[Frontiers In Bioscience, Scholar, 10, 337-349, June 1, 2018]

# Using neuroimaging to uncover awareness in brain-injured and anesthetized patients

**Mackenzie Graham[1], Adrian M. Owen[2], Charles Weijer[1], Lorina Naci[3]**

*[1]Rotman Institute of Philosophy, Western University, London, ON, N6A 5B8, Canada, [2]Brain and Mind Institute, Western University, London, ON, N6A 5B7, Canada, [3]School of Psychology, Trinity College Dublin, Dublin, Ireland*

## TABLE OF CONTENTS



## 1. ABSTRACT

We cast a novel perspective on two distinct populations: patients who become accidentally intraoperatively aware after receiving general anesthesia and severely brain-injured patients who are diagnosed as being in a vegetative state. In both cases, patients are behaviorally non-responsive —and on this basis presumed to lack consciousness— yet, retain covert awareness. In both contexts, detecting consciousness is highly challenging, yet highly important for ensuring adequate patient care. Although great strides have been made in the development of depth-of-anesthesia monitors, these monitors have significant limitations. On the other hand, recent neuroimaging studies on severely brain-injured patients have developed neurobiologically-informed markers of conscious awareness that hold potential for improving monitoring of covert awareness during general anesthesia. Further research is required to determine the implementation of these assessments in the surgical context, and this approach provides promising avenues for improved detection of intraoperative awareness and prevention of accidental awareness under general anesthesia.

## 2. INTRODUCTION

Imagine being on an operating table about to start surgery. Around you nurses, surgeons, and medical staff speak about preparing the surgical procedure. What sounds like casual chatter is part of a very important event that may alter your life forever. A moment later, you can feel the nurses scrubbing your abdomen, and think: “Oh, they are just cleaning me up after the surgery. I woke up. I’m done. It’s all good.” But then, you hear the surgeon speak. He says to the nurse: “Scalpel please!” You try to get someone’s attention, scream, but you cannot move or speak. You think you are dying. This scenario is adapted from a patient who woke up during surgery, a phenomenon known variously as ‘unintended intraoperative awareness’, ‘anesthesia awareness’ and ‘accidental awareness under general anesthesia’ (AAGA) (1).

An estimated 20,000 to 40,000 patients experience AAGA yearly in the United States alone (2). AAGA can be accompanied by intraoperative distress and lead to post-traumatic stress disorder (PTSD) in as many as 70% of those who experience it (1). Psychological harm following AAGA is not confined to PTSD; clinical depression or phobias can also develop (3). Naturally, AAGA can be a major concern for both patients and anesthesiologists (1). Because its risk factors are not yet fully understood, it is difficult to estimate the precise risk of AAGA for individual patients. Additionally, the lack of sensitive depth-of-anesthesia monitoring devices makes prevention and detection of AAGA extremely challenging.

In this paper, we bring our experience with a different patient population —severely brain-injured patients who retain covert awareness despite being clinically diagnosed as being in a vegetative state (VS)— to bear on understanding covert awareness in AAGA patients. Patients in a VS show no behavioral signs of awareness of themselves or of the environment following severe brain injury, and on this basis are presumed to lack consciousness (4). However, studies show that a subset of patients (~14-19%) (5-6) clinically diagnosed as VS can, nevertheless, demonstrate covert awareness through cognitive brain responsivity in neuroimaging tasks, a phenomenon captured by the recently-coined term 'cognitive motor dissociation' (CMD) (7). Like AAGA patients, CMD patients exemplify the notion that loss of behavioral responsiveness does not guarantee loss of consciousness. Indeed, in both cases, this mistaken assumption can result in significant harm to the patient (8-13). Accordingly, there is a need for increased accuracy of assessments that can detect covert awareness in both patient groups. We review strategies for monitoring and detecting awareness in patients receiving general anesthesia, and those clinically diagnosed as VS, by examining the methodology and challenges inherent to each. We argue that recent neuroimaging paradigms for detecting covert awareness in the latter group have the potential to improve monitoring of intraoperative awareness, and suggest strategies for translating these paradigms to the context of clinical aesthesia.

## 3. UNDERSTANDING AAGA

### 3.1. Incidence

Estimates of intraoperative awareness with explicit recall —where postoperative patients can recall events from the operation— range from 0.05% when based on spontaneous report (1), to 0.1-0.2%, when based on structured post-operative interviews, such as the Brice Questionnaire (3, 14). Patients may be reluctant to spontaneously report an AAGA experience, while a proportion of patients may recall AAGA experiences days or even weeks after surgery (14-15). For this reason, post-operative structured interviews provide a more robust, though likely conservative measure of incidence.

The incidence of AAGA without explicit recall is harder to determine, but studies suggest it may be up to 25 times higher than with explicit recall (1, 16). One method for testing AAGA without recall involves the Isolated Forearm Technique (IFT) (16), wherein an inflatable cuff placed at the forearm prevents paralysis of one hand by the neuromuscular blockade delivered as part of the anesthesia drug cocktail. A recent international and multi-center study that used the IFT found that 4.6.% of patients demonstrated conscious awareness (i.e., awareness and response to stimuli in their environment) after the presumed induction of general anesthesia and post-intubation (16). These patients responded to verbal commands by squeezing the researcher's hand, including to questions about pain experience. No patients showed postoperative recall, however, likely due to the anterograde amnesic effects of anesthetics, which may explain the discrepancy between this rate and the one established through post-operative interviews. Implicit memory formation may also take place under general anesthesia independent of explicit recall (1, 17), and potentially lead to adverse long-term psychological effects.

### 3.2. Risk factors

Several risk factors may increase the likelihood of AAGA in individual patients. The most important factor is the under-dosing of anesthesia (3, 15). For some patients, including those with an American Society of Anesthesiologists (ASA) physical status of IV or V (e.g., patients with severe systemic disease, or moribund patients not expected to survive without operation), 'light' anesthesia may be intentionally administered due to the patient's limited cardiovascular reserve. Similarly, surgical procedures in which the anesthetic dose is typically low in the interest of patient safety, such as cardiac surgery (to preserve hemodynamic stability) and caesarean section with general anesthesia (to avoid the respiratory depressant effects of anesthetics on the newborn), tend to result in a greater incidence of intraoperative awareness (3, 18). Although counterintuitive, it is well-established that pharmacological paralysis through neuromuscular blocking agents is also a risk factor for intraoperative awareness (3, 14-15). For example, in a study by Sandin and colleagues, the incidence of AAGA in patients receiving anesthesia without neuromuscular block was 0.1%, compared to 0.18% in patients receiving neuromuscular block (14). This could in part be due to the lack of motor feedback from the patient, which would otherwise alert the anesthesiologist to the possibility of inadequate anesthesia, and trigger dose adjustments that reduce the likelihood of AAGA. Finally, equipment malfunction and misuse of the anesthesia delivery system are risk factors in a minority of cases (4-5%), according to a review of published cases (15). Due to the plurality of risk factors, as well as inter-individual variability, the precise risk of AAGA for any individual patient is currently impossible to determine preoperatively.

### 3.3. Monitoring of awareness during general anesthesia

The development of technologies for accurate depth-of-anesthesia (i.e., 'aware', 'light', 'unaware') monitoring has been a focus of efforts to prevent AAGA. One such technology, end-tidal anesthetic concentration monitors, assesses the concentration of anesthetic gas in a patient's exhaled breath, and allows anesthesiologists to titrate the concentration of anesthetic beyond the threshold thought to permit awareness. The standard index for the potency of volatile anesthetic is the 'minimum alveolar concentration' (MAC), where 1.0 MAC represents the minimum alveolar concentration of inhaled anesthetic required to prevent apparently purposeful movement in 50% of patients in response to surgical incision (19). Gas monitors can alert anesthesiologists to when end-tidal anesthetic concentration falls below a predefined MAC threshold, (typically, 0.7 MAC) (20-21), and prompt measures to avoid intraoperative awareness, such as a deepening of anesthesia. However, gas monitors have several limitations. First, the predefined MAC concentration threshold can fluctuate widely based on the anesthetic, as well as factors not accurately captured by standard threshold modelling algorithms, such as patient age (19), genetic background, intensity of the surgical stimulus, or the use of other drugs in the anesthetic cocktail (22). Second, anesthetic agents with relatively high solubility (e.g., halothane, isoflurane) are more easily absorbed in blood vessel rich tissue groups (e.g., heart, brain, liver, kidneys), which can result in an equilibration delay between end-tidal levels and effect-site concentration (23).

Conversely, newer inhalational agents (e.g., sevoflurane, desflurane) are less soluble and equilibrate more rapidly between the lungs, blood, and central nervous system (19, 24). Thus, relatively small decrements in anesthetic concentration due to routine equipment upkeep errors (e.g., if the vaporiser becomes empty, or is turned off) can quickly lead to adverse consequences, including AAGA (19). Furthermore, the usefulness of MAC as a measure of anesthetic effect is especially diminished when multimodal anesthetic techniques are employed (e.g., an inhaled anesthetic, as well as a neuromuscular blocking drug, opioid analgesic, and intravenous hypnotic agent) (19).

Third, the concentration of the exhaled anesthetic gas is only a proxy measure for the effect site concentration in the central nervous system. Therefore, gas monitors cannot directly interrogate anesthetic action in the brain, or the presence of conscious brain responses.

In contrast to gas monitors, processed electroencephalogram (EEG) monitors use algorithms to continuously analyze EEG signals, and translate any changes into simple numerical indices that indicate whether a patient is conscious, or unconscious (25). Several different processed-EEG monitors are currently available, though not all have been rigorously validated by clinical studies, i.e., by measuring the correlation between processed-EEG values, and the observer's assessment of alertness and sedation (OAAS) scale, as well as using processed-EEG to predict loss of consciousness, using a variety of intravenous and volatile anesthetics (26).

The most widely used processed-EEG monitor, the Bispectral Index (BIS) (2), uses a proprietary algorithm to derive a single number from several EEG sub-parameters (26-27) (Figure 1). Values range from 0 (isoelectric brain) to 100 (fully awake), with a value of between 40 and 60 indicated as an appropriate level for general anesthesia (28-29). We note that, in the clinical anesthesia context, no distinction is made between 'wakefulness' and 'awareness', because, unlike in severely brain-injured patients (see next section), these two dimensions do not dissociate in patients undergoing or recovering from anesthesia.

A significant shortcoming of processed-EEG monitors like the BIS is that they presume uniform changes in neural responses in all patients based on an arbitrarily-defined level of awareness (i.e., fully awake, light anesthesia and deep anesthesia/ unconsciousness), regardless of the type of anesthetic agent used. However, the EEG signal can be affected by several factors, including drugs (e.g., beta-blockers), neurological conditions, (e.g., encephalopathy, dementia, stroke), muscle paralysis, and patient age (22, 25). For example, if a monitor is calibrated to a specific set of variables (e.g., a younger and healthy population), its values cannot reliably be extrapolated to a different population (e.g., older patients with dementia, or pregnant women). Further, studies show that processed-EEG monitors may display readings consistent with deep general anesthesia when awake volunteers have received muscle relaxants (30). Moreover, different anesthetics do not have a uniform impact on processed-EEG monitors. For example, ketamine has been reported to increase BIS value, despite deepening anesthesia, when administered in conjunction with sevoflurane (31). Similarly, increased isoflurane has been reported to increase BIS value when used in conjunction with nitrous oxide and sufentanil (32). BIS values have also been shown to differ with equipotent concentrations of different volatile anesthetics (e.g., halothane, sevoflurane, isoflurane) (33-34). Together these studies suggest that the accuracy of processed-EEG monitors is limited when different anesthetics are incorporated into the anesthetic cocktail (1, 35). The results of the large B-Unaware Trial suggest that processed-EEG monitors like BIS are often insensitive to changes in inhalation anesthetic concentrations (36).

Processed-EEG monitors can reduce the incidence of AAGA, particularly in patients with an *a*

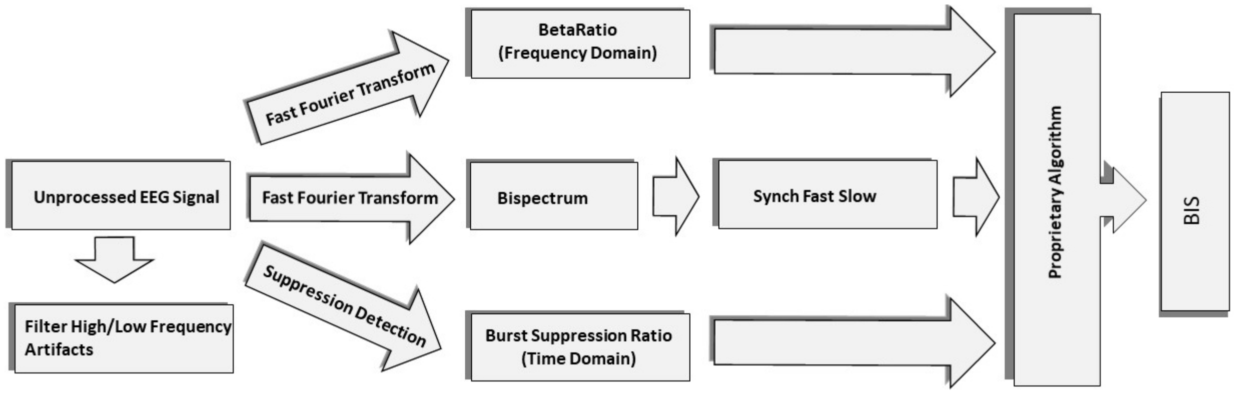


**Figure 1.** A simplified schematic of the generation of the BIS number. The Bispectral Index uses a proprietary algorithm to generate a numerical representation of patient consciousness, from 0 to 100. Initially, an unprocessed EEG signal is measured from an array of electrodes at the front of the scalp. Second, the EEG signal is filtered to remove high and low frequency artifacts. Third, various algorithms are used to calculate the beta ratio, burst suppression ratio, and bispectrum subparameters. Fourth, these subparameters are weighted using a proprietary algorithm, and finally, combined to form the single BIS number.

*priori* high risk of intraoperative awareness. In a large multi-center trial, Myles and colleagues compared the incidence of AAGA (as reported post-operatively by patients), in two cohorts: those receiving routine care, and those receiving BIS-monitoring in addition to routine care (36). In the routine care group, 11 of 1238 patients reported experiencing AAGA post-operatively, while in the BIS-monitor group, 2 of 1225 patients reported experiencing AAGA. The use of the Bispectral Index reduced the incidence of reported cases of AAGA by 82%, when compared to routine care. Nevertheless, Avidan and colleagues found that monitoring with the BIS produced no additional reduction in AAGA, when compared to a protocol based on minimum end-tidal concentration of volatile anesthetics (2). Indeed, both studies identified patients who post-operatively reported experiencing AAGA, despite the BIS showing an 'adequate' level of anesthesia (less than 60) at the time AAGA was likely to have occurred, based on the patients' reports. These studies suggest that processed-EEG monitors can discriminate between conscious and unconscious patients with at most 90% accuracy. In other words, 10% or more of patients who remain aware, may be mistakenly identified as unconscious (22,35).

## 4. UNDERSTANDING CMD

### 4.1. Incidence

It is estimated that there are between 13,000 and 53,000 patients currently in a vegetative state (VS) in the United States (37). The most common acute causes of VS are traumatic brain injury, and hypoxic-ischemic encephalopathy (4). Typically, patients are in a comatose state for several days or weeks (38), before emerging into the vegetative state, which is classified as 'permanent' 3 months after non-traumatic brain damage, or 12 months after traumatic brain injury (4, 39) (Figure 2).

A clinical diagnosis of VS is made on the basis of a standardized clinical behavioral assessment (e.g., the Coma Recovery Scale Revised) (40). VS patients exhibit signs of wakefulness —i.e., periodic eye opening and closing— but show no evidence of voluntary response to visual, auditory, tactile or noxious stimulation, and no evidence of language comprehension, or meaningful expression (4) (Figure 3). The clinical evaluation of behaviorally non-responsive patients is challenging and results in high misdiagnosis rates. Up to 43% of patients initially diagnosed as VS demonstrate (at least minimal) awareness after more specialized behavioral examinations (41).

A subset of patients who repeatedly fail to demonstrate behavioral signs of awareness on specialized assessments, can nevertheless show preserved basic sensory functions and higher cognitive processes, such as emotional and semantic processing, when their brain responses are measured with EEG or functional Magnetic Resonance Imaging (fMRI). In fact, a proportion of these patients (14-19%) (5-6), are even able to demonstrate conscious awareness by modulating their brain activity in different types of neuroimaging paradigms (43-44).

### 4.2. Detecting covert awareness

#### 4.2.1. Command following paradigms

In one such neuroimaging paradigm, patients are asked to imagine performing motor (e.g., playing tennis) or spatial navigation (e.g., moving around their house) mental imagery, for 30-second intervals, followed by periods of rest (44). In another kind of

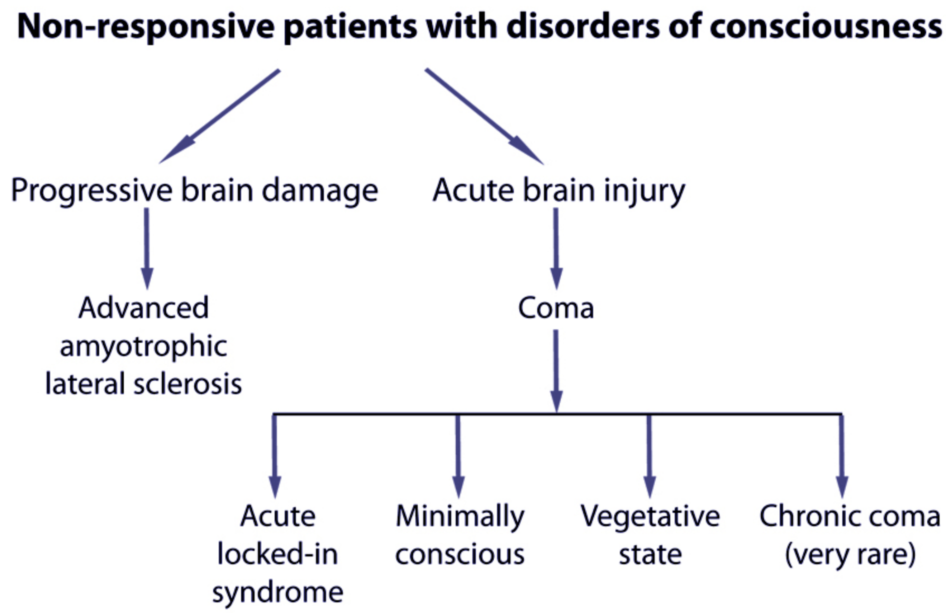


**Figure 2.** Flow chart of patient populations that exhibit non-responsive conditions. (Reproduced with permission from Naci *et al*., 2012.)

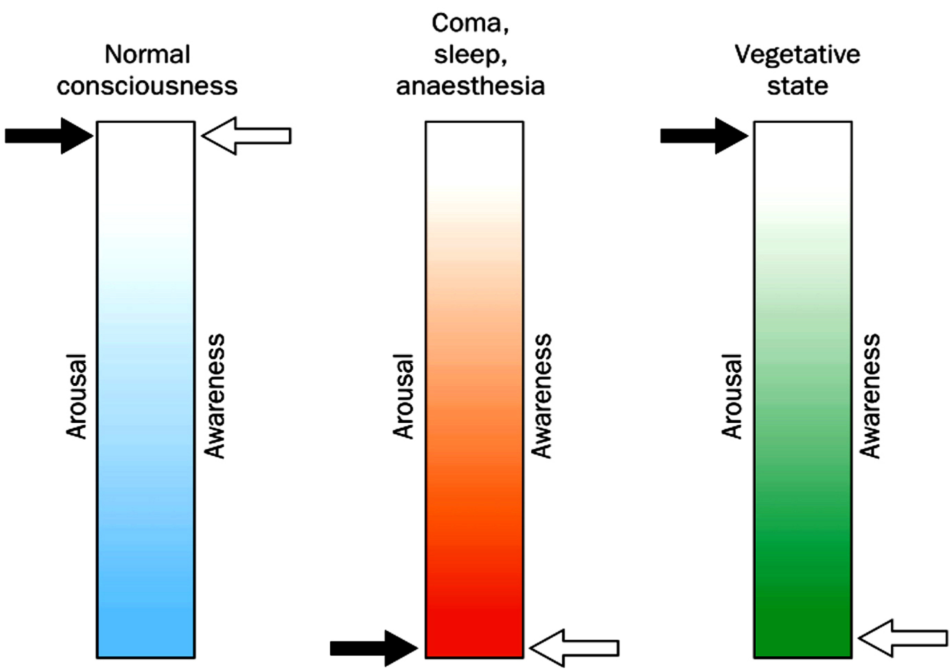


**Figure 3.** Awareness and arousal levels for disorders of consciousness. The level of awareness (of oneself and surroundings) and arousal (eye opening, sleep-wake cycles) for different states of intact, altered or absent consciousness are depicted. (Adapted with permission from (62).

paradigm, patients are asked to either selectively attend to the presentation of a target word while ignoring a non-target word (either "yes" or "no"), or relax, in on-off blocks of 30 seconds (34). Patients who successfully perform these tasks show task-appropriate activity in pre-specified brain regions that is statistically similar to that of healthy controls (Figure 4; Figure 5). These brain responses are reproducible, sustained over long time-intervals, and initiated or terminated according to the examiner's commands, thus allowing researchers to conclude that the patient is consciously aware. However, at most, 19% (5-6) of behaviorally non-responsive patients can demonstrate their awareness via such neuroimaging-based command-following paradigms. Apart from genuine lack of awareness, impaired attention may explain this

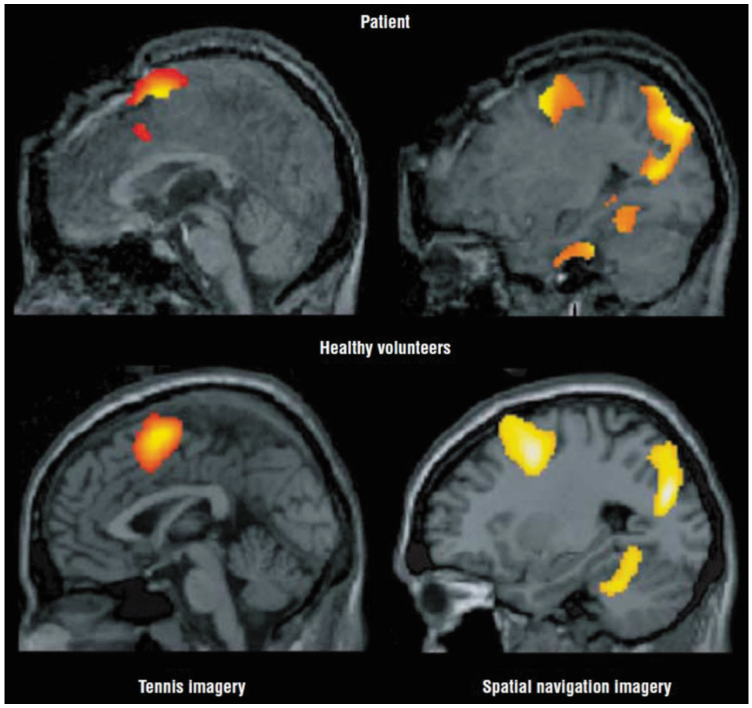


Figure 4. Command-following via mental imagery in one patient clinically diagnosed as being in a vegetative state. The top panel shows the brain activation in responses of the supplementary motor area (SMA) during tennis imagery, and the parahippocampal gyrus (PPA), posterior parietal-lobe (PPC), and lateral premotor cortex (PMC) during imagery of spatial navigation, in a patient who fulfilled all of the internationally agreed criteria for the vegetative state. These responses were indistinguishable from that of a group of healthy volunteers, shown in the bottom panel. Reproduced and adapted with permission from (44).

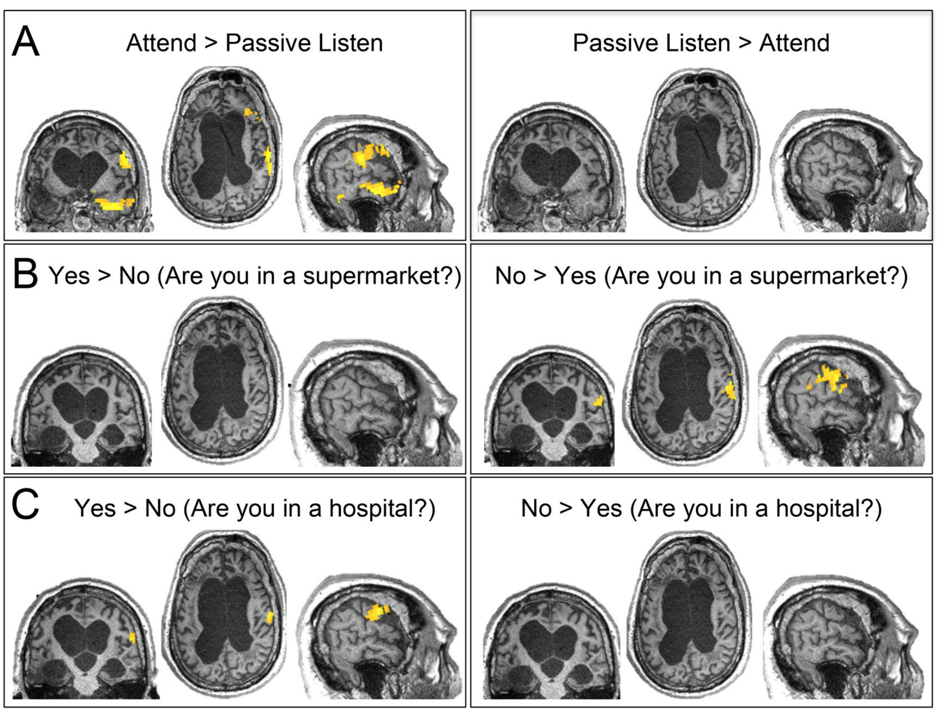


Figure 5. Command-following and communication scans in a patient clinically diagnosed as being in a vegetative state. Brain activity is overlaid on the patient's native anatomic volume. The opposite directions of each contrast (i.e., *a* > *b* or *b* > *a*) are shown on the left and right sides of each panel. A) The command-following scan also served to localize the brain foci of attention unique to the patient. B and C) Selective attention to the answer word (either yes or no) during each communication scan was investigated within these regions. Attention to the answer in each question (B, no; C, yes) significantly activated the precentral or motor region. Reproduced with permission from (43).

low responsivity rate. The requirement that a patient must be able to produce brain responses as prescribed by study instructions, in order to demonstrate that he/she is aware, is likely too stringent and hinders many patients who are aware, but, due to the effects of brain injury, fail to comply with structured instructions.

#### 4.2.2. Naturalistic paradigms

Recently, a different approach has been developed by Naci and colleagues aimed at the roughly 80% of behaviorally non-responsive patients who cannot respond using command-following paradigms (45-47). Rather than relying on the performance of specific mental tasks in response to arbitrary commands, this paradigm involves free-viewing of highly engaging audio-visual or auditory-only movies, which create an immersive experience and capture attention naturally. This leads to better task compliance, reduced movement, (48) and stronger brain activity than epoch-based fMRI task designs (49-50).

Previous studies examining brain activity during movie watching found highly synchronized activity across healthy participants, throughout the brain (51-52). However, prior to Naci and colleagues, it was unclear whether this synchronized activity reflected similar executive function across different individuals in response to the evolving executive demands of the movie plot (45). Naci and colleagues focused on the synchronized brain activity in frontal and parietal regions, known to support executive function (53-56). Not only did these regions display high synchronization across participants, but this synchronization was absent when participants were presented with a scrambled version of the movie that lacked a coherent plot.

Moreover, researchers found that the movie's executive demands, assessed quantitatively with a dual-task procedure in an independent group, predicted activity in these frontal and parietal regions (45). Importantly, the ratings of suspense at various points in the movie —obtained from a third group of participants— showed significant similarity across participants, confirming the common conscious experience of the individuals watching it. Similar to the executive demands, the ratings of suspense predicted activity in the frontal and parietal cortex. Together, these results suggested that the movie's executive demands drove brain activity in frontal and parietal regions, and further, that the synchronization of this activity across individuals underpinned their similar experience. More broadly, these findings suggested that there is a common neural code that underpins similar conscious experiences, which could be used to decode these experiences in the absence of behavior (45).

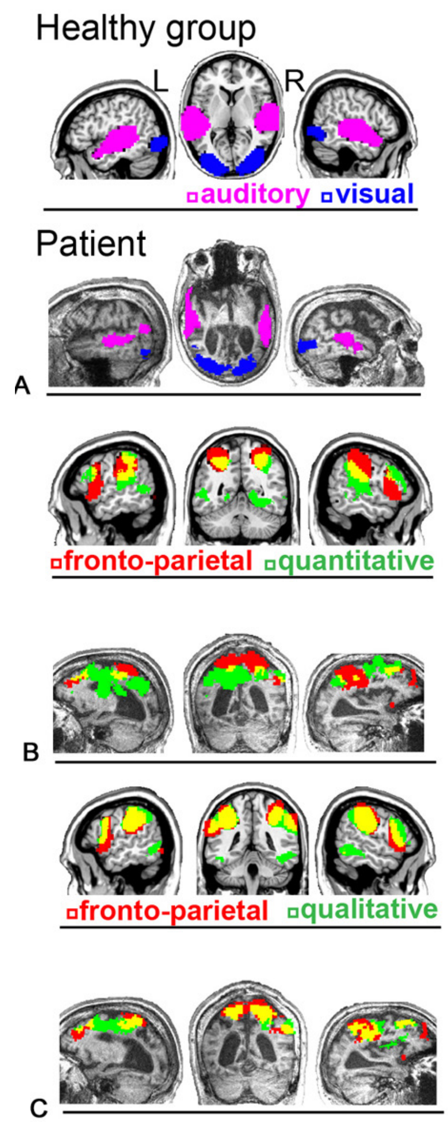


**Figure 6.** Decoding executive function in one patient thought to lack consciousness. *Healthy group*: (*A*) Group-level auditory (purple) and visual (blue) ICs. (*B–C*) The healthy group's activity predicted by the quantitative (*B*)/qualitative (*C*) executive measure (green) is overlaid on the group fronto-parietal IC (red); overlap areas are displayed in yellow. *Patient*: (*A*) The healthy group's auditory and visual ICs predicted significant activity in the Patient's auditory (purple) and visual (blue) cortex, respectively. (*B–C*) The quantitative (*B*) and qualitative (*C*) executive measures predicted activity (green) in the Patient's frontal and parietal regions. Overlap with activity predicted by the healthy group's fronto-parietal IC (red) is displayed in yellow. Reproduced and adapted with permission from (45).

Using this approach, Naci and colleagues demonstrated that a patient who had been behaviorally non-responsive and thought to lack consciousness for 16 years was not only consciously aware, but understood and experienced suspense on a moment-to-moment basis in the same way as every healthy individual watching the same movie (45) (Figure 6). Further, Naci and colleagues developed an auditory-

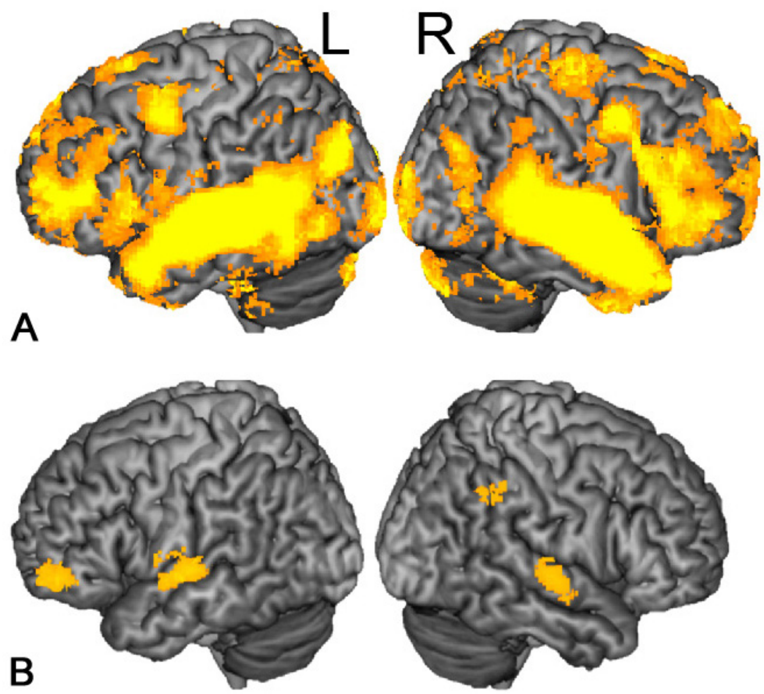


**Figure 7.** Brain-wide inter-subject correlation of neural activity while listening to a suspenseful audio-story during wakefulness and deep anesthesia. (A) The audio-story elicited significant ($p<0.05$; FWE cor) inter-subject correlation across the brain, including frontal and parietal cortex, thought to support executive function. (B) In deep anesthesia, with the exception of a small isolated cluster in the left frontal cortex, inter-subject correlation in frontal and parietal cortex was extinguished, suggesting that understanding of the story's high-level properties, including its narrative was abolished. Warmer colors depict higher t-values of inter-subject correlation. Adapted with permission from (63).

only version of this paradigm for testing patients who have their eyes closed in the comatose state or during deep anesthesia (46). An independent study found that the fronto-parietal activity in response to this audio narrative was extinguished in deeply anesthetized unconscious individuals (Figure 7), further suggesting that the brain responses in these regions could not be realized without the presence of covert conscious awareness (Naci *et al.*, under review).

In addition to providing compelling evidence of preserved awareness, the successful completion of the narrative paradigm not only suggests preserved cognition, such as language comprehension, working memory, and executive function, but critically, more complex mental faculties such as theory of mind, the ability to make morally significant distinctions, and the capacity to experience emotions and reflect about potential future states (57).

## 5. ADAPTING NEUROIMAGING PARADIGMS TO THE ANESTHESIA CONTEXT

Both processed-EEG monitors currently used to track depth-of-anesthesia and neuroimaging paradigms used to detect consciousness in severely brain-injured patients share the common aim of detecting covert awareness in behaviorally non-responsive patient populations. However, they employ fundamentally different approaches. On the one hand, processed-EEG monitors measure the spontaneous EEG signal in response to increasing doses of anesthetics and use elements of this signal to infer when consciousness is absent, based on a database of typical brain activity. On the other hand, command-following paradigms are based on a well-established clinical marker of consciousness (i.e., the ability to follow commands), and the naturalistic paradigm elicits a specific pattern of brain activation underlying executive function, which implies the presence of consciousness. In other words, processed-EEG monitors provide a broad measure of brain activity in response to anesthesia, whereas command-following and naturalistic paradigms elicit specific brain responses that strongly suggest the presence of consciousness. Like other authors (58), we argue that accurate monitoring of awareness during general anesthesia requires an approach that interrogates clinical markers of consciousness, which are abolished in all states of unconsciousness, and resume at a normal level during conscious processing. By contrast, the current generation of processed-EEG monitors does not satisfy this requirement. Therefore, we suggest that the command-following and naturalistic paradigms may be useful in supplementing traditional methods of detecting consciousness in the anesthesia context. The clearly demarcated patterns of brain activity these paradigms are designed to elicit and detect can serve as clinical markers of consciousness, and the employment of these paradigms may help to address the challenge of AAGA.

One potential approach involves adapting neuroimaging command-following and naturalistic paradigms developed for severely brain-injured patients to the anesthesia context. EEG has previously been used to identify covert awareness in behaviorally non-responsive patients with a similar degree of accuracy as fMRI, by detecting characteristic EEG responses indicative of command-following (42). It may be possible to ask intraoperative patients to perform simple command-following mental imagery or selective attention tasks pre- and post- induction, to verify loss of consciousness. The presence of brain responses previously established in healthy controls and patients who harbor covert awareness, would indicate to the surgical team that the patient has regained awareness. In the context of brain injury, the success of command-following paradigms as a measure for detecting awareness is limited by brain-injured patients' inability to sustain attention to arbitrary commands. Similarly, in the anesthesia context, successful compliance with the arbitrary instructions, and engagement with the specific on/off regime of these tasks is likely hampered by disrupted attention due to the anesthesia drug cocktail.

By contrast, the naturalistic paradigm captures attention naturally through an engaging narrative and does not require overt or covert action, and thus, is likely to maximize the chances of detecting awareness in patients who cannot successfully comply with arbitrary study commands. Prior to receiving anesthesia, patients might be instructed to attend to a brief auditory narrative delivered subsequently to the anesthetics. When unconsciousness is reached, the characteristic pattern of fronto-parietal activation observed in healthy controls and brain-injured patients with covert awareness will be extinguished. Conversely, if this pattern is observed it would suggest that anesthesia is 'light' due to high individual tolerance or a medical dosing error and that the patient retains awareness. Indeed, as Mashour suggests, 'light' anesthesia relative to the requirements of a specific patient is the most important risk factor for AAGA (25).

The aforementioned neuroimaging paradigms offer several advantages over current methods for monitoring awareness in the anesthesia context. First, they interrogate the presence of well-understood cognitive responses that strongly suggest the presence of consciousness. Thus, a positive response to these tasks provides strong evidence of consciousness. By contrast, brain monitors provide only an indirect measure of a patient's consciousness —inferred from the degree of resemblance between a patient's EEG, and the EEG pattern of an exemplar unconscious brain— and may fail to accurately capture the patient's conscious brain responses. Further, several studies suggest that BIS values may be drug specific, whereas the aforementioned neuroimaging paradigms interrogate the presence of consciousness with respect to *a priori* benchmarks defined in healthy participants, and therefore are insensitive to the idiosyncratic effects of various anesthetic agents.

Further work is required to translate the naturalistic paradigm to the clinical anesthesia context. For example, efforts are ongoing to adapt this paradigm to portable technologies such as EEG that are practical for the surgical anesthesia environment. Moreover, real-time determination of conscious awareness is a requirement for depth-of-anesthesia monitoring. The implementation of the naturalistic paradigm requires the development of a methodology for detecting, with EEG, the activity in the frontal and parietal brain regions that is characteristic of executive processing, and presenting this information in real-time in a simplified manner that can be interpreted by the surgical team.

Thus, in order to complement existing methods with more accurate neuroscientific paradigms for monitoring depth of anesthesia, novel technology for rapid analysis of large datasets from continuous stimulus processing will be required. We note that the naturalistic paradigm, as we have described it, is unable to anticipate AAGA before it occurs, similarly to the IFT, or current processed-EEG depth of anesthesia monitors. However, a significant harm during AAGA arises from the patient's inability to indicate their awareness to the medical team and the ensuing distress or anxiety (1, 13, 15, 59, 60). AAGA is harmful to patients primarily insofar as it results in painful experience, or causes distress or anxiety, with the latter strongly correlated with the occurrence of negative post-operative sequelae like PTSD (1, 3, 59). Thus, by providing a sensitive indicator of covert awareness, the naturalistic paradigm can quickly alert the anesthesiologist that the patient has become aware,

## 6. ACKNOWLEDGEMENTS

This research was supported by the Canada Excellence Research Chairs (CERC) program and the Canadian Institutes of Health Research. AMO holds a CERC. CW holds a Tier I Canada Research Chair. LN holds a L'Oréal-UNESCO for Women in Science Research Excellence Grant. The authors declare no conflict of interest.

## 7. REFERENCES

1. J.J. Pandit, T.M. Cook The NAP5 Steering Panel. NAP5. Accidental Awareness During General Anesthesia in the United

Kingdom and Ireland: Report and Findings. *The Royal College of Anesthetists and Association of Anesthetists of Great Britain and Ireland* (2014) Available at: http://www.nationalauditprojects.org.uk/NAP5_home

2. M.S. Avidan, L. Zhang, B.A. Burnside, K.J. Finkel, A.C. Searleman, J.A. Selvidge, L. Saager, M.S. Turner, S. Rao, M. Bottros, C. Hantler, E Jacobsohn, A.S. Evers. Anesthesia awareness and the Bispectral Index. *NEJM* 358, 1097-1108 (2008)
DOI: 10.1056/NEJMoa0707361

3. G.A. Mashour, M.S. Avidan. Intraoperative awareness: controversies and non-controversies. *Br J Anaesth* 115 (Suppl. 1), i20-i26 (2015)
DOI: 10.1093/bja/aev034

4. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state. *NEJM* 330, 1572-1579 (1994)
DOI: 10.1056/NEJM199406023302206

5. M.M. Monti, A. Vanhaudenhuyse, M.R. Coleman, M. Boly, J. Pickard, L. Tshibanda, A.M. Owen, S. Laureys. Willful modulation of brain activity in disorders of consciousness. *NEJM* 362, 579-589 (2010)
DOI: 10.1056/NEJMoa0905370

6. D. Kondziella, C.K. Friberg, V.G. Frokjaer, M. Fabricius, K. Moller. Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 87(5), 485-492 (2016)
DOI: 10.1136/jnnp-2015-310958

7. N.D. Schiff. Altered consciousness. In: Youmans and Winn's Neurological Surgery. 7th ed. Eds. R. Winn. Elsevier Saunders New York, New York (2006)

8. R.R. Bruchas, C.D. Kent, H.D. Wilson, K.B. Domino. Anesthesia awareness: Narrative review of psychological sequelae, treatment, and incidence. *J Clin Psychol Med Settings* 18(3), 257-267 (2011)
DOI: 10.1007/s10880-011-9233-8

9. W. Glannon. Anesthesia, amnesia and harm. *J Med Ethics* 40(10), 651-657 (2014)
DOI: 10.1136/medethics-2013-101543

10. C.D. Kent, K.L. Posner, G.A. Mashour, S.L. Mincer, R.R. Bruchas, A.E. Harvey, K.B. Domino. Patient perspectives on intraoperative awareness with explicit recall: Report from a North American anesthesia awareness registry. *Br J Anaesth* 115(Suppl. 1), i114-i121 (2015)
DOI: 10.1093/bja/aev211

11. M. Pistorius *Ghost Boy: The Miraculous Escape of a Misdiagnosed Boy Trapped Inside His Own Body*, Nelson Books Nashville Tennessee (2013)

12. M. Graham, C. Weijer, D. Cruse, D. Fernandez-Espejo, T. Gofton, L. Gonzalez-Lara, A. Lazosky, L. Naci, L. Norton, A. Peterson, K.N. Speechley, G.B. Young, A.M. Owen. An ethics of welfare for patients diagnosed as vegetative with covert awareness. *AJOB Neurosci* 6(2), 31-41 (2015)
DOI: 10.1080/21507740.2015.1014072

13. M. Graham, A.M. Owen, K. Cipi, C. Weijer, L. Naci. Minimizing the harm of accidental awareness under general anesthesia: New perspectives from patients misdiagnosed as being in a vegetative state. *Anesth Analg* (2017)
DOI: 10.1.213/ANE.0000000000002495

14. R.H. Sandin, G. Enlund, P. Samuelsson, C. Lennmarken. Awareness during anesthesia: a prospective case study. *Lancet* 355, 707-711 (2000)
DOI: 10.1016/S0140-6736(99)11010-9

15. M.M. Ghoneim, R.I. Block, M. Haffarnen, M.J. Mathews. Awareness during anesthesia: risk factors, causes and sequelae: a review of reported cases in the literature. *Anesth Analg* 108, 527-535 (2009)
DOI: 10.1213/ane.0b013e318193c634

16. R.D. Sanders, A. Gaskell, A. Raz, J. Winders, A. Stevanovic, R. Rossaint, C. Boncyk, A Defresne, G. Tran, S. Tasbihgou, S. Meier, P.E. Vlisides, H. Fardous, A. Hess, R.M. Bauer, A. Absalom, G.A. Mashour, V. Bonhomme, M. Coburn, J. Sleigh. Incidence of connected consciousness after tracheal intubation: A prospective, international, multi-center cohort study of the Isolated Forearm Technique. *Anesthesiology*, 126(2): 214-222 (2017)
DOI: 10.1097/ALN.0000000000001479

17. J. Andrade, C. Deeprose. Unconscious memory formation during anaesthesia. *Best Pract Res Clin Anaesthesiol* 21, 385–401 (2007)
DOI: 10.1016/j.bpa.2007.04.006

 

18. M.M. Ghoneim Incidence of and risk factors for awareness during anaesthesia. *Best Pract Res Clin Anaesthesiol* 21, 327-343 (2007)
DOI: 10.1016/j.bpa.2007.05.002

19. A. Aranake, G.A. Mashour, M.S. Avidan. Minimum alveolar concentration: ongoing relevance and clinical utility. *Anaesthesia* 68, 512-522 (2013)
DOI: 10.1111/anae.12168

20. M.S. Avidan, E. Jacobsohn, D. Glick, B.A. Burnside, L. Zhang, A. Villafranca, L. Karl, S. Kamal, B. Torres, M. O'Connor, A.S. Evers, S. Gradwohl, N. Lin, B.J. Palanca, G.A. Mashour. Prevention of intraoperative awareness in a high-risk surgical population. *NEJM* 365, 591-600 (2011)
DOI: 10.1056/NEJMoa1100403

21. R.D. Miller, M. Pardo, R.K. Stoelting. *Basics of Anesthesia*. 6th ed., Elsevier (2011)

22. B.J. Palanca, A. Searleman, M.S. Avidan. Current controversies in intraoperative awareness: II. In: *Consciousness, Awareness, and Anesthesia*. Eds. G.A. Mashour Cambridge University Press New York, New York (2010)

23. E. Eger, S.L. Shafer. Tutorial: context-sensitive decrement times for inhaled anesthetics. *Anesth Analg* 101(3), 688-696 (2005)
DOI: 10.1213/01.ANE.0000158611.15820.3D

24. D.K. Gupta, E. Eger. Inhaled anesthesia: The original closed-loop drug administration paradigm. *Clin Pharmacol Ther* 84(1), 15-18 (2008)
DOI: 10.1038/clpt.2008.85

25. G.A. Mashour, B.A. Orser, M.S. Avidan. Intraoperative awareness: from neurobiology to clinical practice. *Anesthesiology* 114(5), 1218-1223 (2011)
DOI: 10.1097/ALN.0b013e31820fc9b6

26. T. Musialowicz, P. Lahtinen. Current status of EEG-based depth-of-consciousness monitoring during general anesthesia. *Curr Anesthesiol Rep* 4(3), 251-260 (2014)
DOI: 10.1007/s40140-014-0061-x

27. I.J. Rampil. A primer for EEG signal processing in anesthesia. *Anesthesiology* 89(4), 980-1002 (1998)
DOI: 10.1097/00000542-199810000-00023

28. G. Schneider. Monitoring anesthetic depth. In: *Consciousness, Awareness, and Anesthesia*. Eds. G.A Mashour. Cambridge University Press New York, New York, 114-130 (2010)
DOI: 10.1017/CBO9780511676291.007

29. J.W. Johansen, P.S. Sebel. Development and clinical application of electroencephalographic bispectrum monitoring. *Anesthesiology* 93(5), 1336-1344 (2000)

30. M. Messner, U. Beese, J. Romstock, M. Dinkel, K. Tschaikowsky. The bispectral index declines during neuromuscular block in fully awake persons. *Anesth Analg* 97, 488-491 (2003)
DOI: 10.1213/01.ANE.0000072741.78244.C0

31. P. Hans, P.Y. Dewandre, J.F. Brichant, V. Bonhomme. Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anesthesia. *Br J Anaesth* 94(3), 336-340 (2005)
DOI: 10.1093/bja/aei047

32. O. Detsch, G. Schneider, E. Kochs, G. Hapfelmeier, C. Werner. Increasing isoflurane concentration may cause paradoxical increases in the EEG Bispectral Index in surgical patients. *Br J Anaesth* 84(1), 33-37 (2000)
DOI: 10.1093/oxfordjournals.bja.a013378

33. J.J. Edwards, R.G. Soto, D.M. Thrush, R.F. Bedford. Bispectral Index scale is higher for halothane than sevoflurane during intraoperative anesthesia. *Anesthesiology* 99, 1453-1455 (2003)
DOI: 10.1097/00000542-200312000-00032

34. G.S. Rao, Z. Ali, R. Madhusudan, J. Patil. Equi-MAC concentrations of halothane and isoflurane do not produce similar Bispectral Index values. *J Neurosurg Anesthesiol* 19(2), 93-96 (2007)
DOI: 10.1097/ANA.0b013e31803062f9

35. N. Jagadeesan, M. Wolfson, Y. Chen, M. Willingham, M.S. Avidan. Brain monitoring during general anesthesia. *Curr Anaesth Crit Care* 3(1), 13-18 (2013)
DOI: 10.1016/j.tacc.2012.12.003

36. P.S. Myles, K. Leslie, J. McNeil, A. Forbes, M.T. Chan. Bispectral Index monitoring to prevent awareness during anaesthesia: The B-Aware randomised control trial. *Lancet*

363(9423), 1757-1763 (2004)
DOI: 10.1016/S0140-6736(04)16300-9

37. J.G. Beaumont, P. Kenealy. Incidence and prevalence of the vegetative and minimally conscious states. *Neuropsychol Rehabil* 15(3-4), 184-189 (2005)
DOI: 10.1080/09602010443000489

38. G.B. Young. Coma. *Ann N Y Acad Sci* 1157(1), 32-47 (2009)
DOI: 10.1111/j.1749-6632.2009.04471.x

39. Royal College of Physicians. The vegetative state: Guidance on diagnosis and management. *Clin Med* 3, 249-254 (2003)
DOI: 10.7861/clinmedicine.3-3-249

40. J.T. Giacino, K. Kalmar, J. Whyte. The JFK Coma Recovery Scale Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 85(12), 2020-2029 (2004)
DOI: 10.1016/j.apmr.2004.02.033

41. C. Schnakers, A. Vanhaudenhuyse, J. Giacino, M. Ventura, M. Boly, S. Majerus, G. Moonen, S. Laureys. Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioural assessment. *BMC Neurol* 9(35) (2009)
DOI: 10.1186/1471-2377-9-35

42. D. Cruse, S. Chennu, C. Chatelle, T.A. Bekinschtein, D. Fernandez-Espejo, J.D. Pickard, S. Laureys, A.M. Owen. Bedside detection of awareness in the vegetative state: a cohort study. *Lancet* 378(9809), 2088-2094 (2011)
DOI: 10.1016/S0140-6736(11)61224-5

43. L. Naci, A.M. Owen. Making every word count for vegetative patients. *JAMA Neurol* 70(10), 1235-41 (2013)

44. A.M. Owen, M.R. Coleman, M. Boly, M.H. Davis, S. Laureys, J.D. Pickard. Detecting awareness in the vegetative state. *Science*, 313(5792), 1402 (2006)
DOI: 10.1126/science.1130197

45. L. Naci, R. Cusack, M. Anello, A.M. Owen. A common neural code for similar conscious experiences in different individuals. *PNAS* 111(39), 14277-14282 (2014)
DOI: 10.1073/pnas.1407007111

46. L. Naci, L. Sinai, A.M. Owen. Detecting and interpreting conscious experiences in behaviorally non-responsive patients. *NeuroImage.* 145(Pt B), 304-313 (2017)

47. L. Sinai, A.M. Owen, L. Naci. Mapping preserved real-world cognition in brain-injured patients. *Front Biosci* 22, 815-823 (2017)
DOI: 10.2741/4518

48. M. Centeno, T.M. Tierney, S. Perani, E.A. Shamshiri, K. St.Pier, C. Wilkinson, D. Konn, T. Banks, S. Vulliemoz, L. Lemieux, R.M. Pressler, C.A. Clark, J.H. Cross, D.W. Carmichael. Optimising EEG-fMRI for Localisation of Focal Epilepsy in Children. *Plos One* (2016)
DOI: 10.1371/journal.pone.0149048

49. A. Bartels, S. Zeki. Functional brain mapping during free viewing of natural scenes. *Hum Brain Mapp* 21(2), 75-85 (2005)
DOI: 10.1002/hbm.10153

50. A. Bartels, S. Zeki, N.K. Logothetis. Natural vision reveals regional specialization to local motion and to contrast-invariant, global flow in the human brain. *Cereb Cortex* 18(3), 705-17 (2008)
DOI: 10.1093/cercor/bhm107

51. U. Hasson, Y. Nir, I. Levy, G. Fuhrmann, R. Malach. Intersubject synchronization of cortical activity during natural vision. *Science* 303(5664), 1634-1640 (2004)
DOI: 10.1126/science.1089506

52. U. Hasson, R. Malach, D.J. Heeger. Reliability of cortical activity during natural stimulation. *Trends Cogn Sci* 14, 40–8 (2010)
DOI: 10.1016/j.tics.2009.10.011

53. A.K. Barbey, R. Colom, J. Solomon, F. Krueger, C. Forbes, J. Grafman. An integrative architecture for general intelligence and executive function revealed by lesion mapping. *Brain* 135, 1154-1164 (2012)
DOI: 10.1093/brain/aws021

54. R. Ptak. The frontoparietal attention network of the human brain: action, saliency, and a priority map of the environment. *Neuroscientist* 18(5), 505-515 (2012)
DOI: 10.1177/1073858411409051

55. J. Duncan. The multiple-demand (MD) system of the primate brain: Mental programs for intelligent behavior. *Trends Cogn Sci* 14(4), 172-179 (2010)
DOI: 10.1016/j.tics.2010.01.004

56. A. Hampshire, A.M. Owen. Fractionating attentional control using event-related fMRI. *Cereb Cortex* 16(12), 1679-1689 (2006) DOI: 10.1093/cercor/bhj116

57. L. Naci, M. Graham, A.M. Owen, C. Weijer. Covert narrative capacity: A cross-section of the preserved mental life in patients thought to lack consciousness. *Ann of Clin and Translat Neurol* 1, 61–70 (2016)

58. M. Boly, R.D. Sanders, G.A. Mashour, S. Laureys. Consciousness and responsiveness: lessons from anesthesia and the vegetative state. *Curr Opin Anesthesiol* 26(4), 444-449 (2013) DOI: 10.1097/ACO.0b013e3283628b5d

59. J.E. Osterman, J. Hopper, W.J. Hernan, T.M. Keane, B.A. van der Kolk. Awareness under anesthesia and the development of post-traumatic stress disorder. *Gen Hosp Psychiatry* 23, 198-204 (2001) DOI: 10.1016/S0163-8343(01)00142-6

60. R. Samuelsson, L. Brudin, R.H. Sandin. Late psychological symptoms after awareness among consecutively included surgical patients. *Anesthesiology* 106, 26-32 (2007) DOI: 10.1097/00000542-200701000-00009

61. L. Naci, M.M. Monti, D. Cruse, B. Sorger, G.A. Rainer, B. Kotchoubey, A. Kubler, A.M. Owen. Brain-computer interfaces for communication with non-responsive patients. *Ann Neurol* 72(3), 312–23 (2012) DOI: 10.1002/ana.23656

62. S. Laureys, A.M. Owen, N.D. Schiff. Brain function in coma, vegetative state, and related disorders. *Lancet Neurol* 3, 537–46 (2004) DOI: 10.1016/S1474-4422(04)00852-X

63. L. Naci, E. Houldin, R. Cusack, M. Arango, C. Harle, A.M. Owen. Processing of complex, real world information as awareness fades under sedation. *Soc Neurosci* (2015)

**Send correspondence to:** Lorina Naci, School of Psychology, Trinity College Dublin, Dublin 2, Ireland, Tel: 3530876885642, Fax: 353018 963 183, E-mail: nacil@tcd.ie

**Key Words:** Anesthesia, Accidental Awareness, Neuroimaging, Severe Brain Injury, Covert Consciousness, Vegetative State

**Send correspondence to:** Lorina Naci, School of Psychology, Trinity College Dublin, Dublin 2, Ireland, Tel: 3530876885642, Fax: 353018963183, E-mail: nacil@tcd.ie