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Chronic disorders of consciousness: role of neuroimaging

E Kremneva¹, D Sergeev¹, E Zmeykina¹, L Legostaeva¹ and M Piradov¹

¹Research Center of Neurology, Moscow, Russia

E-mail: moomin10j@mail.ru

Abstract. Chronic disorders of consciousness are clinically challenging conditions, and advanced methods of imaging for better understanding of diagnosis and prognosis are needed. Recent functional neuroradiological studies utilizing PET and fMRI demonstrated that besides widespread neuronal loss disruption of interconnection between certain cortical networks after the injury may also play the leading role in the development of behaviourally assessed unresponsiveness. Functional and structural connectivity, evaluated by neuroimaging approaches, may correlate with clinical status and may also play prognostic role. Integration of data from various diagnostic modalities is needed for further progress in this area.

1. Introduction

Severe brain injury may end up in a condition when the patient survived coma regains arousal in the absence (or with very little) awareness of himself and surroundings. These conditions are described as chronic disorders of consciousness [1], with the major sub-entities of vegetative state (VS), now also coined unresponsive wakefulness syndrome (UWS) [2], and minimally conscious state (MCS), in turn, subdivided to MCS plus and MCS minus, depending on the level of awareness spared [3]. The underlying cause of the dissociation between wakefulness and awareness seen in this category of patients is believed to be an impairment of the connectivity between structures within the human brain responsible for arousal (i.e., brainstem and hypothalamus) and the content of consciousness (i.e., fronto-parietal cortical network and its connections to the thalamus) [4].

Clinical assessment of consciousness in patients emerging from coma is limited to bedside evaluation of behavioral response to external stimuli, such as purposeful movements, with the rate of misdiagnosis as high as 37–43% [5]. However, advances in neuroimaging made it possible to study brain structures related to conscious behavior, and, moreover, their intrinsic functional connections and interactions that underlie cognitive processing [6].

2. Structural brain imaging

Conventional structural imaging, such as computed tomography or magnetic resonance imaging (MRI) with standard sequences (T1-TSE, T2-TSE, FLAIR) is used to evaluate the localization and severity of the lesion (traumatic or anoxic; Figure 1), but it fails to indicate a specific brain region(s) that can be undoubtedly related to awareness [7]. More sophisticated methods, such as diffuse tensor imaging (DTI) are utilized to study the integrity of white matter – pathways interconnecting cortical and subcortical structures, thus evaluating *structural connectivity* of the areas relevant to consciousness. DTI techniques are based on the assessment of water diffusion properties and are able to reveal structural damage in normally appearing tissue. They can be applied along with sedation to reduce acquisition artifacts due to the patient's movements, as sedation does not affect the data, which is an important limitation in functional imaging [7].



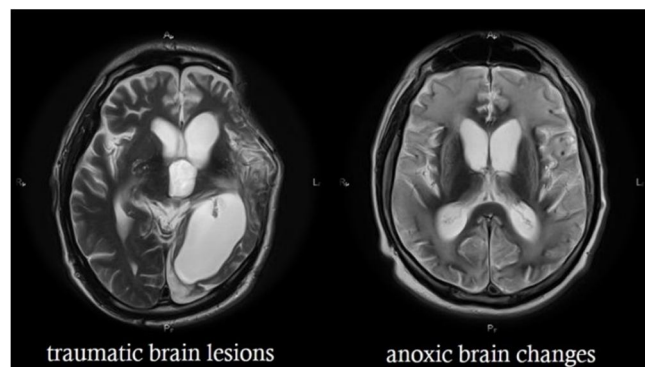


Figure 1. An example of traumatic and anoxic brain lesions leading to chronic disorders of consciousness.

One of the main measurements of the DTI is the fractional anisotropy (FA) that indicates the anisotropy of a diffusion process and describes the integrity of nerve fibers and their direction. It make take values from 0 (isotropic diffusion) to 1 (completely anisotropic diffusion). In the study by Newcombe et al. [8] alterations of FA in VS patients were revealed in supratentorial area (thalamus and corpus callosum) without significant differences in the infratentorial structures (pons and midbrain areas) and were shown to correlate with clinical assessment as measured by Coma Recovery Scale Revised (CRS-R) and functional magnetic resonance imaging (fMRI) activation following an auditory task. DTI showed interconnections between medial prefrontal, medial parietal, and medial temporal cortices within the default network, that is supposed to maintain consciousness [9]. Quantitative DTI techniques may predict clinical outcome after 1 year of traumatic [10] or anoxic [11] injury at the individual-patient level better than structural and clinical assessment (Figure 1).

3. Functional brain imaging

Neurovisualization techniques assessing brain functioning are based on the measurement of the metabolism of brain tissue either directly, as positron emission tomography (PET) with ^{18}F Fluorodesoxyglucose (FDG) radioactive tracer does, or via evaluating the blood flow with $^{15}\text{H}_2\text{O}$ -PET or with functional MRI, that quantifies blood-oxygen-level dependent (BOLD) changes.

3.1. PET studies

FDG-PET studies were the first to demonstrate massive decreases in brain metabolism in disorders of consciousness. The reduction of brain function in VS was shown to be 40–50% of normal values [12]. Later it was shown that some cortical areas are more important in respect with consciousness than others, as patients in VS demonstrated decreased metabolism in a widespread network encompassing frontoparietal areas [13]. Clinical recovery from the UWS did not coincide with the recovery of global metabolic levels; rather, it was paralleled with *functional connectivity* restoration in these areas (lateral prefrontal and posterior parietal regions, midline anterior cingulate/mesiofrontal and posterior cingulate/precuneal associative cortices) and between these regions and the thalamus [14]. These findings lead to the description of awareness network, that may be subdivided into the intrinsic, or default mode network (DMN), and extrinsic, or executive control network (ECN). The latter includes the lateral fronto-parietal brain regions and is related to sensory awareness or awareness of the environment, while the former encompasses the medial prefrontal cortex and the precuneus and bilateral posterior parietal cortices and is responsible to internal awareness [15]. The discovery of these networks gave rise to the understanding that the disorders of consciousness in certain patients represent the disconnection syndromes rather than the consequences of extensive neuronal loss. In VS/UWS patients PET-measured activation in response to noxious stimulus was limited to the primary sensory areas [16], that were disconnected from associative fronto-parietal cortical networks, which

are thought to be essential for conscious perception. At the same time, MCS patients demonstrated activation of higher order associative areas, that indicates partial preservation of this networks integrity [17], while midline regions may remain highly dysfunctional [18]. PET studies also revealed activation in response to the pain in MCS patients similar to that observed in healthy controls, suggesting a possible perception of pain in this patient category. Metabolism in the awareness network was shown to correlate to the CRS-R score [19]. This data suggests that patients in MCS may retain altered self-awareness besides their behavioral response that may be very limited, e.g., due to the motor deficit or aphasia. However, FDG-PET cannot yet disentangle between VS/UWS and MCS at the single-subject level.

3.2. Functional MRI studies

Higher availability of fMRI led to gradual replacement of the PET activation studies in the recent years. Active fMRI paradigms confirmed findings obtained with PET and revealed high level cortical activation in response to visual, auditory and somatosensory stimuli in MCS patients, while only low level cortical activation, limited to the primary sensory areas, was detected in VS/UWS [22]. The VS/UWS patients who showed high level cortical activation later often demonstrated signs of recovery [23]. Furthermore, fMRI studies demonstrated the ability to willfully modulate brain activity in the minority of patients who do not show any clinical signs of awareness. Monti et al. [20] reported clinically VS patient who were able to correctly respond to the questions by imaging different situations that was captured by fMRI. This and several following studies [21] confirm the shortcomings of solely clinical assessment of this category of patients. However, despite certain diagnostic and prognostic potential, fMRI still cannot be viewed as a “golden standard” for covert consciousness detection in behaviorally unresponsive patients, as the absence of cortical activation to certain stimuli does not necessarily coincide with absence of awareness.

Another fMRI approach is used to investigate the spontaneous temporal coherence in BOLD fluctuations related to the amount of synchronized neural activity (i.e., functional connectivity) in the absence of any external stimuli (resting-state fMRI). It allows to detect an activity of several resting state networks, such as the DMN, bilateral fronto-parietal or executive control networks, salience, sensorimotor, auditory, visual systems, and the cerebellar network [6]. The connectivity of DMN was shown to correlate with the level of consciousness according to literature [24] and our own experience (Figure 2).

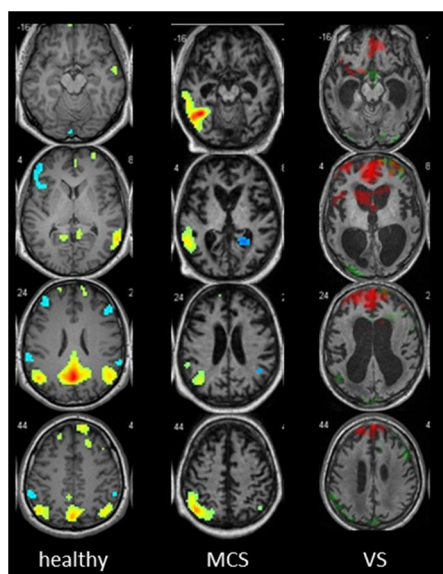


Figure 2. Default mode network (resting-state fMRI) in healthy subject (all components showed), partially preserved DMN in minimal conscious state and almost absence of DMN in vegetative state

However, at the single-patient level, fMRI still fails to reliably distinguish VS/UWS from MCS. Recently, resting-state fMRI was used to investigate functional connectivity between cortical regions and brainstem with the view of finding sites crucial for coma development [25]. A small region in the rostral dorsolateral pontine tegmentum functionally connected to the ventral anterior insula and pregenual anterior cingulate cortex was significantly associated with coma-causing lesions that may be considered as a new functional network relevant to maintaining consciousness.

4. Conclusion

Recent progress in neuroimaging techniques played key role in the understanding of the disorders of consciousness. Structural and functional imaging is the source of insights into intrinsic brain networks interaction crucial for conscious behavior. The next step of development will be the integration of data acquired with different modalities, including neuroimaging and neurophysiological approaches (e.g., TMS-EEG, with the assessment of *effective connectivity*), to develop the single-patient prognostic factors and to clear the paths to treatment and recovery.

Acknowledgments

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