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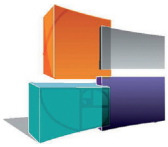

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Assessing consciousness in coma and related states using transcranial magnetic stimulation combined with electroencephalography☆,☆☆

Évaluation de la conscience chez les patients en coma et en états apparentés par stimulation magnétique transcrânienne combinée à l'électroencéphalographie

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ABSTRACT

Thanks to advances in medical care, an increased number of patients recover from coma. However, some remain in vegetative/unresponsive wakefulness syndrome or in a minimally conscious state. Detection of awareness in severely brain-injured patients is challenging because it relies on behavioral assessments, which can be affected by motor, sensory and cognitive impairments of the patients. Other means of evaluation are needed to improve the accuracy of the diagnosis in this challenging population. We will here review the different altered states of consciousness occurring after severe brain damage, and explain the difficulties associated with behavioral assessment of consciousness. We will then describe a non-invasive technique, transcranial magnetic stimulation combined with high-density electroencephalography (TMS-EEG), which has allowed us to detect the presence or absence of consciousness in different physiological, pathological and pharmacological states. Some potential underlying mechanisms of the loss of consciousness will then be discussed. In conclusion, TMS-EEG is highly promising in identifying markers of consciousness at the individual level and might be of great value for clinicians in the assessment of consciousness.

Mots clés :
Troubles de la conscience
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État végétatif
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RÉSUMÉ

Avec les avancées récentes de la médecine, de plus en plus de patients sortent du coma. Cependant, certains restent en état végétatif/syndrome d'éveil non-répondant ou en état de conscience minimale. L'évaluation de leur niveau de conscience reste difficile notamment parce qu'elle repose sur des examens comportementaux qui peuvent être biaisés par des déficits moteurs, sensoriels et cognitifs. D'autres outils d'évaluation de la conscience sont donc nécessaires afin de préciser le diagnostic des patients sévèrement cérébrolésés. Dans cet article, nous exposerons les différents états de conscience altérée survenant à la suite d'une grave lésion cérébrale et les difficultés liées à l'évaluation du niveau de conscience au chevet des patients. Nous décrirons ensuite une technique non invasive, la stimulation magnétique transcrânienne combinée à l'électroencéphalographie à haute densité (SMT-EEG) qui permet de détecter la présence ou l'absence de conscience dans différents états physiologiques,

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pathologiques et pharmacologiques. Des mécanismes potentiels pouvant expliquer la perte de conscience seront ensuite discutés. Dans notre conclusion, nous exposerons les avantages de la SMT-EEG et en quoi cette technique prometteuse pourrait être d'une grande utilité pour évaluer le niveau de conscience au chevet des patients.

1. Disorders of consciousness

Since the invention of mechanical ventilation in the 1950s, many patients survive even after severe brain damage. After the comatose phase where patients lie with eyes closed (i.e., coma), some patients regain full consciousness while some progress to a state of preserved wakefulness in the absence of awareness (i.e., unresponsive wakefulness syndrome). Others show fluctuating signs of awareness but they remain unable to communicate consistently (i.e., minimally conscious state). Finally, some patients fully recover awareness but lack motor output (i.e., locked-in syndrome).

1.1. Coma

Coma is an acute state of non-responsiveness in which patients cannot be awakened even when intensively stimulated [1]. Patients in a coma lack sleep-wake cycles and only show some reflex behaviors [2]. The autonomous functions such as breathing and thermoregulation are reduced and global brain metabolism is significantly diminished [3]. Coma is the result of diffuse cortical or white matter damage and/or an acute lesion in the brainstem [4]. It lasts at least one hour (to be distinguished from syncope) and up to a few days. The prolonged coma also exists but is rare and can last two to five weeks (e.g., pharmacologically-induced coma).

1.2. Unresponsive wakefulness syndrome

This state was first named apallic syndrome [5] or coma vigil [6], and in 1972 it was termed vegetative state [7]. New terminology was proposed in 2010 – the unresponsive wakefulness syndrome (UWS) [8] – to avoid the strong negative connotation with inadvertently risking comparisons between patients and vegetables. The term "UWS" also allows a more precise description of the clinical state, referring to patients that are unable to react to stimuli in a non-reflexive way (hence unresponsive), whilst showing periods of time with eyes opened (hence wakefulness). Clinically, this state is thus defined by wakefulness without awareness, and in which patients are able to open their eyes but remain unaware of the environment and themselves [9]. They only show spontaneous or stimulus-induced reflex behaviors such as grinding teeth, moving eyes, swallowing, chewing, yawning or groaning. This state may be transitory, chronic or permanent.

Although recovery of the sleep-wake cycle is part of the criteria of UWS, recent studies have demonstrated an absence of electrophysiological characteristics of sleep in UWS [10,11]. Brain metabolism is usually diminished by 40 to 50% with impaired cortico-thalamo-cortical circuits but relatively preserved brainstem functions [12]. Brain dysfunctions are more specifically located in the frontoparietal network (including both medial and lateral networks related to self and environment respectively) and in the thalami [13]. During sensory stimulations, UWS patients usually show metabolic brain activation that remains isolated in the primary cortices [14,15]. Finally, top-down processes from frontal to temporal cortices have been shown to be impaired in patients in UWS when measuring the electrical activity during auditory stimulations [16].

1.3. Minimally conscious state

The minimally conscious state (MCS) is characterized by primary inconsistent signs of consciousness [17,18]. The criteria of MCS, introduced in 2002, include reproducible responses to verbal or written commands, visual pursuit, localization to pain, intelligible verbalizations, intentional communication and reaching/holding objects [18]. Adapted emotional behaviors such as smiles, laughs or tears can also be observed [18]. This clinical entity has been recently subcategorized in "minimally conscious plus" (MCS+) for patients who present high-order behavioral responses to stimuli (e.g., response to a command which involves the preservation of language) and "minimally conscious minus" (MCS−) for patients who only show low-level non-reflexive responses to stimuli (e.g., visual pursuit or localization to nociception) [19]. This classification is supported by neuroanatomical data that demonstrate better preservation of language-related networks in MCS+ as compared to MCS− patients [20]. The overall cerebral metabolic activity in MCS patients is usually reduced but the autonomous functions are preserved, and cortico-thalamo-cortical connections are partly restored [21]. The main metabolic dysfunctions appear to be located in the lateral network and in the thalami [13]. When patients recover the ability to functionally communicate or to use objects adequately, this is referred to "emergence of the minimally conscious state" (EMCS) [18].

1.4. Locked-in syndrome

Locked-in syndrome (LIS), also known as pseudocoma, is not a disorder of consciousness per se but can be mistaken as one. LIS is characterized by a complete paralysis of the body resulting from a lesion in the brainstem affecting the pyramidal tract, most frequently due to an ischemic pontine lesion [17]. If the lesion is only restricted to the brainstem, LIS patients have preserved sensory and cognitive functions [22]. The primary way of communication is through vertical eye movements or blinking [23]. Through the recovery of distal movements, such as the tip of a finger or head movement, chronic LIS patients are often able to communicate via a computer and to control their wheelchair. Communication has also been recently made possible by measuring electrical brain activity [24] and pupil size [25]. Finally, many chronic LIS patients report having a happy and meaningful life and the demand for euthanasia, albeit existing, is not so frequent [26].

2. Assessment of the level of consciousness

To date, the level of consciousness is mainly assessed at the patient's bedside by searching for response to command or non-reflexive behaviors in response to sensory stimulations. Assessing the presence or absence of consciousness of non-communicative brain-damaged patients is however difficult, as consciousness is a subjective first-person experience, and one has necessarily to make inferences about its presence based on the patient's behavior. Currently, the diagnostic decision-making process is extremely challenging leading to a diagnostic error rate up to 40% when not assessed with appropriate standardized scales [27]. The Coma Recovery Scale-Revised (CRS-R) has been shown to be the