 2.5% isoflurane is depressing many more brain functions than at 1.5%, and so potentially attaining many more end-points, albeit many that crude clinical examination may not measure. Fig. 6 displays this idea, that has been presented before in different ways (Sanders et al., 2012; Shafer & Stanski, 2008). In an analogy evoking that used earlier by Hopkin (1963), Sleight (2011) elegantly used the image of anaesthesia acting on a bank of binary switches controlling various subsystems of the central nervous system, each dealing with functions like autonomic responses, nociception, memory, etc.

To summarise: Mashour, Sanders et al. and the uncoupling model of Fig. 4 all regard consciousness as consisting of several components, each of which can potentially be measured using discrete end-points. Attainment of *each individual end-point* is by definition an all-or-nothing phenomenon, but *loss of consciousness* in anaesthesia is a graded phenomenon. In Fig. 6, the type of unconsciousness at 'dose A' (e.g., dysanaesthesia) is substantively different from that at 'dose B' (complete mental oblivion).

7. Conclusions and directions for future research

Hypotheses in this field, such as those of Hammeroff, Tononi, Mashour and Sanders et al., are not proposed as definitive answers to stifle all further debate. Rather, their aim is to stimulate the discussion of alternative views so that the original idea can be refined. The model in Fig. 4 is one such alternative view. Dysanaesthesia is not presented as the only possible conclusion from the available evidence, but rather as a hypothesis consistent with much of the evidence and a notion that warrants and lends itself to further examination.

Hypotheses also lead to predictions testable by experiment or observation. In any scenario like anaesthesia where memory is disrupted by drugs, experimentation is difficult. Amnesia makes it difficult to ascertain if the patient experienced an event but cannot recall it, or if they did not experience the event at all. This makes those cases where there is *no amnesia* all the more important for careful interrogation, because they reveal the ways in which events were experienced. In other words, one learns relatively little from the many patients who can report nothing, but much from those few that recall something.

The dysanaesthesia hypothesis leads to the specific prediction that patient reports of awareness during anaesthesia might involve coherent thoughts (that are not dreams) – some unrelated to surgery – and/or reports of a 'neutral' experience of surgery. However, in the majority of cases, the effect of general anaesthesia is indeed mental oblivion, with no explicit recall. In patients with no recall, it is impossible to ascertain what mental state they may have been in during surgery. In some other cases, there is true awareness with recall of pain or distress; this is distinct from dysanaesthesia. It remains to be seen what proportion of cases might fall into these separate categories. The dysanaesthesia hypothesis itself needs to be refined to ascertain if all sensory inputs require uncoupling for satisfactory anaesthesia, or only some (e.g., pain but not touch or auditory, etc.).

The role of neuromuscular blockade warrants much investigation. The relative incidence for awareness with *adverse recall* seems to be: complete paralysis > IFT (some neuromuscular blockade used) > unparalysed (no neuromuscular blockade). Furthermore, the incidence of response to command is much higher in IFT than in completely unparalysed patients, who invariably do not respond to command (i.e., dysanaesthesia more common in IFT than in the completely unparalysed). Unparalysed patients can rarely report neutral experiences, but adverse reports seem absent. Sandin et al. (2000) described two unparalysed patients who made no attempt to move despite their understanding of the situation. A hypothesis is required to explain why completely unparalysed patients do not respond like IFT patients when, on the face of it, they should be in a similar state of 'equivalent' motor capacity.

One speculation that could be formulated is that 'peripheral' paralysis (i.e., at the level of the neuromuscular junction) in some way contributes to arousal and the brain state. At any given anaesthetic concentration, an increasing degree of neuromuscular blockade makes first dysanaesthesia, and then adverse experience of awareness more likely as this arousal from paralysis increases. A possible mechanism is that the ability to move (even when not fully exercised) provides reassuring feedback to the central nervous system. Paralysis of any part of the body reflexively heightens anxiety in some as yet unknown way (Dissanayaka et al., 2010), perhaps in a manner akin to dyspnoea triggered by perceived increase in the effort of breathing (Lansing, Gracely, & Banzett, 2009). In this scheme, unparalysed patients retain reassuring feedback from the muscles and so are less aroused. This means any given anaesthetic dose has a greater relative hypnotic effect. A prediction of this hypothesis is that recall after anaesthesia with paralysis will more likely be expressed in negative ways (i.e., true awareness with adverse experience), whereas recall with partial (i.e., IFT) or no paralysis will more likely be neutral (i.e., akin to dysanaesthesia). If such a mechanism is confirmed, these aspects of motor control and feedback may need to be factored into the model in Fig. 4.

The concept of dysanaesthesia is of clinical relevance. If an IFT-positive response is accepted as evidence of dysanaesthesia, then practising anaesthetists need to appreciate that about one-third of their paralysed patients may in fact be (at some

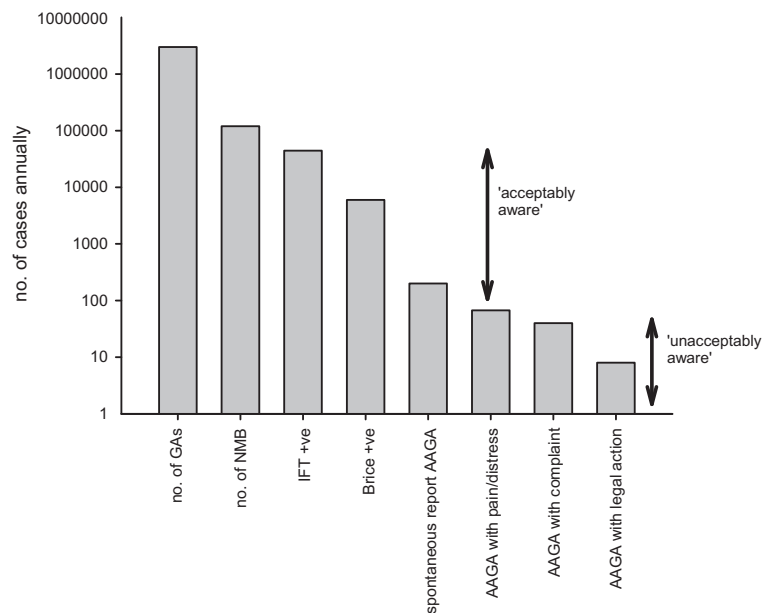


Fig. 7. An overview of the different incidences of awareness, in relation to the number of general anaesthetics administered in the UK ('No. of GAs', first bar; ~3,000,000). The y-axis is a logarithmic scale. 'No. of NMBs' refers to the estimated number of cases where neuromuscular blockade is used. 'IFT +ve' is that number of patients responding to command during the isolated forearm technique. 'Brice +ve' is the number of patients responding positively to a Brice questionnaire about recall of events during anaesthesia. AAGA in the last three bars is accidental awareness with pain/distress, formal complaint and legal action, respectively. The data is from evidence cited in Pandit et al., (2013). The vertical arrow ('acceptably aware') represents that proportion of patients likely to be 'dysanaesthetic'; i.e., the difference between the number who are IFT positive and those who experience adverse recall ('unacceptably aware').

time) aware of surgery (Russell, 2013a; Russell, 2013b). Only a few patients (~1:500) may recall this afterwards on direct (Brice) questioning. It is perhaps surprising that the incidence of recall is not higher, but this may be due to the direct drug effects on memory, or indirect effects via impaired perception (Fig. 3), or due to the nature of questioning. Mashour et al. (2013) have shown that detection of reports can vary fivefold depending on the type of questioning used, and Deeprose and Andrade (2006) have noted that the relative purity of a test of explicit memory is inversely related to its sensitivity.

Fewer patients (~1:15,000) spontaneously report awareness (Pandit, Cook, Jonker, & O'Sullivan, 2013a; Pandit, Cook, Jonker, & O'Sullivan, 2013b), compared with those who respond positively to Brice interview (~1:500). However, a higher proportion of the spontaneous reports (one-third) will involve pain or distress than occur with either the IFT-positive or Brice-positive cohort. Dysanaesthesia can be regarded as the logical precursor of awareness with recall, which arises at a somewhat lower dose than complete mental oblivion (Fig. 6). Thus there appear to be different incidences for different 'types' of awareness during general anaesthesia (Fig. 7). These 'types' may not have exactly the same neural mechanisms in how they are brought about. The number of IFT-positive cases is much larger than the number responding positively to a Brice survey, which in turn is very much larger than the number who spontaneously report awareness, and so on. If a monitor were calibrated only to detect the neural activity underpinning awareness with recall of pain/distress then it would miss all that related to more neutral recall (such as dysanaesthesia). It would then be a potentially 'specific' but not a 'sensitive' diagnostic tool.

The dysanaesthesia hypothesis coupled with an IFT-positive response is a potentially very useful end-point for clinical studies. If the chosen end-point for studies on awareness/anaesthetic mechanisms is to be 'a spontaneous patient report of awareness' (incidence ~1:15,000) then any study sample size needs to be in the hundreds of thousands. If the end-point is 'a positive response to a postoperative Brice survey' (incidence ~1:500), the sample size still needs to be in the thousands. However, if the end-point is 'IFT-positive response' (i.e., incidence ~1:3) then meaningful experiments might be conducted with sample sizes in the dozens or hundreds (Russell, 2013a; Russell, 2013b).

Turning to mesoscopic and molecular models, it has been noted that different agents act in different ways (Pandit & Buckler, 2009; Pandit, Winter, Bayliss, & Buckler, 2010). Drugs like propofol are thought to be predominantly GABA-ergic; ketamine probably acts on NMDA receptors; volatile agents act on a range of molecular targets, including background potassium channels; nitrous oxide may enhance noradrenergic transmission (Lee, Ku, Noh, et al., 2013); dexmedetomidine may inhibit the central noradrenergic system (Sanders & Maze, 2012; Sanders et al., 2012). Therefore, it is clear that combinations of these agents within the experimental paradigm of IFT-experiments may offer insights into both mechanisms of action of agents, as well as therapeutic means to minimise IFT-positive responses (and therefore minimise risk of accidental awareness during anaesthesia). Because they act by different molecular mechanisms, it would be especially intriguing if some agents were associated with higher (or lower) incidences of awareness with recall, or dysanaesthesia, than others.

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