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Consciousness Impairment: Expanding Possibilities for Diagnostic Prognosis

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Abstract

Consciousness impairment is a devastating brain condition that remains little understood, but for which an increasing range of diagnostic technologies offer prospects for improved patient outcome. Behavioral assessment batteries, the prevailing diagnostic tool, are now supplemented by neuroimaging technologies that offer high quality, objective data for consciousness determinations. Novel classification technologies, to date used chiefly in research settings, can be expected to offer a qualitatively new dimension in consciousness assessment.

Keywords: *Consciousness Impairment; EEG; FMRI*

Introduction

In 1968, when neurological criteria for death determinations were first adopted, brain science was relatively uncharted. Known then were the rudiments of nerve function, including action potential propagation, synaptic transmission, the identity of a handful of neurotransmitters, and only the first of an upcoming stream of brain based physiological processing mechanisms, edge and motion detection cells [1]. This 'cellular level' understanding of nerve operation now comprises but a small fraction of the knowledge since accumulated, which has grown to include global state interactions, tasking networks, dynamical activity patterns, and large scale circuits [2-4], to name several. The newly accumulated knowledge has not only assisted in sketching a panorama of the brain's geographical terrain, physiologically as well as anatomically, but it has also acted as a springboard for investigative strategies intended to unravel the complexities of its operation affected in brain diseases. A leading premise now underpinning much of this work is the disease modified circuit architecture model. This premise postulates that information is structured to flow along defined routes of transmission analogous to electrical circuits; hence, according to this model, brain diseases are due to inexact, incorrect, or deficient manners of forming these routes, which are dictated at the level of synaptic connectivities [5].

Influenced by this conception, and developing in parallel with circuit based, disease models, is an extensive and expanding research domain that is devoted to characterizing neural network operation. Network topologies, notably, are now the subject of intense study with various mathematical models that seek to discern functional elements in their underlying microarchitecture [6,7]. The evolution of network research and the circuit based disease strategy are illustrative for the way in which a battery of widely differing experimental technologies can be entrained to focus on a single, powerful, concept to elucidate its details. It is illustrative also, however, of how the power of a single image of brain operation can entrain the process of hypothesis construction so that avenues to other explanatory options may be postponed for later discovery. It is also, thus, a testimony to the ever receding geographical horizon of brain complexity [8], that needs to be made amenable to characterization in order to yield fruitful forms of neurological intervention for brain disease therapy.

Diagnosis for the Consciously Impaired Patient

Something of this discrepancy between the knowledge gleaned in early stages of neuroscience with its limited relevance to medical intervention, and a prospective and receding horizon of therapeutic goal setting, is now seen in treatments intended to minister to the patient who exhibits some form of conscious impairment. Conscious impairment is increasing in prevalency, and it is, therefore, highly desirable to have treatment options. Feigin., *et al*. study of individuals suffering stroke between 1990 and 2010 [10], for example, shows a decided increase in stroke prevalence that is correlated with a nearly 40% reduction in the mortality to incidence ratio. Among other factors affecting this ratio, improved emergency room care and life-saving technologies have increased the survival rate of patients who experienced an incident of brain damage. Such patients may and often do become comatose, a condition predisposed by stroke. Coupled with population demographics that are trending grayward, the improved medical scenario thus portends a distinct upward swing in the incidence of this type of brain disease.

Patients suffering coma show continuous absence of eye-opening and any spontaneous stimulus induced arousal or voluntary responses, meaning they are neither awake, which signifies a brain stem lesion, or aware, which reflects a lesion of the cortico-thalamic network [11]. Such patients may undergo trajectories through variable states of consciousness, either to deeper comatose states with eventual death, or upwards to minimally conscious states with their greatly improved chances of recovery [12,13]. Intermediate cases such as the earlier designated vegetative state, now known as unresponsive wakefulness syndrome, display wakefulness, that is, they may show eye opening, but their motor responses are reflexive only and so they do not display awareness. The minimally conscious state may be more responsive, as for example, MCS plus with intelligible very responses to a command, or less responsive, for example, MCS minus with visual pursuit and emotional responses only. (The case of locked in syndrome is a rare event where the corticospinal and corticobulbar pathway has been substantively injured [14]). Assessing these multiple states is thus critical to patient management, with its possibility for therapy.

It is at this level of assessment, however, where the current methodological and technological approaches not only show the great amount of knowledge that has been accumulated, with its improved understanding that may be used to better patient oversight, but where also the sort of information provided offers still only a little insight into the physical features that contribute to patient status. Hence, it reveals a horizon yet to be reached at a conceptual level with regard to patient physiology, and at a clinical level with regard to determining the salient features needed in order to therapeutically intervene. Current methods now largely used for consciousness assessments, for example, rely principally on behavioral monitoring; yet, nearly 40% of these patients are misdiagnosed. This significant statistic has led to increasing emphasis on neuroimaging and electropotential recording technologies that make it possible to objectively study cognitive processing either complementary to or even independent from behavioral assessments. Their objective reliability thus offers to the physician the opportunity for a presumed closer correspondence to patient status than might be availed from a patient either incapable of knowing, communicating, or of reliably assessing – and perhaps even being liminally influenced by – physician monitoring.

Existing imaging technologies vary according to the structural and functional information needed and include among their principal tools positron emission tomography (PET), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), diffusion tensor imaging, and electroencephalography (EEG) or transcranial magnetic stimulation EEG (TMS/EEG) [15,16]. PET studies with radioactive tracers are capable of showing, for example, that patients in the vegetative state are hypometabolic, indeed substantially so, with reductions in metabolic levels of nearly 40% [17]. Given the high proportion of energy consumed by the brain, the total reduction in body metabolism is substantial. Significantly, this reduction is selectively localized to the frontoparietal networks and midline network and associative cortices, a revelation also provided by PET technology [18]. Recovery from unresponsive wakefulness syndrome coincides with connectivity and, presumably, metabolic, restoration [19]. FMRI studies have been used for the purpose of assessing brain activity in consciously impaired patients on the presupposition that activity is a reflection of the presence of either wakefulness, or wakefulness and awareness processes. For example, in minimally conscious patients associative cortices exhibit high activity levels; patients in the vegetative state, by contrast, have only variable or low cortical activation [20,21]. Prognostically, greater activity levels have been correlated with improved patient outcome [22]. Because of impracticalities in the use of fMRI, such as the size of the instrumentation and its limitation in use to hospital facilities, smaller devices that are portable and that can be employed in clinics or even home settings like TMS/EEG have been developed [23]. In this latter technique subsets of cortical neurons are stimulated by TMS which are then monitored by EEG recording techniques that employ high density recording sites. These smaller units, for example, have successfully distinguished in several instances between patients who were neither awake nor aware and patients who were wakeful but unresponsive [24].

Content Based Consciousness Assessment

Despite significant advances in the ability to assess consciously impaired patients, however, the parameters actually monitored by these technologies do not directly reveal information that is salient with regard to consciousness, particularly the patient's sense of awareness, which remains a clinical unknown at a semantic and representational level, that is, at a level that ultimately is comparable to linguistic based communication . Yet their improved insight into status also metaphorically replicates the consciousness paradigm that is awaiting the next upward stage in its trajectory. It is with the intention of managing the semantic content to be inferred from brain activity, as opposed to inferences about brain state activation, that qualitatively new approaches to elucidate what brain states actually mean have been undertaken.

These new approaches are to date restricted to the research setting and generally have yet to be exploited in the medical setting as viable medical devices or device/approaches. Nonetheless they afford the prospectus for revealing distinguishing features of brain activity patterns that can be correlated with objective features of the world. In particular, they offer the prospect of revealing semantic content, as opposed to the presence of brain activation alone. While this is not quite the same as representational imagery of the sort needed for intersubjective communication, it does signify an advance over existing imaging techniques in exposing the structure of the information content that the brain may actually be using.

In such 'decoding' approaches that have evolved to date the central technical concern is that of 'classification', that is the association of a brain state as imaged in its activity pattern with an externalized feature, object, or event. The oldest of these, mass univariate analysis, is based on a general linear model in which sequential brain regions are monitored for specific mental activity at a specific brain location [25]. It is presumed here that mental contents are distributed over populations of cells; hence, they presume an underlying neural connectivity architecture uniting them that is due to neural recurrency. The technology is used to assess the covariance between multiple single units, which serves as a determinative as well as a diagnostic feature that is relevant to how select images are encoded. In fMRI imaging, for example, the presentation of a single object will activate long regions of the occipital cortex originating at multiple sites; thus, monitoring covariance is a technical objective thought to link the neural activity patterns to a structured representational content [26].

Classification methodologies have approached the assessing of information content from several perspectives. In multivariate decoding brain patterns are assessed on the basis of previously determined correlations between a respective image and the activity patterns [27]. For this purpose it is necessary to 'train' the classifier to label, that is, associate a brain pattern with a particular image. Training data sets are therefore needed to identify unique patterns of activity so that the test data may correctly identify observed patterns with a unique image. Because of intrinsic stochastic and other sources of variation in activity patterning these must be statistically processed, often with Gaussian type filters, to assess statistically significant differences or similarities among patterns [28].

In the multivariate classification approach it is necessary to 'learn' to classify each image representation in the brain patterning. This requirement necessarily limits image assessment to identifiable images, leaving many potential representations unclassifiable. Attempts to overcome this limitation have therefore attempted to expand the range of accessible imagery through an approach known as model-based classification, where classification models are used to 'predict' patterns that may then be associated with an image that is not part of the training data [29]. Applying the model to novel activity patterns common informational features within a given the pattern can be associated with an object element. The approach can potentially reduce the size of the training range needed, and, conversely, extend the extrapolation to a much broader range of imagery. Such an approach has been used, for example, to expand relationships among word data sets [30].

For the consciously impaired patient these new technologies begin to offer the promise of communication at a level more closely approximating the sorts of symbolical representations that humans use to convey conceptual content to others. The answers to the questions of what the patient may be thinking, how well or poorly he is doing so, and what may be affecting this are, therefore, made more tractable than in the solely qualitative answers obtained from the current medical imaging analysis alone. These latter reveal a capacity for consciousness, but do not quantitatively indicate the level at which that capacity may be used.

Expanding Diagnostic Possibilities for Consciousness Assessment

On the other hand, while these new technologies may offer significant qualitative advances to the physician in the type of knowledge acquired, they do relatively little to explain either the mechanism that generates the particular form of brain activity that is being classified or what information, if any, is internally activated by the patient. This gap in understanding is revealing for again opening the spectrum of explanatory and interventional possibilities to a wider and, to date, largely unidentified property scope than is encompassed by strictly neuronal features. It is likely that representations are not, for example, the exclusive province of circuit connectivity architectures [31,32]; hence they reveal that there are as yet unknown features about how the brain functions to engage our subjective sense. Discoveries of the contribution of electrical gap junctions to the structuring of brain oscillations, glial cell participation in signal transmission, and transient dynamical assemblies [9], for example, present just some current observations not easily framed by network and circuit models that need to be more adequately understood to assist the development of interventional strategies.

Thus, while it is clear that connectivity organization plays a very significant role in structuring representational activity it is much less clear that such activity is structured solely via circuits or confined only within them. Existing emphases on circuit based operation, that have the effect of entraining hypothesis building around it, therefore, like limit cycle attractors, postpone the evolution of new understanding and new possibilities for intervention. However, their inability to explain new discoveries is significant for underscoring the need for and possibility of new therapies when such discoveries are made. Their postponement, moreover, is an ongoing reminder of the medical mystery that lies latent in each patient.

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