REVIEW

CURRENT OPINION

Consciousness and responsiveness: lessons from anaesthesia and the vegetative state

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Purpose of review
The aim of this article is to review recent behavioural and neuroimaging studies in anaesthesia and the vegetative state.

Recent findings
These studies highlight possible dissociations between consciousness and responsiveness in both these states.

Summary
We discuss future avenues of research in the field, in order to improve the detection of awareness during anaesthesia and the vegetative state using neuroimaging and neurophysiologic techniques.

Keywords
anaesthesia, consciousness, responsiveness, vegetative state

INTRODUCTION

Consciousness has been defined as 'what abandons us every night when we fall into dreamless sleep' [1]. This definition has relevance for anaesthesia, as both patients and anaesthesiologists assume that general anaesthesia is associated with unconsciousness similar to a dreamless sleep [2■■]. It has also relevance for the vegetative state (VS), wherein clinicians and family members wish to detect any ability to be aware in behaviourally unresponsive patients [3].

DETECTING AWARENESS UNDER ANAESTHESIA AND IN THE VEGETATIVE STATE

We regard consciousness as a process that encompasses awareness of the environment and internal states such as dreaming or pain. A primary aim of anaesthesia is to prevent the experience of surgery; this may be achieved through inducing unconsciousness. However, it has also been argued [2■■] that some forms of internal consciousness may be acceptable during anaesthesia if it is associated with dreaming unrelated to the surgery (with the exception of rare dysphoric experiences). This has led to description of the term connectedness to distinguish experience triggered by an external event ('consciousness connected to the environment' such as wakeful consciousness) from internally generated experiences ('consciousness disconnected from the environment' such as dreaming). Critically for anaesthesia, consciousness (such as a dream) can occur without experience of external stimuli that may include surgery.

In VS, the goal of accurately detecting the presence of consciousness is different. UK laws defined the VS as 'a clinical condition of unawareness of Self and Environment' and allows treatment withdrawal of thoroughly clinically documented VS. Indeed, the law states: 'It is declared that despite the inability of a patient to give a valid consent, [...] the responsible medical practitioners may lawfully discontinue all life-sustaining treatment and medical support measures (hydration by artificial

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KEY POINTS

- Studies reveal 40% misdiagnosis of behavioural unresponsiveness, both under anaesthesia and in the VS.
- Lack of spontaneous movement also misdiagnoses unconsciousness in 17–28% both under anaesthesia and in the VS.
- To date, current clinical electroencephalographic markers of awareness still fail, both under anaesthesia and in the VS.
- To advance the field, a mechanistically grounded 'consciousness-meter' is needed.

means) designed to keep the patient alive in his existing permanent VS'. In the case of VS, detecting environmental connectedness and the possibility for responsiveness is also desirable, in order to provide appropriate analgesic treatment and to attempt to establish communication with the patient. Detecting consciousness in a nonresponsive patient is also likely to have deep consequences in his/her daily care. In a recent survey of attitudes towards end of life in noncommunicative patients [4], 67% of medical and paramedical personnel stated that end-of-life was acceptable for unaware VS patients, but only 30% stated that is was acceptable in minimally conscious state (MCS), wherein signs of cognition are present. Finally, an accurate diagnosis is crucial not only for daily management (particularly, pain treatment) and end-of-life decisions, but also has prognostic implications as patients in MCS have more favourable functional outcomes as compared to those in VS [5].

Currently, however, our ability to distinguish consciousness from unconsciousness in anaesthesia and VS is insufficient due largely to the difficulty of behavioural assessment. Furthermore, even if no behavioural signs of consciousness are present, new evidence suggests that a significant proportion of anaesthetized and VS patients can remain aware. Finally, the present population-based markers of brain activity designed to detect consciousness in both these states are likely to be insufficient to detect awareness in individual patients. We will review these issues below in more detail and discuss possibilities for further improvements.

FORTY PERCENT MISDIAGNOSIS OF BEHAVIOURAL UNRESPONSIVENESS, BOTH UNDER ANAESTHESIA AND IN THE VEGETATIVE STATE

The use of neuromuscular blockade was introduced into the practice of clinical anaesthesiology in the 1940s and the ensuing paralysis precludes one major sign of insufficient anaesthesia: spontaneous patient movement. Although the absence of spontaneous behavioural responsiveness with paralysis is often confused for unconsciousness, recent studies using the isolated forearm technique (IFT) have provided evidence of connected consciousness and of the possibility of reproducible response to command in anaesthetized patients – goal-directed responsiveness [6]. In the IFT, a cuff on the arm is inflated after anaesthesia is achieved, but before neuromuscular blockade is induced. One of the patient's hands is, thus, not paralyzed, allowing them to communicate through predefined hand movements; however, interestingly, patients do not move their hands spontaneously. Commands administered during IFT are of the form: 'If you can hear me, squeeze my hand' [7]. More complex commands such as: 'if you are comfortable, squeeze my hand twice,' are also usually performed. In most findings of positive IFT responses, the patient shows intact cognition. However, patients showing response to commands rarely present spontaneous responsiveness. A recent Medline systematic review of IFT studies [6] revealed positive responses in a median of 37% of patients (range 0–100%). Even recent studies with modern anaesthetic techniques show a large proportion of patients responding to command during IFT anaesthesia, which are not reliably detected by electroencephalography (EEG)-based anaesthesia monitors [8,9]. Fortunately, IFT studies suggest that even in the presence of a response to command, explicit episodic recall of surgical events is infrequent [9,10]. Indeed, prospective studies of awareness and recall reveal an incidence of 0.1–0.2% [11,12,13▪], suggesting that intraoperative consciousness occurs significantly more frequently than consciousness and episodic memory formation. In sum, IFT data suggest that behavioural responsiveness, as reflected by a response to command, may occur during anaesthesia despite patients appearing spontaneously unresponsive; the lack of spontaneous movement does not inform us as to the conscious state of the patient.

Behaviourally differentiating MCS from VS is also challenging. Numerous behavioural rating scales have been developed and validated to assess the level of consciousness in MCS and VS [14]. However, the detection of voluntary behaviours is often difficult because we can only infer the presence or absence of consciousness based on behaviours [3]. Signs of consciousness can easily be missed due to the possible presence of sensory and motor impairment, aphasia, or fluctuating arousal levels in severely brain-damaged patients

[15]. A recent study confirmed previous reports of a very high rate of misdiagnosis in noncommunicative patients, with 41% of patients erroneously classified as VS based on clinical signs, whereas formal behavioural assessment diagnosed MCS [16]. This misdiagnosis, thus, occurs if one does not use appropriate behavioural coma scales for the patients' behavioural assessment, even if the caregivers are aware of the distinction between clinical entities such as VS and MCS. The clinical usefulness of different behavioural tools is also variable [17]. Indeed, the John Fitzgerald Kennedy Coma Recovery Scale-Revised (CRS-R [18]) is to date the only scale that systematically incorporates behavioural diagnostic criteria for MCS versus VS. However, the reliability of behavioural assessment using this scale is also dependent on the rater's previous experience with the use of this tool [19]. Finally, preliminary evidence suggests that accurate detection of MCS depends not only on the scale used, but also on the time spent behaviourally assessing the patient [20].

LACK OF SPONTANEOUS MOVEMENT MISDIAGNOSES UNCONSCIOUSNESS IN 17–28% BOTH UNDER ANAESTHESIA AND IN THE VEGETATIVE STATE

Even if the usual primary aim of anaesthesia is to suppress all forms of conscious experience, dreaming frequently occurs in behaviourally unresponsive patients. Recent studies indeed showed an occurrence of dream reports in at least 27% of patients anaesthetized with propofol and 28% of patients undergoing desflurane anaesthesia [21]. Given the amnesia induced by these anaesthetic agents, these data likely underestimate the real prevalence of dreaming in these conditions. Importantly, in this recent 300-patient study, experience of surgery was not described by any patient reporting anaesthesia-related dreams [21]. Of course it is unclear when these dreams occur, and it appears most likely that these remembered reports occur on emergence from anaesthesia, though this does not exclude the possibility of intraoperative dreams. For this reason, as mentioned above, some authors consider that anaesthesia-related dreams might not be problematic if their content is unrelated to the surgery [6]. Indeed, dreams are no longer regarded as reports of near-miss awareness experiences [22]. In other words, disconnected consciousness might be sufficient for a nontraumatic surgery. However, to our knowledge, data concerning the psychological outcome of patients with or without dreaming during anaesthesia concomitant to surgery are currently unavailable.

Recent functional neuroimaging studies in patients in VS also demonstrated that a significant proportion of patients retained some awareness, even if they seem at the bedside behaviourally unresponsive. The neuroimaging paradigms allowing us to detect this covert (connected) consciousness ask participants to activate specific brain regions in response to commands [23]. Using such a paradigm, a recent functional MRI study [24] showed that 17% of patients who had been diagnosed as VS on the basis of repeated clinical behavioural assessments could respond to command, and were, thus, in fact conscious. Using EEG at the bedside, a similar approach [25] showed that 19% of a cohort of VS patients was able to modulate their EEG responses to command. Further studies are, however, needed to confirm these results on larger patient groups and using different analysis methods [26]. These techniques have recently been extended to allow two-way communication ('yes' and 'no' answers to questions) with a limited number of nonresponsive patients [24]. An important caveat of active paradigms is the following: although the patients responding to command are likely to be conscious, nonresponsive patients in these paradigms might also be conscious, but not recognized as such due to the insensitivity of these methods to detecting consciousness in the absence of the patient's collaboration [27]. In this context, it has been shown that some MCS or locked-in syndrome patients, who are conscious, can respond to commands at the bedside, however, they occasionally do not show task-relevant brain activation in response to the instruction to perform the task [28]. This finding reinforces the need for research on neural correlates of consciousness (NCC) that do not depend on the patients' collaboration, in order to reliably detect awareness in patients unable to perform these active tasks.

CURRENT CLINICAL ELECTROENCEPHALOGRAPHY MARKERS OF AWARENESS FAIL, BOTH UNDER ANAESTHESIA AND IN THE VEGETATIVE STATE

Current EEG markers used in a clinical setting for measuring brain activity during anaesthesia currently fail to accurately detect the patients' level of consciousness. For example, the Bispectral Index (BIS) has reproducibly been shown not to be superior to end-tidal anaesthetic-agent concentration monitoring in the prevention of anaesthesia awareness [29,30]. Although the BIS prevented awareness during total intravenous anaesthesia with propofol [31], it does not reliably distinguish between patients responding or not responding to command in studies using IFT during propofol anaesthesia [8,32]. Finally, even if some rapid eye movement-like electroencephalogram phenomena (e.g. a loss of slow waves and spindles, and an increase in higher frequencies) have been detected during, for example, propofol-induced anaesthesia [21], their precise relationship to anaesthesia awareness or dreaming is currently unknown.

The BIS has also been recently tested as a clinical measure of the level of consciousness in VS [33]. Even if a group-level difference was present between VS and MCS, the BIS failed to separate these two patient populations at the individual level. EEG spectral characteristics in VS are also highly variable [34]. A recent study from our group more precisely showed that spontaneous EEG features, taken alone, failed to differentiate MCS from VS at the individual level [35].

In conclusion, despite the clinical need for accurate diagnosis of consciousness in anaesthesia and VS, at the individual level, high rates of misdiagnosis persist, and clinical markers of brain activity currently fail at the individual level. In both cases, more neural markers of brain activity reliably detecting consciousness are, thus, needed. The next section will review potential candidates recently emerging in the neuroscience literature, and discuss their potential relevance and/or limitations for a routine clinical use.

THE NEED FOR A MECHANISTICALLY GROUNDED 'CONSCIOUSNESS-METER'

Current approaches to detecting neural markers of general anaesthesia are often empirical rather than principled, that is, they compare the waking to the anaesthetized state and identify differences. However, this results in an 'anaesthetic meter' that may be restricted to one or several drugs. What is required for both anaesthesia and VS is a true 'consciousness meter' that is based in the neurobiology of consciousness and that follows a known or putative NCC across different pharmacologic or pathologic states. The safest approach to design a clinical marker of consciousness that would be widely applicable is to identify specific markers of brain activity vanishing in all states of unconsciousness, as compared to normal wakefulness, and resuming to normal level during recovery of consciousness. However, research aiming at identifying NCC faces the problem that they can depend on the physiological or pathological condition generating the state of unconsciousness [27] and may be confused with the behavioural response used to validate the conscious experience [36]. To overcome these limitations, a mechanistic approach, searching for common abnormalities in different unconscious states, is desirable [37]. Furthermore, we may also derive mechanistic insight from studies of individuals possessing normal consciousness. In order to be used in a clinical setting, the measurements to be designed have also to be portable, for example, they should ideally be obtained using a few EEG electrodes [25]. In the perioperative setting, functional MRI and metabolic measures are not currently feasible. For clinical anaesthesiology, markers of NCC would have to be amenable to real-time analysis and ideally predict forthcoming changes in conscious level or content. As such, we will focus our present review on EEG, identifying possible EEG NCC, and discussing their potential clinical applicability.

Gamma activity in the EEG has been suggested since a long time ago to be linked to consciousness [38]. Indeed, it vanishes during dreamless sleep, and recovers at awakening. Gamma power is also modulated by attention and conscious cognitive processing [39]. However, in a recent study we showed that EEG gamma power is actually increased during propofol-induced loss of responsiveness without recall of conscious content [40]. This finding may impact upon the general applicability of gamma power as a clinical marker of awareness. High-gamma has been found to be susceptible to the effects of propofol in humans [41] but this was identified using electrocorticography rather than scalp EEG. The gamma bandwidth is also difficult to assess given the frequent confound of electromyography.

Alpha power, coherence and synchrony have also recently been proposed to be a marker of anaesthesia-induced unconsciousness, especially under propofol sedation [42,43]. However, alpha power and synchrony do not systematically differentiate between mild sedation (where consciousness is present) and unconscious states. According to two recent studies [40,44▪], an increase of EEG delta power seems to be the most reliable spectral marker for loss of responsiveness during propofol sedation and it is plausible that this is associated with the fading of consciousness. In comatose patients, however, power spectrum features are highly variable, and delta power alone cannot to date differentiate VS from MCS [35]. Furthermore, delta power increases during slow-wave sleep and is, therefore, not uniformly associated with the ability to tolerate a surgical stimulus or resistance to arousal from a putatively unconscious state.

Long latency-evoked potentials have also been proposed as another candidate consciousness marker under anaesthesia. They seem to vanish during anaesthesia-induced unresponsiveness and to return to normal patterns during recovery [45]. However, long latency event-related potentials in response to the patient's own name are present in many VS patients [46], although typically with a lower amplitude as compared to normal individuals. It is, thus, possible that long latency evoked potential components might persist in the absence of awareness. To our knowledge, studies using own-name responses have not been conducted during anaesthesia.

Feedback connectivity from frontal to parietal cortex is another neural marker recently evidenced to discriminate between propofol-induced unresponsiveness and normal wakefulness, especially under propofol sedation [47■,48]. A similar finding was suggested for isoflurane-induced unresponsiveness in animals [49]. Preliminary evidence suggests that this marker can differentiate coarse levels of consciousness under anaesthesia in surgical conditions [50], showing its potential clinical applicability. However, further study is required to understand the correlation of impaired feedback connectivity and reduced consciousness under anaesthesia. This is especially important as feedback connectivity from frontal to parietal cortex has also been shown to be impaired in patients in VS, but preserved in MCS [51]. Studies on larger patient populations are needed to confirm these findings and real-time analysis has not yet been investigated.

Finally, the loss of complexity/differentiation of brain responses to stimulation by transcranial magnetic stimulation (TMS) is a promising marker for loss of consciousness, both in anaesthesia and in VS [52]. An early study [53] showed that TMS pulses administered during slow wave sleep evoked activity only local to the TMS focus; in contrast, TMS applied during conscious wakefulness led to a spatiotemporally complex pattern of activity with several distinct components over time, consistent with a rich underlying effective and functional connectivity. This finding of a decreased complexity of the response during loss of responsiveness has recently been replicated in other states associated with unconsciousness including deep midazolam sedation [54] and in VS as compared to MCS [35]. Larger studies validating the ability of this technique to reliably identify patients' consciousness level under various anaesthetics and in patients are ongoing.

CONCLUSION

In the future, research on anaesthesia and VS would greatly benefit from the acquisition of data using the same paradigms and neuroimaging modalities in different states such as coma, various anaesthetic conditions, sleep, sleepwalking, lucid dreaming, and seizures [27]. A deeper understanding of precise NCC during sleep or anaesthesia dreaming is also urgently needed. Most studies investigate NCC in these states by merely comparing a given level of sedation or a given sleep stage to normal wakefulness. To advance the field, studies comparing brain activity under IFT anaesthesia with or without response to commands, are also crucial. In the VS patient populations, comparing brain activity in individuals with or without a response in active volitional paradigms is critical [23]. Finally, a more refined distinction between neural correlates and clinical outcomes of a state of unconsciousness (the absence of any conscious contents) versus a state of conscious disconnectedness (the absence of perception of the environment) during anaesthesia is essential [6].

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Conflicts of interest

There are no conflicts of interest.

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