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Diagnosing disorders of consciousness: Technological convergence in assessment options

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Abstract

Disorders of consciousness (DOC) are a clinically significant and personally tragic class of health impairments posing significant diagnostic challenge. Uncertainties in the understanding of consciousness and the inability of patients to communicate their physical status pose obstacles to the resolution of states with overlapping manifestations. The increasing demographic of a susceptible patient population, moreover, further exacerbates the impact of these disorders. Attempts to resolve the ambiguities of consciousness have yielded a complex pattern of diagnostic approaches that prioritize behavioral assessment, but nonetheless require supplemental technological methods to objectively diagnose underlying neural correlates. The principal technologies used in today's clinical setting include the neuroimaging and electropotential technologies, each of which offer distinct advantages for diagnosis. Neuroimaging enables the precise spatial resolution of brain domains associated with arousal and awareness, consciousness features that are impacted by DOC, but lacks temporal fidelity. Electropotential recordings, by contrast, are capable of recording electrical signals on physiological time scales but are unable to precisely pinpoint their origin. Current developments in both technology classes are overcoming the technical limits of each. Supplemented by parallel developments in digital processing and artificial intelligence, qualitatively new dimensions of analysis can be expected, including distinct physical signatures, dynamic causal relations, representational information content, and elicitation paradigms for detecting covert awareness.

Introduction and Background

Disorders of consciousness are a clinically significant and personally tragic class of health impairments that present significant diagnostic challenge. This challenge is multi-faceted. Despite its evident reality, consciousness itself poses an enigma. It has often been related to subjective awareness, a philosophical equation that is conceptually elastic, or with attention access. Difficulties in communicating with patients that present similar, or overlapping, manifestations add additional obstacles to arriving at satisfactory conclusions. This complex scenario has today led to an equally complex pattern of diagnostic approaches attempting to balance the behavioral and partially subjective detection of DOC disorders against technologies intended to provide more objective clinical criteria of neural correlates that are impaired in DOC [1].

The principal sources of consciousness disorders are traumatic brain injuries and stroke, factors that are numerically significant and demographically influenced. Feigen et al's study of stroke victims between 1990 and 2010 [2], for example, reveals a decided increase in the incidence of stroke during this interval, a circumstance that appears to relate directly to a nearly 40% reduction in the morbidity to prevalence ratio of stroke victims **(Figure 1)**. Of these, a small, but nonetheless significant percentage, develop some form of disorder of consciousness [3]. Improved medical care, thus, and the rising demographic of a susceptible, elderly population are yielding an upturn in DOC incidence that is likely to be sustained for the foreseeable future.

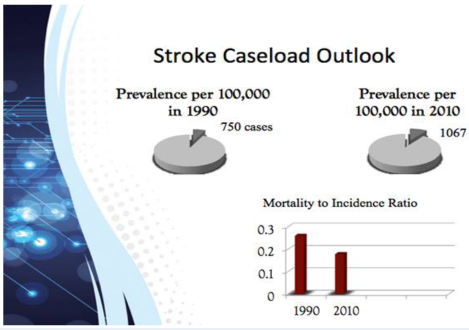

Figure 1: Data taken from Feigin et al study[2]. Increased prevalence of stroke seen against reduced mortality to incidence ratio for the interval 1990 - 2010.

Stroke or trauma patients that survive severe cases of brain injury may end up in coma, due to structural or metabolic lesions in the brain stem reticular system or to extensive cerebral damage. These may die, recover fully, evolve into some intermediate state of consciousness, or progress through variable trajectories of such states. Although patients can improve, they may also linger in a condition of DOC for prolonged intervals, or even remain there permanently. Among the clinically designated entities of DOC are coma, unresponsive wakefulness syndrome (UWS), formerly termed the vegetative state, minimally conscious state(s) (MCS), and locked in syndrome (LIS) [4-6]. Categorical distinctions have been recognized for MCS, which distinguish between linguistic comprehension, designated MCS+, and contingent behavior, MCS-. A transient period of disorientation associated with emergence from MCS has also been designated, the acute confusional state (ACS).

Coma presents as an acute state of unresponsiveness where no arousal can be detected. Global impairment of the arousal system in coma is due to extensive bilateral lesioning of the cerebral hemispheres and/or a traumatic lesion to the brainstem or bilateral thalami. Signs of arousal are seen in patients with UWS that have been shown to coincide with a restoration of the brain stem reticular system. Despite the presence of intact neural correlates of arousal and behavioral indicators of wakefulness, however, context dependent behavior is generally absent. Typically, UWS patients have extended lesions of the neocortex and thalamus and display widespread fiber tract damage. By contrast, MCS patients exhibit a limited awareness seen, for example, in intelligible verbalization and responsiveness to commands. LIS is a rare condition in which consciousness has been preserved, but extensive damage to the cortico-spinal and cortico-bulbar pathways results in the near total loss of control over all voluntary muscles except those of the extrinsic eye muscles [7]. Communication with the LIS patient is therefore mediated only through small eyelid movements.

For DOC patients, diagnostic accuracy is a significant variable affecting prognosis and therapeutic outcome. DOC patients display varying responses to therapy, and rehabilitation is premised on diagnostic assessment [8]. Clinical diagnoses rely chiefly on behavioral indicators, the current gold standard, and a number of assessment scales are now in use. Of these, the Coma Recovery Scale has been determined by the American Congress of Rehabilitation Special Interest Group to have the strongest content validity, based on the Aspen criteria [9]. Scales similarly prioritizing the detection of sensory, communication, and arousal ability, but varying in relative diagnostic emphases, are also commonly used in European clinics [10,11].

Despite the widespread use of behavioral assessment, measures of their diagnostic reliability nonetheless indicate that nearly 40% of DOC patients are misdiagnosed [12]. Factors accounting for misdiagnosis are multiple and include on the part of the patient motor impairment, sensory deficits, altered cognition, and fluctuations in vigilance. This salient figure has impelled considerable effort in the identification of methods capable of objectively assessing the neural correlates of consciousness impairments. A number of these methods are now used in the clinical setting.

Accordingly, this review will focus on the improved diagnostic discrimination brought to the assessment of DOC by these 'objective' methods. It will compare existing capabilities and limitations encountered in neuroimaging vs electropotential technologies and will discuss proposed strategies that are intended to expand technology versatility and symbiosis for DOC diagnosis.

Neuroimaging in Consciousness Assessment

The most widely used neuroimaging technologies for diagnosing DOC today are positron emission tomography (PET) and structural and functional magnetic resonance imaging (MRI/fMRI) [13]. These technologies are distinctive for the high spatial resolution brought to the diagnostic setting. Functional MRI, for example, is capable of resolving spatial images of the brain to within 1 mm or slightly better, though significantly improved signal to noise ratios are optimally obtained at 3 - 5 mms. For a single brain 'slice' at this resolution the brain's surface area can be parceled into roughly 10,000 discriminable voxels. Estimates of neural density within these volumes, however, place the numbers of neurons at about 1 million (and an equally large number of associated glial cells); hence, activity signals obtained by fMRI reflect the contribution of large neuron groups. While this scale of resolution does not permit the isolation of activity from individual neurons, like that achieved invasively with intracranial, electrode recording, fMRI technology can easily resolve regions of interest of most brain nuclei. Significantly, numerous studies show that functional activity zones in the brain are composed of neuronal populations, rather than localized to a single or several cardinal neurons. Indeed, a general premise regarding representational brain activity has been the involvement of large groupsof neurons [14]. The visual presentation of a single object will activate, for example, long regions of the occipital cortex at multiple sites; consequently, this has resulted in the technical objective of monitoring the activity covariance of these sites in order to link neural activity patterns to a structured representational content in classification technologies [15].

For disorders of consciousness this high spatial resolution is pertinent for the diagnosis of constructs like arousal and awareness. Patients having UWS display minimal brain activity over much of the fronto-parietal and associative cortices and extrinsic connectivities with the thalami; the presence of brain stem activity, on the other hand, distinguishes UWS from coma, a state in which lesioning of the brain stem is extensive. It is possible, additionally, to identify MCS patients, which have been clinically diagnosed as UWS on the basis of behavioral criteria, by the presence of significant cortical activity, a characteristic of less severe disorders of consciousness and a diagnosis on which beneficial therapies reserved for the latter class of patient depend.

Parameters that are assessed in imaging technologies do not directly reflect the neural activity that is occurring in the brain, however, and so are linearly unrelated to the physiological activity per se. PET technology, for example, offers the diagnostic prospect of distinguishing unique compositional changes, which typically take place on time scales much different from the dynamics of neuron activation. The use of PET imaging has been significant, on the other hand, for identifying several key DOC features. For instance, by employing radio labeled glucose tracers it has been possible to detect significantly reduced metabolism in the UWS patient [16], nearly half that observed in the minimally conscious state. Since brain metabolism levels are normally significantly elevated in relation to total bodily metabolism, this observation is also indicative of a very substantial change in the body's metabolism.

In the case of fMRI, parametric determinations are made on the basis of the variation in the blood oxygenation level dependent (BOLD) signal. This signal is positively related to increased neural activity due to increases in oxygen consumption needed to sustain the ongoing molecular events associated with neural activity. Since multiple cellular events in the region of interest require oxygen consumption, the effect is physically removed from the neural activity that is occurring, and so exhibits, temporally and qualitatively, a different dynamic - the time lag of the BOLD signal associated with the onset of neuronal activity, for instance, often displays a 'dip' rather than a rise in activity, due to a brief delay preceding increased blood flow. BOLD signaling has a temporal resolution of a few seconds, several orders of magnitude slower than the spiking activity that is used by the brain for information exchange and that occurs on the timescale of several milli seconds. Despite its qualitative assessment of actual brain activity, however, fMRI technology is capable of reflecting the cumulative effect of electrical events occurring in a given voxel, a factor that has led to its widespread use for assessing domain specific and quantitatively approximate activity changes.

Electrophysiological Diagnosis of DOC

Unlike neuroimaging technologies, that are capable of resolving activity in microvolumes of brain tissue, electropotential monitoring technologies used clinically lack the ability to discriminate between signals originating from closely opposed tissue loci. On the other hand, they offer considerably improved temporal resolution of brain signals, and so are capable of directly monitoring the time occurrence of physiologically relevant events. Electropotential recording technologies, additionally, offer the significant advantage of physical convenience when compared with the scale of equipment needed for neuroimaging.

The electroencephalogram (EEG) permits the direct, noninvasive measurement of spontaneous brain electrical events by electrodes applied to the scalp [17]. This obvious advantage in methodology is offset, however, by the diminished electrical signal actually recorded, which is on the order of 10 to 100 uvolts. By contrast, direct cortical recording from brain tissue can obtain voltage signals some 10 to 50 times greater in amplitude. Since 1990, however, EEG recording technology has been significantly improved by signal digitizing and processing algorithms that enhance the signal to noise ratio of the recorded electrical events, thereby permitting the detection of signals otherwise hidden by background noise.

The technology's temporal precision enables direct observation of the electrical signatures of brain activity, which can be elicited by external stimulation and referenced to the time of onset of a generated electrical event [18]. Due to the low amplitude of the signals recorded from the scalp, however, these evoked potentials must be averaged; hence, the evoked potential is a time locked average of multiple EEG signal responses [19]. Existing stimulation protocols rely on either auditory or somatosensory stimulation to yield detectable signals. Auditory evoked potentials that are currently used clinically include, for example, the N100, P300, and N400 potentials; additionally, the N20 potential, elicited by somatosensory stimulation, is also frequently employed. A variety of paradigms that are capable of distinguishing brain states in the DOC patient are now available. The mismatch negativity, for instance, an early negative waveform elicited by a deviant tone in a repetitive series, is detectable in the MCS patient, but seldom observed in patients diagnosed with UWS [20,21]. Similarly, assessment batteries that combine categorically different potentials in varied paradigms have been successfully employed to distinguish among UWS, MCS, and LIS states [22]. Using vibrotactile stimuli in concert with the evoked P300 potential, for example, such batteries successfully detected the potential under MCS and LIS conditions, but not in the UWS patient. Additionally, signatures of consciousness have included low frequency and delta power and EEG waveform complexity.

Prospective trends in diagnosis

Advances in diagnostic technologies for DOC have been considerable, and offer to the physician a greatly improved ability to arrive at an objective and, in many cases, more certain diagnosis than behavioral assessment alone. Uncertainties surrounding the concept of consciousness, however, mean that the development and improvement of DOC diagnosis will for the foreseeable future continue to use a multipronged strategy that is directed toward progressively refining both behavioral and technological approaches.

For the latter, technology evolution will likely expand on developments now underway in three separate domains: these can be expected to include 1) diminishing limitations in current neuroimaging and electropotential technologies, 2) expanding the available range of detection paradigms and prioritizing context dependent technology use, and 3) refining the discrimination of subcategories of clinical entities.

For fMRI technology, the BOLD signal poses an intrinsic physical barrier to enhanced temporal and event resolution. Parallel developments in signal processing and pattern recognition technology, however, offer the prospect of improved signal resolution and the characterization of distinct state specific patterns of activity that can identify information structure contained in the neural activity of the brain [23]. Classification technologies, in particular, possess multiple processing strategies that range from reinforcement learning on trained data sets to predictive formats that enable the extraction of object feature elements [24]. Artificial intelligence promises to extend these capabilities further through unsupervised learning, a machine learning form more closely analogous to that of the brain that is capable of de novo extraction of pattern correlations. The technology's independence from the need for training on data sets promises to greatly extend image detection possibilities [25].

New imaging paradigms, further, seek to make inferences about functional activity. Existing evidence shows that such functional relations are dispersed throughout the brain; hence, by determining these relations it may be possible to assess how interareal domains are impacted in DOC, a point pertinent for the globally distributed dynamics of consciousness [27]. Use of the dynamic causal modeling method, for example, has shown that intrinsic connectivities in the default mode network are disrupted in UWS patients [28]. A characteristic observation in these patients is enhanced oscillatory strength in the posterior cingulate cortex. This is contrasted with heightened inhibitory input and diminished oscillation seen in MCS and normal individuals. Thus, a significant advantage of novel paradigms is the functional characterization of global brain events and the identification of signature biomarkers that can characterize distinct DOC states [29].

The limitation in spatial resolution that is the hallmark of electropotential recording technology, on the other hand, is not due to an intrinsic physical obstacle, as in the case of imaging technologies; limitations are imposed, rather, by patient risks introduced through the use of invasive and focally placed electrodes that could otherwise significantly amplify signal strength. Attempts to improve spatial resolution non-invasively, therefore, have focused on technological advances in source electrode density like that used in high resolution EEG recording [30]. Localization errors have been shown, in fact, to decline with increasing electrode numbers, though at diminishing returns, up to a high of 128 channels.

Compact portable devices, additionally, extend the availability of electrical monitoring beyond the clinic to the homebound patient [22]. These devices can incorporate high channel density with available computing hardware and couple these to equipment for modulating stimulation paradigms. A recently developed commercial system, for example, includes an EEG cap, active electrodes, auditory and vibrotactile stimulators, earphones for clinical personnel, and an ordinary laptop device for signal processing. This system has been used successfully for discriminating DOC states in the clinic, and so offers the sophistication of clinical technology on an ongoing basis to an intermittently examined group.

The advantage of directly recording electrical events on physiological time scales, moreover, is increasingly exploited either to couple electropotential diagnosis with neuroimaging [31] or to develop wholly new, functionally based paradigms [32]. The need to assess the presence of a covert awareness, for instance, has provoked several imaging studies attempting to elicit the patient's active role in manipulating cognitive processing, a paradigm that may be even better suited for direct electrical activity monitoring [5].

Importantly, neuroscientific discoveries that are advancing the basic understanding of brain operation will afford opportunities for diagnostic development to structure synergies with research explorations, particularly in the areas of global brain dynamics. Indeed, dynamical operation in the form of attractors and transient states [33] are proving to be fundamental features of brain physiology that are amenable to electrophysiological analysis. Given their global and hierarchical significance in brain operation, these are likely to be significant to DOC, which almost certainly entails the compromise of extended brain faculties [34].

Conclusion

The evolution in neuroimaging and electropotential technologies used for diagnosing DOC give evidence of the complexity as well as the significance of consciousness impairment. For the DOC patient this is both a boon and a promise. These technologies can be expected to reveal important details such as activity signatures and causal relations, as well as identify global and hierarchical features that are represented by imaging activity. Underlying uncertainties about the holistic role of consciousness, however, testify to the medical mystery that is a part of each patient and that remains an ongoing revelation.

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