Sleep and memory consolidation in disorders of consciousness

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Background: Acute traumatic or non-traumatic brain injuries can cause severe impairments in wakefulness and cognition [2]. In the neurological literature, chronic states of impaired consciousness are termed disorders of consciousness (DOC), mainly referring to two distinct syndromes: the unresponsive wakefulness syndrome (UWS; syn. vegetative state) and the minimally conscious state (MCS) [4, 6, 8]. Since the mid-1990s, there has been growing evidence that UWS patients and, to an even greater extent, MCS patients retain various cognitive functions despite severe brain injury. However, studies that provide insight into residual learning abilities of DOC patients are scarce, which is in contrast to the fact that therapeutic rehabilitation approaches operate under the assumption that some mechanisms of memory formation are preserved [1, 5, 7, 11]. This lack of knowledge can lead to the implementation of non-specific therapeutic measures and to deficits in the prognosis of the functional outcome of those affected. Over the past two decades a plethora of studies have pointed to a link between sleep and neuronal plasticity in the healthy brain (e.g. [3]). Understanding sleep patterns and assessing the effects on memory formation in DOC could therefore contribute to the development of innovative rehabilitation techniques in the future. In the present investigation we first characterized the organization of behavioural and neurophysiological sleep patterns in UWS and MCS patients in a clinical environment over a 24 h cycle. Building on these findings, in the second and still ongoing project we investigate to what extent and how sleep can contribute to the processes of memory consolidation in DOC patients, as it is the case in healthy individuals.

Methods: During the first part of the project the distribution of sleep and wakefulness was evaluated over a 24 h period by means of polysomnography (electroencephalography, electrooculography, electromyography) and video recordings in a total of 32 DOC patients (16 UWS, 16 MCS), and 10 clinical control patients with severe tetraplegia. Three independent raters scored the patients' polysomnographic recordings according to sleep scoring criteria that were adapted to the altered brain activity of the patients.

The second study will encompass 50 patients diagnosed with DOC, consisting of 25 individuals with UWS and 25 with MCS, spanning both traumatic and non-traumatic brain injuries. This comprehensive approach aims to enhance our understanding of how sleep influences memory consolidation in DOC patients. According to previous experience, a sample size of 50 patients is a realistic target value that is sufficient to capture medium to large effects (e.g. determination coefficients > 0.1 and ratio differences between groups of at least 0.3 – 0.35).

Based on our observation that DOC patients sleep very frequently during the day, EEGs are recorded between 12 and 4 pm to assess sleep-dependent memory formation. In a "test" phase, subjects are presented with three auditory learning paradigms (aversive conditioning, noise learning and word-pair learning), followed by either a therapy (wake) or a rest phase (sleep). The paradigm is then repeated as a "retest". Whether sleep impacts the individual learning ability is investigated by analyzing changes in relevant event-related potentials (ERPs) between the "test" and "retest" phases while participants are awake.

Results: The first study revealed that nearly all patients (with the exception of one patient in the UWS group) showed behavioral and electrophysiological evidence of sleep. Patients in the Control and MCS group spent significantly more time asleep at night than during day, a pattern that was not observed in UWS patients. DOC patients (particularly UWS) exhibited less REM sleep compared to control patients. A significant proportion of UWS patients (44%) and some MCS patients (12%) exhibited no REM sleep, while all control subjects (100%) showed evidence of all sleep stages and sleep spindles. In addition, 62% of UWS patients and 21% of MCS patients revealed no sleep spindles. In the remaining DOC patients with sleep spindles, their number and amplitude were significantly lower than in the control subjects [10].

In the second study, we have acquired and analyzed 12 datasets so far. Among them, six patients showed no significant cognitive ERPs in response to auditory stimuli. Accordingly, four of these patients were diagnosed with UWS and two with MCS-.

In contrast, the remaining six patients, five of whom were diagnosed with MCS and one with UWS, showed relevant cognitive ERPs in the EEG. Learning effects were visible in four of the six MCS patients with cognitive ERPs.

Conclusions: In DOC patients the distribution of sleep markers over a 24-hour period deviates significantly from the standard sleep-wake cycle pattern. These dif-

ferences in the sleep pattern of DOC patients are not driven by external variables such as severe immobility or the hospital environment.
Further, learning effects on cognitive ERPs indicate preserved learning abilities, especially among MCS patients. More data are needed to draw conclusions about the effects of sleep on learning capability in DOC patients.
Outlook: Positive results in the ongoing project would suggest that the targeted incorporation of sleep in the rehabilitation process can counteract neuronal degradation and support task-related plasticity processes. Research on sleep-related memory consolidation processes can help to improve therapy approaches, for example by implementing exercises that benefit from subsequent sleep before regular sleep times. In addition, cognitive effort can lead to an improvement in the quality of sleep for patients. In this case, positive effects on patients' health (including the immune system) can be expected. Future studies could further investigate the extent to which sleep quality can be increased in DOC patients through targeted sleep interventions (e. g. transcranial electrical stimulation of slow oscillations; see [9]) and the associated learning and plasticity processes can be further improved.

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