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Connectivity biomarkers can differentiate patients with different levels of consciousness

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HIGHLIGHTS

- No voluntary brain activation is needed to examine the level of consciousness.
- Connectivity in the EEG distinguishes different levels of consciousness.
- Partialized coherence, directed transfer function, and generalized partial directed coherence distinguish MCS from VS patients.

ABSTRACT

Objective: In the present study, we searched for resting-EEG biomarkers that distinguish different levels of consciousness on a single subject level with an accuracy that is significantly above chance.
Methods: We assessed 44 biomarkers extracted from the resting EEG with respect to their discriminative value between groups of minimally conscious (MCS, $N = 22$) patients, vegetative state patients (VS, $N = 27$), and – for a proof of concept – healthy participants ($N = 23$). We applied classification with support vector machines.
Results: Partial coherence, directed transfer function, and generalized partial directed coherence yielded accuracies that were significantly above chance for the group distinction of MCS vs. VS (.88, .80, and .78, respectively), as well as healthy participants vs. MCS (.96, .87, and .93, respectively) and VS (.98, .84, and .96, respectively) patients.
Conclusions: The concept of connectivity is crucial for determining the level of consciousness, supporting the view that assessing brain networks in the resting state is the golden way to examine brain functions such as consciousness.
Significance: The present results directly show that it is possible to distinguish patients with different levels of consciousness on the basis of resting-state EEG.

1. Introduction

Distinguishing between patients in a minimally conscious state (MCS), vegetative state (VS, also known as unresponsive wakefulness syndrome), and conscious patients is still a matter of research. It is a current debate if it is better to examine consciousness by using active paradigms, like motor imagery or voluntary counting (Owen et al., 2006; Boly et al., 2007; Bekinschtein et al., 2009; Schnakers et al., 2008b; Monti et al., 2009; Schnakers et al., 2009a; Monti et al., 2010; Cruse et al., 2011; Fellinger et al., 2011; Goldfine et al., 2011; John et al., 2011; Lechinger et al., 2012; Liang et al., 2012), or if it is more appropriate to distinguish patients without tasks that require active cooperation. The rationale for the first type of consciousness-test is obvious. If a patient is able to follow commands he does not fulfill the criteria of being unresponsive to the environment, and, as such, falls out

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of the clinical definition of being unconscious. Even though this test is straightforward with respect to the diagnostic criteria, it only works for patients who are conscious but nevertheless appear to be unresponsive, like patients with a total locked-in syndrome. This test may rarely distinguish VS from MCS patients since MCS patients may lack of understanding the instructions or may not be able to follow the paradigm for a sufficient period of time due to attention deficits. In addition, locked-in patients may respond only if they are willing to do so. The psychological situation of a severely disabled patient is comparable to the situation of patients after spinal cord injury. There is a phase of depression, which eventually coincides with noncooperation (Trieschmann, 1988). Thus, a patient may be able to respond, but is depressed and refuses to cooperate. In such a case, no voluntary brain activation can be detected. Carrying this thought to excess, the only value of active paradigms would be that they are most likely to identify a patient with severe brain injury diagnosed as unconscious as conscious and with the cognitive ability to understand and participate in the task. While in most cases, an experienced neurophysiologist will easily distinguish the EEG of healthy participants from patients, it is difficult or impossible to distinguish a patient in MCS from a VS patient (see the Supplementary Section for an example).

Against this background, there is a need for reliably assessing consciousness without the need for cooperation of the patient. In the present study, we wanted to examine the discriminative value of a list of biomarkers. These biomarkers can be extracted from the resting EEG (that is, EEG recorded while the patient is not performing any task) and should be used to distinguish different levels of consciousness.

Finding correlates of consciousness is not only a debate of clinical research but expands to the field of cognitive neuroscience and, specifically, sleep research. The earliest approach of distinguishing different levels of consciousness by resting-EEG features was the assessment of power spectra or power ratios. Deep sleep, anesthesia, VS, but also other clinical conditions are characterized by EEG-slowing, that is, a predominance of slow frequencies in the EEG (Wehrli an Loosli-Hermes, 2003). Accordingly, the proportion of slow oscillations in the delta and theta range was found to be higher in patients with disorders of consciousness compared to conscious individuals, while alpha activity is diminished (Davey et al., 2000; Coleman et al., 2005; Babiloni et al., 2009; Leon-Carrion et al., 2008, 2009; Cimenser et al., 2011; Lehembre et al., 2012). However, reduced alpha power was also found for patients with locked in syndrome (Babiloni et al., 2010), possibly because EEG-slowing is a general correlate of brain damage, so that assessing frequency spectra is not feasible to detect consciousness.

The interdisciplinary nature of neurosciences, for example cooperations with mathematicians and computer scientists, opened the door to a new world of quantitative EEG analysis with many alternatives to computing power spectra. One such alternative is to assess information theoretical measures, that is, the information content of the EEG signals. EEG entropy was assessed in MCS and VS patients and was found to be distinctive in these patient groups when patients with a chronic course were excluded from the analysis (Gosseries et al., 2011). Newer approaches of EEG-analysis focus on connectivity. The earliest form of connectivity measures is the coherence, which was found to be reduced over damaged structures in a VS patient (Davey et al., 2000). During anaesthesia, alpha coherence shifts from occipital to frontal regions (Cimenser et al., 2011). Lehembre et al. (2012) compared coherences, the imaginary part of coherency, and the phase lag index between MCS and VS patients and found no difference between patient groups for coherences, but for the imaginary part of coherency and for the phase lag index. Schnakers et al. (2008a) found that patients with different levels of consciousness have significantly altered values at the EEG bispectral index. The bispectral index is based on the power spectrum, the bicoherence, and the burst supression ratio. However, despite yielding significant differences on group level, the bispectral index does not allow to distinguish patients on a single-subject level, that is, it can not be used for diagnostic purposes. Recent approaches can be seen in the concept of Granger causality, which can be described as the values of one signal predicting the future values of another signal (Granger, 1969). Pollonini et al. (2010) found significantly reduced connections revealed by granger causality in MCS patients compared to patients with severe neurocognitive disorders. A similar approach was used by Boly et al. (2011), who examined effective connectivity in MCS and VS patients with dynamic causal modeling and reported impaired top-down processes in VS compared to MCS patients. Accordingly, Varotto et al. (2014) found reduced information capacity in VS patients, detected as significant decrease in delta band connectivity and alpha hyperconnectivity. The authors used a new EEG biomarker, the partial directed coherence (PDC). In contrast to the entropy which was used by Gosseries et al. (2011), the PDC worked for patients in a chronic vegetative state. Most interestingly, Varotto et al. (2014) interpret the reduced delta band connectivity as disturbed cortico-subcortical connections, probably due to the widespread fiber degeneration in the chronic patient group. The alpha alternations are seen as autonomous cortical alpha oscillations disconnected from the modulating structures, i.e., oscillating cells or small networks of cells without function. Yet, it has to be shown if such alterations do not just differ between patient groups but allow to distinguish between them on a single subject level.

To summarize, the wave of computer sciences introduced a few biomarkers which are candidates to distinguish MCS from VS patients. Nevertheless, recent studies reported significant differences on group level while there is no biomarker which, being extracted from the resting EEG, allows to distinguish these groups on a single subject level. In the present study, we assessed the discriminant value of a number of EEG biomarkers by use of machine learning techniques. We wanted to identify those markers which discriminate VS from MCS patients and check the sanity of the resulting discrimination by classifying healthy participants against patients. We wanted to identify markers that reveal a classification accuracy that is significantly above chance. Such high-discriminative biomarkers could be used to answer the clinical question of whether a patient is conscious, minimally conscious, or unconscious. In addition, the difference between patient groups with respect to high-discriminative biomarkers should shed more light on the underlying pathophysiology of disorders of consciousness.

2. Materials and methods

2.1. Ethics

The study was approved by the local Ethics Committee (Ethics Commission Salzburg/Ethikkommission Land Salzburg; number 415-E/952) and was designed according to the Declaration of Helsinki. Written informed consent was obtained from all controls and from the families or guardianship of all patients.

2.2. Definition of groups

In order to perform classification a definition of consciousness has to be made. In research on disorders of consciousness, consciousness is equivalent to a certain index on some behavioral scale. A good choice for such a scale is the Coma Recovery Scale Revised (CRS-R, Giacino et al., 2004). It is used to discriminate between VS and MCS patients. The CRS-R has six sub-scales (auditory, visual, motor, oromotor/verbal, communication, and arousal),