The State of Consciousness in Patients in the Vegetative and Minimally Conscious States

O estado de consciência em pacientes em estado vegetativo e em estado de consciência mínima

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Abstract
Brain-injured patients may, with the assistance of life support, continue to perform basic bodily functions, but yet be deficient in wakefulness, awareness, decision making or other overt manifestations of consciousness. Here, we review two neurological states observed in brain injured patients with different degrees of brain impairment, the vegetative state (VS) and the minimally conscious state (MCS), and we discuss how these states are diagnosed through assessing patient behavioral responses during clinical examination. We consider how functional neuroimaging has revealed preserved cognitive capacities in patients that were supposed to be in the VS and has introduced a new diagnosis, cognitive motor dissociation. We review the GW Theory proposal that consciousness arises from functional connectivity (FC) of widely separated brain regions. We discuss how such high FC underlies the Default Mode Network (DMN), a group of neural circuits that are active when an individual is not involved with external tasks and engages in introspective thinking. Finally, we discuss the finding that the level of FC of the DMN is diminished in brain injured patients and the proposal that the level of residual DMN FC in brain injured patients is an index of their consciousness.

Keywords: disorders of consciousness, vegetative state, minimally conscious state, Global Workspace Theory, functional connectivity, Default Mode Network.

Resumo
Pacientes com lesão cerebral, quando assistidos, podem continuar a desempenhar funções fisiológicas básicas, mesmo estando com a vigília, a atenção, a capacidade de decisão e outras funções de consciência prejudicadas. Revisamos aqui dois níveis de distúrbio de consciência o estado vegetativo (VS) e o nível de consciência mínima (MCS), e discutimos como são diagnosticados através das respostas comportamentais durante o exame clínico. Abordamos como a neuroimagem funcional revelou capacidades cognitivas preservadas em pacientes supostamente em estado vegetativo, introduzindo um novo diagnóstico: a dissociação cognitivo-motora. Revisamos a proposta da Global Workspace (GW) teoria de que a consciência surge a partir de um alto grau de conectividade funcional (FC) entre áreas cerebrais distantes. Discutimos como esta alta conectividade é a base do Default Mode Network (DMN), uma rede neural ativada quando o indivíduo não está envolvido com tarefas externas e se volta para atividade mental introspectiva. Finalmente, discutimos os achados de redução do nível de FC no DMN em pacientes com lesão cerebral e a proposta de que o mesmo poderia ser um índice do nível de consciência nesses pacientes.
1. Introduction

Patients with severe brain injury, both traumatic and non-traumatic, may pose for the physician difficult patient care decisions of great medical and ethical importance. Improved emergency room and intensive care treatment have increased the rate of survival of a greater and greater number of patients with severe brain damage and the resulting disorders of consciousness (DoC). The assessment of prognosis and end-of-life decisions for such patients, including the withholding and withdrawing of life-sustaining treatment and the accompanying ethical and legal issues, pose major challenges for the clinician. The establishment of criteria for end-of-life decisions is of particular concern because the rate of misdiagnosis of patients with DoCs is very high, reaching approximately 40% (Schnakers et al., 2009). In making such assessments, physicians have attributed great significance to the capacity of the patient for wakefulness, awareness, decision making and other aspects of consciousness, which may be difficult to discern accurately. These issues have recently come to the fore because of the availability of new means for imaging covert consciousness-related brain activity and new insight into the nature of the brain activity that underlies consciousness.

2. Review

The impairment of brain function following severe brain trauma can take many forms, ranging from loss of neocortical function, to the more severe impairment when brainstem function is lost, to the extreme resulting from whole brain death (Laureys, 2005). The medical community has categorized the resulting DoCs based on the nature, duration and extent of the functional impairment. Devising meaningful categories for these DoCs has been a challenge because at least initially the definitions of the categories were based on patient behavior in clinical examinations and the definitions did not take into account the nature of the brain damage itself. Also, the prognostic value of the DoC categories was limited because patients in the same DoC category could have widely differing courses of recovery. Also, as the means for assessment of brain function improved through the application of modern functional imaging techniques, the ability to evaluate residual function in the brain increased. When this new information was considered together with new understanding of consciousness arising from basic research and theoretical neuroscience, physicians began to have deeper insight into how brain injury might affect consciousness. The term vegetative state, a DoC category first proposed in 1972 (Jennett & Plum, 1972) refers to patients who, as described by the Multi-Society Task Force on PVS/UWS (1994), have unawareness of self or of the environment, but have preserved vegetative nervous system function, such as preserved sleep wake cycles, respiration, digestion or thermo-regulation, after severe brain damage. Unlike coma, which may last for only days or weeks, the vegetative state, also called “unresponsive wakefulness syndrome” (Laureys, Owen, & Schiff, 2010) may continue for even decades and be chronic, or it can be transitory and be the prelude to recovery. For those patients for whom this condition persists for at least one month, the term “persistent” was added (Andrews, 1999). In 1994, patients who had remained in the vegetative state for one year after traumatic injury or for three months after non-traumatic injury, the persistent vegetative state was defined as irreversible by the Multi Society Task Force on the PVS/UWS (1994).
In 1996 the term minimally conscious state (MCS) was introduced to describe a distinct clinical condition with “severely altered consciousness in which minimal but definite behavioral evidence of self or environmental awareness is demonstrated” (Giacino et al., 2002). Diagnosis of the MCS requires at least one of the following criteria: ability to follow simple commands; performance of gestural or verbal yes/no responses, irrespective of accuracy; patient reaction to noxious stimuli; purposeful behavior including appropriate expression of emotion; vocalization or gestures in response to questions, reaching for, touching or holding objects in an appropriate manner; eye movement or fixation in response to salient stimuli, all of which are taken as evidence for awareness (Giacino et al., 2002). If a patient carries out these behaviors in a manner that is appropriate and predictable, the conclusion is that the patient possesses at least minimal consciousness. Other means for assessment include measuring the patient’s motor responses to painful stimuli, and testing for a corneal reflex, which takes place when the cornea is stroked with a cotton swab. The Glasgow coma scale gives a numerical assessment of the outcome after cardiac arrest (Teasdale & Jennett, 1974). The application of these criteria has the advantage that they can be standardized and administered in the clinic by the physician without need for special facilities or equipment. There are, however, numerous difficulties including the observation that awareness may change dramatically over a period of several hours. Thus the possibility of misdiagnosis is great, an outcome that may lead to inappropriate medical management and incorrect evaluation of patient quality of life.

The foregoing assessments rely upon measuring patient behavioral responses during a physician’s clinical examination. Since the implementation of a radically different approach for patient assessment, modern functional neuroimaging (Laureys et al., 2004), the validity of tests based solely on behavior has been questioned. At least two forms of neuroimaging may be employed. These are fMRI, which measures increases in blood oxygen levels, and PET, which measures oxygen/glucose uptake, both methods detecting active brain regions. Imaging assays can provide assessments of brain injury in the early stages post-trauma, which facilitates selection of the optimal treatment and making informed decisions about life support. However, they have limitations. The level of activity and the inferred level of consciousness may fluctuate spontaneously or in response to pharmacologic treatment (Dolce, Quintieri, Serra, Lagani, & Pignolo, 2008). Also, fMRI is prone to artefacts arising from patient movement. Furthermore, to deduce the functionality of brain activity, activity patterns seen in brain-injured patients must be normalized to the anatomy of the average, healthy brain, which may not be accurate. In addition, these techniques are not generally available in clinics. They may be difficult to apply and they require further testing for their optimization and validation.

One unexpected impact of imaging has come from the revelation of covert forms of consciousness in brain-injured patients who were completely unresponsive in the behaviorally based assays. The disparity between behavioral and imaging assessments may arise when motor functions that are required for a behavioral response are dissociated from the cognitive functions that arise from residual levels of consciousness. Thus, damage to thalamo-cortical fibers may dissociate motor function from neocortical function, limiting or eliminating behavioral responses although a form of consciousness persists. Such patients were at first referred to as being in a functional “locked-in” state, but later were termed as having cognitive and motor dissociation (Laureys & Schiff, 2012). Because of the chance that behavioral tests that require motor activity may not be valid, new neuroimaging assays for covert consciousness have been developed. These sensitive imaging procedures have been used to investigate the level of awareness in the VS and in the MCS.
In one famous, early-reported case, a patient in the VS was tested for residual auditory function and speech processing by exposure to intelligible speech and unintelligible controls (Owen et al., 2005). PET imaging revealed peaks of auditory cortex activity similar to those of healthy controls upon intelligible speech exposure. The conclusion that patient function was partially preserved was supported by a different test, fMRI analysis of responses to semantically ambiguous sentences, which are known to induce heightened activity in healthy individuals. In a second case, a patient in the VS was asked to imagine that she was playing tennis and was asked to respond mentally to questions (Owen et al., 2006). The fMRI responses were similar to the responses of normal individuals, suggesting that cognitive functions were preserved although dissociated from motor function. In other tests dependent upon what is called “guided imagery, if a patient imagining a personally familiar face activates the fusiform face area, the capacity for top down control of cognition is indicated. Such studies have suggested that certain individuals in the VS may be capable of activation of emotional brain networks (Sharon et al., 2013).

The recognition of the complex relationship between brain injury and brain function has led to a consideration of the highly challenging question of how brain activity in fact establishes consciousness. Consciousness-related brain activity in the normal individual has been linked to three physiological brain functions (Seth & Baars, 2005). The first is irregular, low amplitude electrophysiological activity in the 20-70 Hz range in the fully conscious individual while in the unconscious state, such as during anesthesia, coma or sleep, EEG activity is more regular, higher in amplitude, and of much lower frequency, approximately 4 Hz. The second property is the reliance of consciousness on the integrity of cortical brain regions and the thalamus. Consciousness is lost if the brainstem or thalamus are damaged, while impairment following damage to sensory cortex is selective and may involve, for example, loss of face recognition, color vision, etc., depending on the region damaged. The third property observed in fMRI studies is the appearance during conscious brain function of coordinated cortical activity that spreads from the sensory cortex to the parietal, prefrontal, and medial-temporal cortices. Such spreading cortical activity is induced by tasks that are novel and that engage our consciousness, while tasks that are routine and do not engage our conscious attention induce activity that is restricted and local.

These observations suggest that consciousness arises from the sharing or transmission of information between functionally distinct, widely separated brain regions. In a model described by B J Baars (Baars, 2005), consciousness arises from a “distributed society of specialists that is equipped with a working memory, called a global workspace, whose contents can be broadcast to the system as a whole”. The Global Workspace Theory (GW), first proposed by Baars (Baars, 2005) and modified by others (Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006; Dehaene, Kerszberg, & Changeux, 1998; Dehaene & Naccache, 2001) proposes that consciousness operates in a global workspace that may be compared to a darkened theater. In this theater, the many specialized functions of the brain, such as the sensory modalities (vision, hearing, touch etc.) as well as the capacity for language and access to memory, are represented, much as actors in a play. In the unconscious state, these modalities operate independently, but by exercising the “top-down” function of attention, the brain can cast a spotlight onto a particular function, such as vision, bringing what is within our sight into our consciousness. This recruitment to consciousness engages large numbers of neurons that are widely spread in the brain, giving rise to the spreading function seen with fMRI. This recruitment makes information that resides in the remote regions available to the processes operating consciously and provides the individual with the subjective experience of the conscious state. Functions not engaged operate unconsciously in the surrounding darkened theater. By shifting the focus of attention (represented by the spotlight), new brain functions can be brought into the conscious realm.
To relate these theoretical considerations to actual brain function in normal and impaired brains, researchers have quantitated long-range signaling. Long range signaling is indicated by high functional connectivity strength (FCS), observed by resting state fMRI. FCS refers to the strength of activities that are synchronous in spatially distributed brain networks (Barkhof, Haller, & Rombouts, 2014). In keeping with the GW theory, long-range signaling indicated by high FCS has been proposed to integrate information residing in diverse brain areas and is taken as evidence of higher cognitive function.

One example of the greater ability of FCS measurement to reveal consciousness-related brain activity compared to conventional task-related fMRI came from studies of the brain’s “pain matrix” in brain injured patients (Kotchoubey et al., 2013). Patients in the VS and in the MCS were exposed to sounds of cries that in healthy individuals induced an empathetic response and activated the pain matrix. FCS measurement distinguished the pain matrix response of the MCS patients from the response of the VS patients while fMRI showed no difference.

The brain regions whose high FCS indicate aspects of consciousness, such as awareness, reside predominately within a part of the brain called the default mode network (DMN). The DMN was identified as a brain region that manifests a baseline state of brain activity, a state observed when a person is lying quietly, with eyes closed, and whose activity decreases when goal directed behavior is initiated (Raichle et al., 2001; Raichle & Snyder, 2007). The DMN was later regarded as regions active during mind wandering and self-reflective meditation, for example when a person is not focused on performing an external task (Buckner, Andrews-Hanna, & Schacter, 2008).

fMRI studies show that persons with brain injury exhibit diminished FCS within the DMN and it has been proposed that the degree of DMN disruption is an index of the degree of impairment of consciousness (Wu et al., 2015). The extent of maintenance of DMN activity may in turn be a biomarker for consciousness and a means for predicting recovery outcome. The facts that the brain regions that display high FCS attributed to consciousness are widely separated, and that the extent of the connectivity is variable from cases to case or time to time indicate that consciousness is a spectrum and not categorical (an individual is not either conscious or unconscious). Because the activity indicative of consciousness is distributed in the brain, there is no single “consciousness area”. It is likely that further development of imaging assays will provide a clearer picture of the capacity for consciousness in brain injured patients.

Shea and Bayne (Shea & Bayne, 2010) have argued that declaration of a patient as conscious versus not conscious should perhaps not be established by fulfilling a set of pre-established criteria. Instead, the clinical evidence for function may be considered as components of a syndrome, and are manifestations of brain function with a common root cause. This view would introduce flexibility into the declaration of conscious/not conscious, flexibility that may stem from greater insight into the root causes of impairment, but which may also place a greater judgmental burden on the physician with the challenge of making life or death decisions.

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References


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