# Circadian rhythms in patients with disorders of consciousness – Quantification and therapeutic implications

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## Understanding circadian rhythms

Many biological and psychological processes of virtually all living beings follow a circadian (latin: circa 'around', dies 'day') pattern. This means that they are rhythmic with a period length of approximately 24 hours. Circadian rhythms are controlled by the internal biological clock which is located in the suprachiasmatic nuclei of the hypothalamus [1, 2]. In healthy individuals consciousness also fluctuates in a circadian pattern with these fluctuations being closely linked to the sleep-wake rhythm. Light serves as the primary pacemaker [3]. A misalignment between the internal and external time, as seen in shift work, or a decoupling of the internal biological clock from peripheral rhythms (e. g., in the liver, pancreas, kidney, heart, or lungs), can impair cognitive abilities (e.g., attention) and the immune system [4]. Post-comatose patients with disorders of consciousness following severe brain injuries are often affected by circadian rhythm disorders [5–8], meaning that their rhythms do not follow a natural 24-hour cycle. In our studies we have demonstrated that more intact rhythms (i.e., rhythms that are closer to 24 hours) in temperature [9] and melatonin sulfate [10] are associated with higher arousal levels or a richer behavioral repertoire in patients with disorders of consciousness.

## Challenges and solutions in assessing circadian rhythms

In the last decades accelerometry, that is the measurement of physical activity, has frequently been used to investigate circadian rhythms or the sleep-wake cycle in patients with disorders of consciousness with the major advantage of being a cost-efficient and easy to use tool that is also suitable for long-term investigations. However, the use of accelerometry in this patient population may be limited as the patients often suffer from severe motor impairments and are reliant on care. Thus, movement data may not solely reflect the patients' activity but rather passive movements due to nursing activities or therapies. To address this issue we recorded physical activity via wrist accelerometry in 30 patients with disorders of consciousness over a period of 7 – 8 consecutive days [11]. To monitor passive movements of the patients, clinical staff and family members indicated the type of movement that was performed by using a tablet in the patient's room. We used this information to clean the patients' movement data post hoc. The cleaned data revealed that patients in a minimally conscious state exhibited stronger activity during both day and night, and also showed a more pronounced rhythm as compared to unconscious patients. Our analyses also indicate a risk of overestimating the integrity of the patients' circadian sleep-wake rhythms as well as the strength of these rhythms in the uncorrected data. Thus movement data needs to be corrected carefully when investigating circadian rhythms in patients with disorders of consciousness.

## Enhancing circadian rhythms in patients with disorders of consciousness

Based on these findings the question arises as to whether it is possible to re-entrain circadian rhythms in patients with disorders of consciousness and to improve their clinical condition in consequence. In a follow-up study [12] we investigated whether light therapy, which has proven effective in stabilizing circadian rhythms in healthy individuals, can also shift the patients' rhythms closer to a 24-hour cycle. To answer this question we recorded skin temperature over 7–8 consecutive days in 17 patients with disorders of consciousness in each of two conditions: (i) in a habitual light condition where patients were in a room with standard clinic lighting, and (ii) in a dynamic daylight condition where patients were in a room with 'biodynamic' lighting that is characterized by an overall higher illuminance, stronger circadian effectiveness, and dynamic variations in the spectral composition (as found in natural daylight). The results indicate that just one week of stimulation with biodynamic daylight (i. e., light resembling daylight in intensity and spectrum) could stabilize the rhythms of patients with disorders of consciousness and shift the

patients' rhythms closer to a healthy 24-hour rhythm. Additionally, on a behavioral level, patients in the biodynamic daylight condition showed a greater reactivity to external stimuli (i. e., higher scores during behavioral assessments using the Coma Recovery Scale-Revised [13]).

**Conclusion**

In summary, our findings indicate that circadian rhythms are closely linked to the clinical condition of patients with disorders of consciousness. Furthermore, adequate room lighting in intensive care units and long-term care facilities may represent a promising therapeutic approach to improve rhythm entrainment in patients with severe brain injuries.

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