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Editorial

Sleep patterns open the window into disorders of consciousness

See Article, pages xxx–xxx

The presence of sleep-wakefulness cycles is one of the main clinical symptoms marking the transition from coma to chronic disorders of consciousness (DoC). That is, eyes of coma patients are regularly closed while eyes of DoC patients are sometimes closed, sometimes opened. But does it mean that they really sleep? Landsness et al. (2011) published a broadly cited study in which they reported that only one group of DoC patients (those with the diagnosis of Minimally Conscious State, or MCS: Giacino et al., 2002) slept in the exact physiological sense of this term, i.e., they had regular circadian changes of EEG, electrooculogram (EOG), and muscle tone similar (though not identical) to those of healthy humans. Another DoC group with the diagnosis Unresponsive Wakefulness Syndrome (UWS; syn. Vegetative State: Laureys et al., 2010) had, in contrast, nothing more than the simplest behavioral sign of opening and closing their eyes, but no sleep-like dynamics of neurophysiological parameters.

Although based on a small patient sample, the publication by Landsness et al. (2011) elicited a strong resonance. Circadian rhythms belong to the most basic physiological functions underlying behavior of all mammals. There is a running discussion around the question, to what degree UWS patients still possess residual cognitive capabilities. The answers to this question vary from "none" to "a large set of cognitive functions including semantic processing and sometimes even subjective awareness". If the result is generalizable that UWS patients do not have even elementary circadian rhythmic activity, then the search for higher-level cognitive processing in these patients would obviously be futile, and the data seemingly indicating such high-level processing could be suspected as artifacts. The UWS patients themselves, whose circulation and respiration systems are regularly working, would in this case be regarded as "biological heart-lung machines" rather than human (or even animal) beings. This view would have huge consequences from both medical and ethical points of view.

Happily, for patients and their families, the claim of Landsness et al. (2011), like many sensational claims about UWS, could not be replicated in subsequent studies. Among others, Arnaldi et al. (2015), Cologan et al. (2013) and Forgacs et al. (2014) found in the EEG of UWS patients various sleep components such as K-complexes, Slow Oscillations and REM-sleep (for an interim summary, see Table 1 in Pavlov et al., 2017). At present, we know exactly that (i) both UWS and MCS patients do sleep but (ii) their sleep is clearly abnormal, and probably more abnormal in UWS than MCS. This is not very much, however! We do not know how these sleep components are represented in DoC patients' sleep; we do not know the exact extent of their deviation from normal sleep, and *a fortiori* we do not know the functional meaning of these deviations. We do not even know why sleep in patients with severe brain lesions is abnormal. Is it so due to the lesions, or rather, due to "external" factors such as the continuous light and sound disturbances in the clinics, pain, prophylactic interventions (which are also necessary at night time), immobility etc.?

The severe abnormality of DoC patients' sleep is the main reason of the lacking answers to many questions. Standard sleep evaluation criteria like those of Rechtschaffen and Kales (1968) or Iber et al. (2007) cannot be applied to these pathological sleep patterns without adjustment. Alternative (always simplified) scoring criteria for severely brain injured patients (e.g., Valente et al., 2002) do not allow a detailed analysis of sleep stages and sleep components, and methods of "blind" mathematical analysis of EEG sleep data (e.g., Wislowska et al., 2017) may yield uninterpretable results and can substantially complement but not substitute expert consensus (e.g., Warby et al., 2014).

Another important point is that due to the specific life schedule in intensive care units and rehabilitation hospitals patients have enough opportunities to sleep during the daytime, which can strongly affect their night sleep. Therefore, standard polysomnographic recordings over the night hours (e.g., Wislowska et al., 2017; Pavlov et al., 2017) are not very informative as far as we do not know how awake the patients were on the preceding day.

The publication of Sebastiano et al. in this issue of *Clinical Neurophysiology* marks a new step in the study of the circadian activity in DoC (Sebastiano et al., 2018). The authors recorded polysomnography (PSG) during 19 h (2 p.m. to 9 a.m.) on a representative sample of ninety-one chronic (several years after the accident) DoC patients. Two experienced neurophysiologists evaluated PSG traces independently of each other, and were blinded concerning the diagnosis. After consensus discussion, interrater agreement could be attained for 95.2% of all evaluated 30-s epochs.

Circadian EEG changes were observed in all UWS (n = 55) and MCS (n = 36) patients. However, in 19 UWS patients the changes were limited to mere periodic amplitude changes with lower amplitudes during sleep episodes as compared to wakefulness. Non-REM sleep stage 2 was observed in most UWS patients – and in all except one MCS patients. Slow Wave Sleep was found in some 30% of UWS patients and in 86% of MCS patients. REM sleep was present in about 50% of the patients, slightly but not

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significantly more frequently in MCS than UWS. Both UWS and MCS patients were characterized by frequent awakenings and highly fragmentary sleep. The time of non-REM sleep (stage 2 and Slow Wave Sleep) was strongly and positively related to patients' neuropsychological status, as measured by the Coma Recovery Scale-revised (CRS-r: Giacino et al., 2004).

Why are these data important? Firstly, they show the heterogeneity of the UWS population that consists of at least two clearly different subgroups with distinct electrophysiological signs (see Kotchoubey, 2005; Kotchoubey et al., 2005). Whereas the heterogeneity of MCS population has been recognized before (Bruno et al., 2011), UWS patients are still frequently regarded as being "all similar", which is obviously wrong. Secondly, patients in a better clinical condition were characterized by longer episodes of distinct non-REM sleep as compared with patients in a more severe condition. Also, the number of sleep spindles was larger in the former than in the latter. This finding is particularly intriguing given the fact that non-REM sleep, and particularly spindle activity, plays a vital role in the consolidation of memory traces, thus building a skeleton of the entire cognitive system (Diekelmann and Born, 2010; Rasch and Born, 2013).

What, however, is the cause and what is the effect in the latter correlation? At first glance, it appears that more benign brain lesions may determine both positive sleep patterns and less severe neuropsychological deficits, as compared with more severe brain lesions. But it is also plausible that the preserved oscillatory components of the non-REM sleep promote learning and acquisition of new information, thereby contributing to healthier responses to CRS-R test. Of course, both causal chains can coexist and interplay, and the available data do not permit to disentangle this interaction. Further studies with equally representative DoC samples are necessary, which would, firstly, comprise the entire 24 h cycle, secondly, describe the exact distribution of sleep components over this time, and thirdly, compare sleep patterns not only with the actual patients' state but also with their later clinical outcome.

Conflict of interest

The authors declare no conflict of interest.

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