Detecting awareness after acute brain injury

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Advances over the past two decades in functional neuroimaging have provided new diagnostic and prognostic tools for patients with severe brain injury. Some of the most pertinent developments in this area involve the assessment of residual brain function in patients in the intensive care unit during the acute phase of severe injury, when they are at their most vulnerable and prognosis is uncertain. Advanced neuroimaging techniques, such as functional MRI and EEG, have now been used to identify preserved cognitive processing, including covert conscious awareness, and to relate them to outcome in patients who are behaviourally unresponsive. Yet, technical and logistical challenges to clinical integration of these advanced neuroimaging techniques remain, such as the need for specialised expertise to acquire, analyse, and interpret data and to determine the appropriate timing for such assessments. Once these barriers are overcome, advanced functional neuroimaging technologies could improve diagnosis and prognosis for millions of patients worldwide.

Introduction

Detection of signs of preserved awareness in patients after severe acute brain injury who are being treated in the intensive care unit (ICU) is both clinically and scientifically challenging.[1,2] Currently, there are few tools used in clinical practice that objectively measure brain function, which means that treatment decisions are largely determined by unreliable behavioural responses that are dependent on various clinical and environmental considerations. Signs of awareness are one of the most important factors in the decision-making process surrounding goals of care, which can include access to rehabilitative resources or the withdrawal of life-sustaining measures.[3] Given that withdrawal of life-sustaining measures is the leading cause of death in the ICU,[4,5] accurate detection of preserved awareness, whether overt or covert, is of paramount importance.

Panel 1: Glossary

Disorders of consciousness
A group of conditions in which an individual's level of consciousness is impaired after a brain injury, including coma, the vegetative state, and the minimally conscious state. Disorders of consciousness are characterised by alterations in arousal or awareness (or both).

Coma
A state of profound unconsciousness in which an individual is unresponsive to external stimuli and cannot be awakened.

Vegetative state or unresponsive wakefulness syndrome
A condition in which a person appears to be awake but shows no signs of awareness. People in a vegetative state or with unresponsive wakefulness syndrome might retain basic reflexes and can open their eyes spontaneously, but there is no evidence of purposeful behaviour.

Minimally conscious state minus
Patients who have the minimal measurable, and at times inconsistent, evidence of consciousness with no language preservation and show at least one of the following behaviours: visual fixation, object localisation, object manipulation, automatic motor responses, visual pursuit, and localisation to noxious stimuli.

Minimally conscious state plus
Patients who show signs of language function through the ability to either command follow, recognise objects, or produce intelligible verbalisation.

Covert awareness or cognitive motor dissociation
Patients with evidence of covert command following based on functional MRI or EEG responses but with no behavioural signs of language function or command following.

Yet, awareness can be difficult to measure and could go unrecognised in many patients in the ICU. In the past couple of decades, several functional neuroimaging methods have been developed that can detect preserved awareness, even in the absence of any behavioural response. In this Personal View, we argue that there is a compelling case for adopting these tools as standard of care in the acute stages after a severe brain injury. We first outline the most promising functional neuroimaging approaches and comment on their profound diagnostic and prognostic implications. We then describe how these methods could be implemented more broadly to increase their accessibility in centres across the world. Finally, we consider outstanding questions and discuss future directions for the field as a whole.

Disorders of consciousness

Acute severe brain injury can result in various different disorders of consciousness, characterised by disruptions in arousal, awareness, or both (panel 1).[6] Acute disorders of consciousness, as described in this Personal View, pertain to the period of ICU management occurring within the initial 28 days after a severe brain injury.[7] The causes of acute disorders of consciousness can be broadly divided into two categories: structural and metabolic.[8] Structural causes include traumatic brain injuries, intracerebral haemorrhages, and ischaemic stroke, whereas metabolic causes include cardiac arrest and asphyxiation. Coma, the most severe form of disorders of consciousness, involves a complete absence of wakefulness and awareness, with no eye opening.[9] By contrast, the vegetative state, or unresponsive wakefulness syndrome is characterised by a state of wakefulness without awareness as evidenced by spontaneous eye opening but no meaningful interaction with the environment.[10] When a patient is able to show signs of awareness through their behaviour, they are classified as being in a minimally conscious state.[11] This state can be further subdivided into those without language preservation (known as minimally conscious state minus) and those with language preservation (known as minimally conscious state plus; panel 1).[12] The outcomes of acute disorders of consciousness vary from complete functional and neurological recovery to protracted vegetative or minimally conscious state and, in many cases, death from the withdrawal of life-sustaining measures, highlighting the complexity and diversity of these conditions.[6]

Pathophysiology

Although various injuries can lead to acute disorders of consciousness, the underlying pathophysiology typically involves a widespread decrease in excitatory synaptic activity throughout the cortex.[13,14] This decrease in neuronal firing is caused by the structural loss of synaptic inputs or a reduction in inputs to neurons in the thalamus and neocortex.[15] The ascending reticular activating system (ARAS) plays a central role in the pathophysiology of disorders of consciousness.[16,17] The ARAS is a bundle of neurons that originate in the brainstem and project diffusely to the thalamus, hypothalamus, basal forebrain, and cerebral cortex and is crucial to maintaining awareness. Through projections from the thalamus to the cortex, the ARAS activates cortically based awareness networks.[16,18] Thus, disruption of the ARAS leads to impaired transmission of neuronal firing that is essential for maintaining awareness, resulting in impaired consciousness.[6] This disruption is a result of direct damage to the ARAS itself, or secondary injury mechanisms, such as inflammation, excitotoxicity, and oxidative stress, which can further damage the ARAS and surrounding structures, prolonging the disturbance in consciousness. A comprehensive analysis of coma-causing lesions has revealed that damage to the pontine tegmentum, and more specifically the left parabrachial nucleus, is strongly associated with coma after severe brain injury.[19]

Assessment of consciousness in the ICU

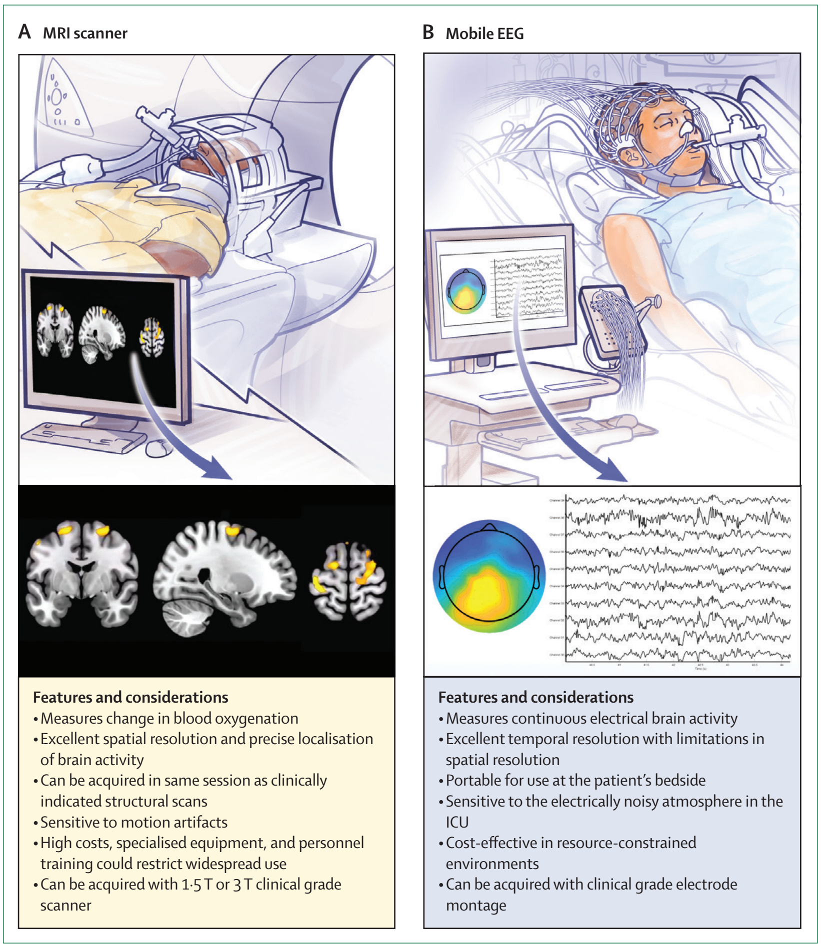
Challenges in assessment

It is often challenging to determine the extent of preserved awareness in a patient with severe brain injury. The ability to follow behavioural commands (eg, “open your fist if you can hear me”) is the gold standard for determining whether or not a patient is aware, because consistent and repeatable responses to a specific command do not occur in the absence of awareness.[20,21] However, behavioural examinations often miss subtle responses, and conscious patients are misclassified as unconscious approximately 40% of the time.[22] In a case report from 2006, it was shown for the first time that a female patient who fulfilled internationally agreed clinical criteria[23] for the vegetative state was in fact covertly aware, despite showing no behavioural signs of following commands.[24] The key observation was that she was able to wilfully respond to commands by modulating her functional MRI (fMRI) activity during a mental imagery task. Because overt (ie, behavioural) following of commands is widely accepted as evidence of consciousness in patients with brain injury, covert following of commands (observed through volitional changes in brain activity) can be used to make the same inference.[20] This occurrence, referred to as covert awareness or cognitive motor dissociation,[25] has been corroborated by numerous follow-up observational studies with fMRI and EEG.[26–28] Indeed, these studies have shown that 15–20% of chronic behaviourally unresponsive patients are in fact aware.[29] In response, multiple international bodies—including the American Academy of Neurology and the European Academy of Neurology—now recommend that functional neuroimaging measures should be used to probe for preserved awareness in some patients who appear to be behaviourally unresponsive.[7,30]

Contemporary assessment

In the acute setting, the Glasgow Coma Scale[31] is typically used to measure behavioural responsiveness and awareness; other scales, such as the Full Outline of Unresponsiveness Score[32] and Coma Recovery Scale-Revised[21] are also used but less frequently.[33] However, these behavioural examinations are often confounded by motor deficits, aphasia, fluctuating vigilance, or sensory impairments during the acute stage of injury, leading to erroneous results.[34] Examiner biases in how subtle behavioural responses are interpreted also reduce the accuracy of these tools.[21] Indeed, although the Coma Recovery Scale-Revised is the most comprehensive and sensitive behavioural assessment of awareness, it fails to detect preserved awareness in approximately 20% of unresponsive patients.[27,35,36] Thus, no tool currently exists in standard clinical practice that can accurately and reliably detect awareness in the ICU, which creates uncertainty for families and physicians making decisions about the continuation of life-sustaining treatments.

In a prospective study from 2017, task-based fMRI and EEG were used for the first time in the ICU to address the extant problem of searching for awareness in behaviourally unresponsive patients.[37] On the basis of imaging findings, four of 16 patients who were assessed in the ICU showed a level of consciousness that was inconsistent with their behavioural diagnosis. This apparent dissociation indicated that task-based neuroimaging in the ICU was feasible, and that it could have a role alongside traditional methods of clinical assessment. 2 years later, EEG and a command-following task were used in a prospective study to show that 16 (15%) of a consecutive series of 104 patients with



A MRI scanner

Features and considerations
- Measures change in blood oxygenation
- Excellent spatial resolution and precise localisation of brain activity
- Can be acquired in same session as clinically indicated structural scans
- Sensitive to motion artifacts
- High costs, specialised equipment, and personnel training could restrict widespread use
- Can be acquired with 1·5 T or 3 T clinical grade scanner

B Mobile EEG

Features and considerations
- Measures continuous electrical brain activity
- Excellent temporal resolution with limitations in spatial resolution
- Portable for use at the patient's bedside
- Sensitive to the electrically noisy atmosphere in the ICU
- Cost-effective in resource-constrained environments
- Can be acquired with clinical grade electrode montage

Figure 1: **Functional MRI and EEG application in the intensive care unit**
(A) Representative visual schematic of a patient with critical illness undergoing functional MRI to assess for covert awareness. Functional MRI activity shows a positive result during a command-following task. (B) Representative visual schematic of a patient with critical illness undergoing an EEG assessment to assess for covert awareness. EEG activity on the topographic plots show a positive result during the test.

severe brain injuries seen in the ICU were covertly aware.[38] Moreover, behaviourally unresponsive patients who had a positive EEG response to the command-following task were 4·6 times more likely to have a good functional recovery than were those who did not show a response on EEG. A follow-up study with 89 additional patients found that those with EEG evidence of command-following also recovered more quickly than those who did not show a response on EEG.[39] These and other studies confirm that, as has also been shown in chronic disorders of consciousness,[40,41] functional neuroimaging can provide important new prognostic indicators of recovery in the ICU in the absence of any behavioural signs of awareness.[42–45]

Although these findings suggest that neuroimaging with fMRI and EEG might enhance both diagnosis and prognosis of patients with severe brain injury in the ICU, there is no agreement about the standard approach that should be adopted, in part because many technologies and methods are available (figure 1). Methodologically, three general approaches are used for assessment: command-following tasks, passive processing, and resting-state techniques.

Command-following tasks

In command-following tasks, patients are asked to do a mental imagery task that requires wilful modulation of brain activity in response to an external command. Here, a positive neuroimaging result depends on participant cooperation, which does not occur in the absence of awareness.[20] Motor imagery (eg, imagining playing tennis or imagining opening and closing one's hand) and spatial navigation (eg, imagining walking through one's home) are the most frequently used command-following tasks to assess for covert awareness.[24,37,46] Of note, some ICU studies have opted to use a motor action task, in which unresponsive patients are instructed to open and close their hand (even though, by definition, they cannot), rather than to imagine that action.[38,39] Typically, these command-following tasks that assess for covert awareness in fMRI and EEG take 5 min or less. Automated pupillometry measurements combined with a mental arithmetic task is an emerging method for identifying covertly aware patients, with a similar success rate as fMRI and EEG.[47]

Passive techniques

Passive processing tasks assess brain activity in response to external stimuli and do not require active participation of the patient. These techniques provide information about preserved brain functioning, and by proxy, could serve as an index of the extent of injury.[40] When high-level auditory tasks have been used (eg, speech sounds), both fMRI and EEG studies have found a correlation between the extent of brain activation and the degree of functional recovery among individuals in the ICU.[42–45] Nevertheless, although these techniques have considerable prognostic potential, it is important to note that awareness is not necessarily required for a positive response to occur, as similar neural signatures have been observed in healthy individuals during anaesthesia or sleep.[48,49] Covert cortical processing is a diagnostic term that has been proposed to characterise patients who show responses in the association cortex to speech stimuli but who do not show evidence of language function on behavioural examinations.[6,50]

Resting-state tasks

Resting-state techniques measure spontaneous correlated patterns of brain activity in the absence of external stimulation. These patterns can be used to identify networks that are associated with various brain processes, including those that support awareness.[51] There is emerging evidence from prospective studies that resting-state techniques can predict the extent of awareness at ICU discharge,[52] as well as long-term recovery from severe brain injury with a higher precision than that of standard clinical tools.[53–58] The high sensitivity of these measures is due to both EEG and fMRI capturing patterns of brain activity that can be objectively quantified. Hence, intact resting-state connectivity could indicate a preserved capacity for the integration of widescale neuronal function that supports awareness and accurately predicts functional outcome.

Clinical implications of detecting covert awareness in the ICU

Detecting awareness in behaviourally unresponsive patients can have profound implications for clinical decision-making.[59] If a patient is known to be covertly aware, discussions regarding care are likely to be entirely different than if the patient is assumed to have no awareness—eg, the discussions could range from aggressive rehabilitation to withdrawal of life-sustaining measures.[3] Moreover, patients with critical illness who are covertly aware might be able to understand conversations around them and perceive pain, challenging assumptions based solely on behavioural assessments.[35] Since the majority of deaths in the ICU after severe brain injury follow the withdrawal of life-sustaining measures,[4,5] accurate and precise assessment of awareness is essential to avoid inappropriate or premature withdrawal.

Advanced neuroimaging techniques also have the potential to provide positive prognostic indicators, which historically have been absent among traditional clinical approaches to management. Existing clinical tools can reliably predict poor recovery—ie, a clinical outcome no better than vegetative state or severe disability with total dependency—but they cannot determine the patients who will have a good outcome.[60] Existing prognostication models (eg, after cardiac arrest, stroke, or traumatic brain injury) are heavily influenced by the amount of awareness, which is crudely assessed with tools such as the Glasgow Coma Scale.[61–63] As described previously, evidence from prospective observational studies has shown that patients with covert awareness (identified through functional neuroimaging) are significantly more likely to have a positive recovery and achieve it more rapidly than are those without covert awareness.[38,39]

When to use advanced neuroimaging in the ICU

The decision about when to use advanced neuroimaging to detect covert awareness in the ICU has multiple considerations. These considerations apply equally to traumatic, anoxic, ischaemic, and haemorrhagic conditions, as well as metabolic and viral encephalopathies that have rendered patients unresponsive.[38,39,43,64] Advanced neuroimaging should be considered in any patients who do not show signs of behavioural command-following with serial, standardised neurological assessments, unless brain death has been confirmed or there are definitive poor prognostic markers (eg, bilaterally absent N20 component of a somatosensory evoked potential in patients who have sustained hypoxic injury).[65–68] The use of advanced neuroimaging would include patients in a coma, vegetative state, and those who are minimally conscious but cannot follow commands (ie, minimally conscious state minus).[69] Recent guidelines[7] from the American Academy of Neurology suggest that advanced neuroimaging is not necessary in patients who are in a minimally conscious state. By contrast, the European Academy of Neurology guidelines endorse task-based fMRI and EEG techniques in any patient without command-following at the bedside, including those diagnosed with a minimally conscious state.[30] We support the European guidelines on this point, because although some patients in a minimally conscious state can exhibit rudimentary signs of awareness (eg, visual fixation, tracking, and localisation of painful stimuli), the fact that some can also follow commands in neuroimaging tasks indicates that they have a greater level of awareness than can be inferred from such behavioural signs.[27,38,29]

When considering the use of advanced neuroimaging, it is also crucial to exclude confounding medications, such as high-dose sedation and anxiolytics. Although the exact threshold for appropriate sedation doses varies by patient, it is important to note that the presence of moderate sedation should not be seen as a substantial barrier to testing for covert awareness. Instead, such sedation should be viewed as a clinical consideration to be mindful of when interpreting results. This view is supported by the findings of the largest prospective observational study assessing for covert awareness to date, which revealed that 67% of covertly aware patients were under a moderate dose of sedation at the time of testing.[39] Medical conditions such as raised intracranial pressure, haemodynamic instability, metabolic derangement, seizures, and hydrocephalus should also be considered before considering use of advanced neuroimaging. Although a specific timeframe cannot always be adhered to, because these medical contraindications are temporally variable, whenever possible, neuroimaging should be initiated as soon as patients become haemodynamically stable and, for patients treated with hypothermia for hypoxic–ischaemic brain injury, when rewarming is completed.[70,71] Moreover, given that discussions with families and surrogate decision makers regarding the continuation (or withdrawal) of life-sustaining therapy typically happen within the first 10–14 days after a brain injury, and in many cases much earlier,[5,72] advanced neuroimaging should be initiated before these discussions. Findings of prospective observational studies have shown that, whenever feasible, testing patients at least twice during the acute phase of injury increases the chance of detecting covert awareness.[37,39]

Clearly, advanced imaging will be unnecessary for some patients—eg, when behavioural command-following is detected. Decision trees have been

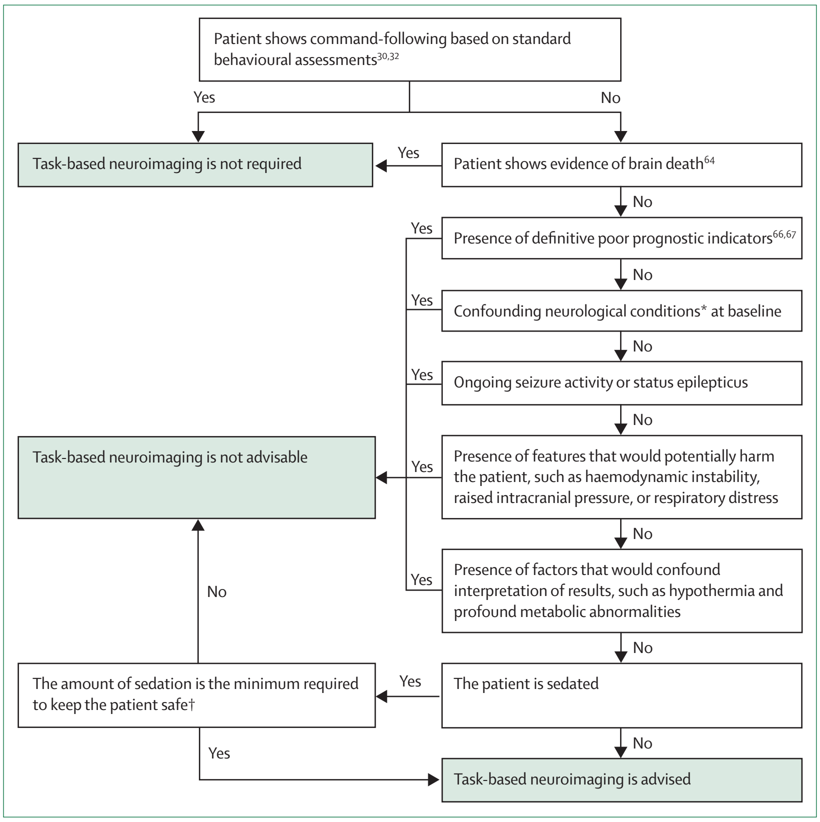


***Figure 2:* Decision tree to guide the initiation of tasked-based functional MRI and EEG in the intensive care unit**

*Conditions that would impair cognitive function, such as advanced neurodegenerative conditions or static encephalopathy. †Sedation requirements vary among patients; in most cases, the aim should be to reduce sedation doses to the lowest amount necessary to ensure patient safety and stability during testing for covert awareness.

established for when to start advance neuroimaging in chronic disorders of consciousness,[73,74] and similar procedures could be adapted to take account of the unique circumstances of acute critically ill patients (figure 2).

Disclosing results of covert awareness

Conveying the findings of functional neuroimaging assessments to families and clinical teams requires a delicate balance, because complex results often need to be translated into relatable terms, and the potential emotional effects need to be carefully considered.[75,76] In a qualitative interview study, families consistently expressed a strong preference for being informed about the outcomes of fMRI and EEG assessments, even when the imaging results were inconclusive.[77] Although covert awareness indicates a more favourable prognosis than if no awareness can be detected, it does not guarantee full functional or neurological recovery. Some patients might never regain behavioural awareness, and those who do could require full-time care due to severe disabilities.[39] It is crucial to communicate these wide-ranging outcomes clearly to families, adapting the approach to avoid overwhelming surrogate decision makers with excessive information. Shared decision-making should be an integral part of this process, allowing families to actively participate in determining the best course of action based on the available information. Detecting covert awareness should be viewed as one of many multimodal tools in the ICU decision-making process, augmenting current prognostic and diagnostic tools rather than replacing them.

A particular area for ethical and practical concern is how to interpret negative findings. Processes to analyse neuroimaging data are designed to mitigate false-positive results—ie, to minimise the possibility that a patient will be classed as aware when they are not. Due to the strict statistical corrections imposed, one can be confident that a positive result is indeed indicative of covert awareness.[20,78] However, interpreting negative results in a command-following task is considerably more challenging, because a patient might not necessarily be unaware, they just might not hear or comprehend the stimuli, be delirious, have confounding medications, or not have the cognitive capacity to complete the task despite retaining some awareness. These possibilities are highlighted by findings of a prospective study that showed false-negative rates of more than 30% in healthy controls (ie, people without traumatic brain injury who couldn't complete the task),[37] although other studies show lower false-negative rates.[24,46,79] All these factors need to be carefully conveyed to families when negative findings are observed. However, the risk of a false-negative result should not pose a barrier to the use of functional neuroimaging, given that it is a positive—not negative—result that influences action.[80] For example, if a scan shows no evidence of awareness, the patient's status has not changed. By contrast, if a scan would have detected awareness but has not been done, the patient could prematurely undergo withdrawal of life-sustaining therapies or be given an inaccurate prognosis.

Towards clinical implementation of advanced neuroimaging

Despite evidence showing that functional neuroimaging can detect covert awareness and contribute to prognostication in behaviourally unresponsive patients in the ICU, implementation of advanced imaging techniques such as fMRI and EEG as a standard of care has happened rarely.[33] In a survey by the Curing Coma Campaign, only 7% of 230 centres reported using advanced neuroimaging in routine acute coma clinical care.[33] Yet, most MRI scanners are equipped with functional neuroimaging capailities, and EEG is readily available in most hospitals. Covert awareness can be detected with clinical grade 1·5 T MRI scanners and clinical grade EEG montages.[38,43,79] However, the expertise required to acquire, process, and interpret neuroimaging data is often not available outside of academic and specialised medical centres. Nevertheless, these methods might be adopted more widely if the technical and practical requirements for implementing these techniques were disseminated more widely.

Implementation of advanced neuroimaging into routine clinical care could be supported by several initiatives. For example, clear evidence-based clinical guidelines need to be established for identifying patients with acute brain injury who would benefit from advanced neuroimaging. Eligibility for task-based neuroimaging should be determined through decision trees to rule out contraindications (figure 2). The risk versus benefit of transporting patients to MRI scanners should be considered and, whenever possible, fMRI scans should be paired with clinically indicated structural scans. fMRI and EEG protocols and stimuli can be acquired from specialised centres, and openly available code and stimuli are becoming increasingly accessible. Data analysis should adhere to published statistical protocols to minimise false-positive results and to facilitate data sharing across centres. Interpretation of neuroimaging data requires training of personnel, which might not be available locally; professional societies that endorse advanced imaging methods should offer educational workshops to address this need. A model that has been proposed for data analysis involves so-called hub-and-spoke centres, whereby functional neuroimaging data are collected remotely by small centres (referred to as spokes) and transferred to specialist centres (hubs) for analysis, interpretation, and reporting.[81] This model eases both financial and knowledge burden for non-academic centres that would benefit from functional neuroimaging but do not have the expertise to report on the findings. Emerging pupillometry techniques that can detect covert awareness could represent a more accessible method in settings where advanced fMRI and EEG are unavailable, and these methods could be used in a wider group of patients for whom neuroimaging is contraindicated. However, these methods remain to be validated in a large cohort of patients at multiple centres.[47]

Conclusions and future directions

For patients in the ICU with acute brain injury who do not show behavioural signs of awareness, fMRI and EEG have been used in similar ways to detect covert command-following.[82–84] By measuring changes in blood oxygenation, fMRI provides excellent spatial resolution, allowing for precise localisation of brain activity. However, fMRI can be sensitive to motion artifacts, which can be challenging to manage in the ICU setting as patients can experience involuntary movements. The advantages of EEG are that it provides continuous data on electrical brain activity, is portable and can be used at the bedside, and is more cost-effective than fMRI. However, EEG has limited spatial resolution and is sensitive to the electrically noisy atmosphere in the ICU.[59] Guidelines from the European Academy of Neurology[30] suggest that both fMRI and EEG should be used to probe for covert awareness, as multiple techniques and tasks can improve detection accuracy and provide patients with their best chance of displaying preserved cognitive abilities.[37,85,86]

fMRI and EEG are the most developed and widely used functional neuroimaging technologies in the area of acute brain injury, but several alternative approaches are emerging for detecting covert awareness in the ICU. Functional near-infrared spectroscopy (fNIRS) is an optical neuroimaging technique that that can be used at the bedside to measure neural activity with few safety risks or disruptions to patient care.[87] Often considered the optical equivalent to fMRI, fNIRS is portable, inexpensive, and provides good temporal and spatial resolution while being less susceptible to motion artifacts. Like fMRI, fNIRS infers brain activity through neurovascular coupling by estimating concentration changes in oxygenated and deoxygenated haemoglobin. fNIRS has been used to detect covert awareness in chronic disorders of consciousness,[87,88] and studies are

Panel 2: Clinical case study

A male aged 41 years was in a head-on motor vehicle accident. The patient’s initial assessment on the Glasgow Coma Scale score by emergency services was 3 (eyes=1, verbal=1, and motor=1). The patient was endotracheally intubated and was admitted to the intensive care unit.

At initial neurological examination, the patient was comatose and had no motor or eye-opening response with sluggishly reactive pupils. Initial head CT was suggestive of diffuse axonal injury. By day 8, the patient was stable enough to have an MRI and had a Glasgow Coma Scale score of 4 (eyes=2, verbal=1, motor=1) with an eye-opening response to pain. At the time of imaging, neurological examination revealed reactive pupils, with corneal and cough reflexes present. Structural MRI revealed restricted diffusion bilaterally within the white matter tracts with the greatest restriction surrounding the areas of haemorrhagic diffuse axonal injury. During the same scan, the patient underwent a functional sequence to look for evidence of covert awareness. When asked to perform the mental imagery task to imagine playing tennis, the patient was able to wilfully modulate their brain activity by producing consistent and repeated neural responses in the premotor cortex (as exemplified in figure 1A). Thus, despite no behavioural evidence of consciousness, the fMRI data confirmed that the patient was entirely aware because he was able to complete the neuroimaging command-following task. Over the next 13 days, the patient had incremental increases in behavioural measures of awareness. By day 15, the patient could localise to painful stimuli and by day 21, the patient was able to behaviourally command follow. The patient was discharged on day 29 to an inpatient rehabilitation centre. By 6 months after the injury, the patient was independent in all activities of daily living and returned to work on a full-time basis.

Search strategy and selection criteria

Key references for this Personal View were identified by searches on PubMed and MEDLINE between Jan 1, 2017 and March 31, 2024, and references from relevant articles. The search terms "functional neuroimaging", "covert awareness", "cognitive motor dissociation", "intensive care unit", "brain injury", "fMRI", and "EEG" were used to find full-length papers published after 2005, with no language restrictions . The final reference list was generated on the basis of relevance to the topics covered in this Personal View.

currently underway to evaluate its utility in an ICU setting.[89] Transcranial magnetic stimulation with EEG (TMS-EEG) is a neuroimaging technique that combines brain stimulation through magnetic pulses with the recording of electrical brain activity, the complexity of which can be measured and quantified through a measure known as the perturbational complexity index.[1] TMS-EEG directly measures neuronal interactions, thereby providing a more accurate assessment of brain dynamics that can differentiate between states of consciousness with high specificity and sensitivity.[81,87] Other advantages are that TMS-EEG can bypass sensory and motor systems, and requires no cognitive effort from patients, making it an attractive tool for assessing the capacity for having preserved awareness in the ICU.[1,90,91]

Beyond developments in technologies themselves, functional neuroimaging needs to be tested in large multicentre studies involving hundreds or even thousands of patients. Although individual studies have shown promise in elucidating the relations between neuroimaging findings and patient outcomes, the variability in patient populations, imaging protocols, and health-care practices across different ICUs necessitates aggregating patient data on a large scale. Moreover, key questions remain regarding whether patients with covert awareness in the ICU are likely to regain behavioural awareness more quickly than those who are not covertly aware. Although further research is necessary, the available evidence suggests that functional neuroimaging can profoundly influence the evaluation and clinical management of patients with acute severe brain injury (panel 2). Functional neuroimaging tests will inform discussions about continuation of life-sustaining therapies and drive efforts to develop interventions that facilitate recovery and improve quality of life in these patients.

Contributors

KK, BLE, and AMO equally contributed to the conceptualisation, writing, revision, and editing of the manuscript.

Declaration of interests

KK and BLE declare no conflicts of interest. AMO is the Chief Scientific Officer of Creyos, a company that provides online neuropsychological assessments for various conditions such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. The activities of the company have no overlap whatsoever with the content of this Personal View.

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