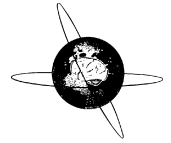




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Letter to the Editor

Approaches to sleep in severely brain damaged patients: Opposite or complementary? Reply to “Sleep and Circadian Rhythms in Severely Brain-Injured Patients - A Comment”

We thank Schabus, Wislowska, Angerer and Blume (Schabus et al., 2018; in the following SWAB) for their stimulating comments to the article of Rossi Sebastiano et al. (2018), as well as to our own comments to that article (Kotchoubey and Pavlov, 2018). SWAB made several important and constructive suggestions concerning the study of sleep in patients with Disorders of Consciousness (DoC) and other severely brain damaged patients. Unfortunately, it remains not quite clear from their text whether they conceive of their suggestions as *complements* to (and improvement of) the approach realized by other authors (e.g., Rossi Sebastiano et al., 2015, 2018; Pavlov et al., 2017), or as an *alternative* to it. As we shall see, this makes an important difference.

1. Length of recording. The studies of sleep in DoC began “naturally” with routine night sleep recordings, but we fully agree with SWAB that this is definitely not enough. One of our patients with the diagnosis Vegetative State (VS) did not display any EEG signs of sleep during the night whatsoever, but slept during afternoon and demonstrated a classical REM pattern between 6:00 and 6:30 pm. Obviously a conclusion about circadian activity based on nightly recordings can be false, just because patients can sleep on other times of the day. Thus, in our new yet unpublished study we collected 24 h polysomnographic data in patients in VS, minimally conscious state (MCS) and an adjusted control group consisting of conscious tetraplegic patients. A brief review of the data is presented in Fig. 1.

The solution proposed by SWAB is less clear. On the one hand, they cite publications of their group (Wislowska et al., 2017; Wielek et al., 2018) claiming to have used 24 h polysomnography, but in fact, the night was defined in those studies as time between 11 pm and 5 am, the daytime as 8 am to 8 pm, and the resting time was arbitrarily cut away leaving us with only 18 h. On the other hand, they indicate that recording periods even longer than 24 h may increase the reliability of assessment of circadian activity. 48, 72 h, or 7-day recordings would deliver more trustworthy data. Again, we agree in principle with the last idea (eventually one 24 h recording might happen on an unrepresentative day!), but the trivially true rule “more data are better than less data” does not take into account cost-benefit considerations. Resources are always limited. Having a total of 28 recording days, is it better to collect data from a sample of 28 DoC patients 24 h each, or to record four patients during 7 days? We presently believe that 24 h recordings can be considered as a necessary *minimum* for the assessment of circadian rhythms and enough to draw careful conclusions about the presence of sleep-wake cycles with sufficient precision.

2. Additional measures. SWAB find important to record additional physiological parameters beyond the routine polysomnography (PSG), such as melatonin rhythm, body or skin temperature, or actigraphy. We are ready to embrace this suggestion and do not doubt that these measures can enhance our knowledge about the nature of DoC. We would, however, disagree with the idea (if there is such one) to use these measures *instead of* PSG. SWAB do not explicitly suggest to abandon the central sleep measures and to restrict to the recordings of peripheral variables only. But because they (correctly!) criticize the extant EEG studies of sleep in DoC, and oppose them to the studies of peripheral cyclicality cited in a manifestly positive tone, their text might be understood in this way. Of course, circadian rhythms involve the whole organism; however, the dynamics of patients' *brain* is of particular interest. Sleep is not just an about 24 h rhythmic change of an organism's state but a set of mechanisms for highly complex and intensive information processing (Diekelmann and Born, 2010; Stickgold et al., 2009; Vorster and Born, 2015), differently distributed across its stages and phases. These mechanisms can only be explored by means of central neurophysiology.

3. Scoring versus automatic assessment. Also in this case, we fully agree with three key statements of SWAB: that sleep scoring in the population of patients in DoC is extremely challenging; that scoring rules must be made more transparent; and that methods of automatic EEG evaluation (including, but not restricted to, the power analysis, the complexity analysis, and methods of machine learning) can substantially contribute to our understanding of sleep processes in DoC.

On the other hand, the arguments and conclusions that SWAB draw from these statements are not always convincing. The arguments are well known from the old-age and boring discussion whether medical decisions should/can be made by medical experts or by machine algorithms. The fact that a human activity requires a high level of expertise is usually regarded as indication that *more* (not less) effort should be invested in this activity. Every expertise is effortful and expensive. For example, the contemporary standard of the clinical diagnostics of DoC is Coma Recovery Scale-Revised (CRS-R), but the number of neurologists able to apply this scale with a high level of interrater reliability is very limited. Is this an argument to abandon this scale and replace it with another method only because it could be used by a larger group?

As there is no algorithm up to date in general medicine just to measure a patient and to compute her diagnosis and treatment without a trained medical doctor, we do not know any method of the evaluation of human sleep that could not only complement but replace visual scoring, even in healthy individuals. SWAB recommend the study of Wislowska et al. (2017) as an example of the successful purely automatic EEG data analysis, but we can read in that paper that “lastly the data was visually inspected for

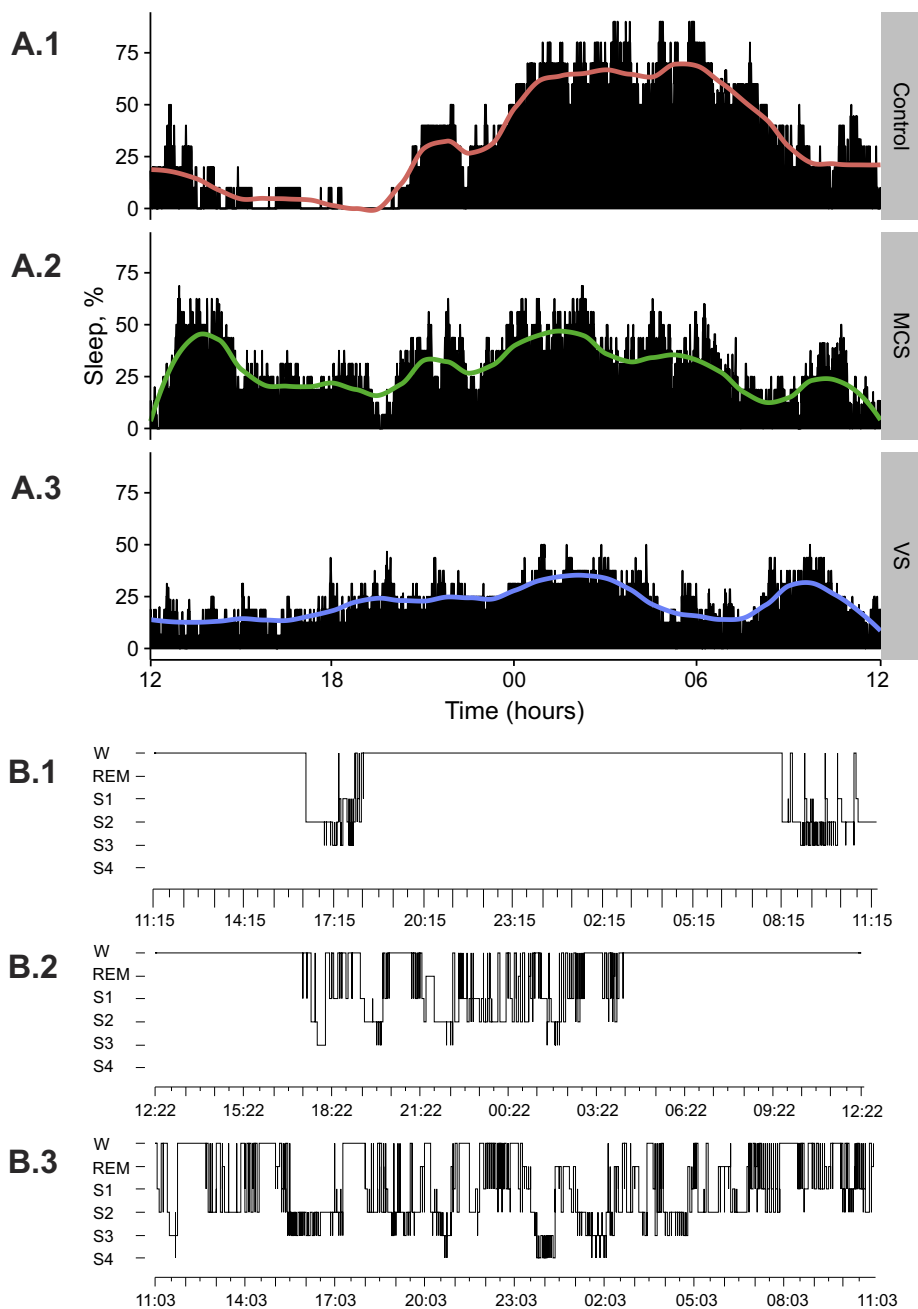


Fig. 1. (A) Mean percentage of sleep to different times of the day per a 30-s epoch (black columns) for tetraplegic patients (A.1), VS (A.2), and MCS (A.3). Solid lines show the results of smoothing according to the Loess algorithm with a span of 0.2 by means of ggplot2 R package (Wickham, 2016). Averaged for day (8 am–8 pm) and night (8 pm–8 am), the percentages of sleep time for tetraplegic patients ($N = 10$) are $13.2 \pm 10.7\%$ and $51.6 \pm 12.9\%$, resp.; for VS ($N = 16$), $18.9 \pm 14.3\%$ and $24.5 \pm 22.6\%$, resp.; for MCS ($N = 16$), $23.1 \pm 13.6\%$ and $33.9 \pm 15.9\%$, resp. (means \pm SD). In absolute terms, VS patients slept between 8 pm and 8 am 174 ± 160 min (155 ± 89 min), MCS patients 239 ± 110 min (230 ± 123 min). Data in parentheses are from Rossi Sebastiano et al. (2018); note the astonishing similarity of the data obtained on two very different patient samples. B: Examples of 24 h hypnograms of DoC patients: a patient who slept on the day but remained awake during the night (B.1); a patient with several close-to-normal sleep cycles in the night (B.2); a patient with a rather disorganized sleep pattern (B.3).

remaining artefacts". Why did not the authors rely solely upon automatic artefact rejection procedures?

The argument that scoring criteria developed in normal population (e.g., AASM criteria) cannot be transferred to DoC population without adjustment is correct, but can be applied, with more strength, to automatic methods. Even if such a method works in normal subjects (which is a big question), this does not mean that it would also work in DoC. The method would have to prove its

validity on DoC patients in which – circularly – its results would be compared with the results of visual scoring.

4. Organizational issues. In their last two paragraphs, SWAB made some suggestions how to improve the organization of sleep DoC studies. We welcome these suggestions without restriction. Particularly, we appreciate the idea to use the platform of the "Disorders of Consciousness Special Interest Group" of the International Brain Injury Association. We are also ready to provide SWAB

with our above-mentioned dataset to develop and compare different methodological approaches.

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Conflict of interest

None.

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