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EEG entropy measures indicate decrease of cortical information processing in Disorders of Consciousness

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HIGHLIGHTS

- EEG entropy analysis was able to relate to different types of Disorders of Consciousness (DOC).
- Local information content in the EEG by means of permutation entropy was reduced according to the severity of the DOC.
- DOC patients showed altered directed information flow in the EEG by means of symbolic transfer entropy, indicating impaired feed-backward connectivity.

ABSTRACT

Objective: Clinical assessments that rely on behavioral responses to differentiate Disorders of Consciousness are at times inapt because of some patients' motor disabilities. To objectify patients' conditions of reduced consciousness the present study evaluated the use of electroencephalography to measure residual brain activity.
Methods: We analyzed entropy values of 18 scalp EEG channels of 15 severely brain-damaged patients with clinically diagnosed Minimally-Conscious-State (MCS) or Unresponsive-Wakefulness-Syndrome (UWS) and compared the results to a sample of 24 control subjects. Permutation entropy (PeEn) and symbolic transfer entropy (STEn), reflecting information processes in the EEG, were calculated for all subjects. Participants were tested on a modified active own-name paradigm to identify correlates of active instruction following.
Results: PeEn showed reduced local information content in the EEG in patients, that was most pronounced in UWS. STEn analysis revealed altered directed information flow in the EEG of patients, indicating impaired feed-backward connectivity. Responses to auditory stimulation yielded differences in entropy measures, indicating reduced information processing in MCS and UWS.
Conclusions: Local EEG information content and information flow are affected in Disorders of Consciousness. This suggests local cortical information capacity and feedback information transfer as neural correlates of consciousness.
Significance: The utilized EEG entropy analyses were able to relate to patient groups with different Disorders of Consciousness.

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1. Introduction

The concept of consciousness has been and still is a matter of debate and, so far, no unifying definition has been formulated. The term consciousness is often equaled with the term awareness, referring to a person's subjective phenomenological experience of the self and the environment (Posner, 2007). Although the terms are not identical they are often used interchangeably. Furthermore, a conscious experience is not regarded as an all or none-phenomenon but as a state on a continuous spectrum (Laureys, 2004). This implies that intermediate states of consciousness, such as minimally consciousness, do also exist. In clinical terms, a patient is considered minimally conscious if he or she shows some form of awareness of the self or the environment. In case a patient is not able to show any signs of awareness during repetitive clinical testing, he or she is considered unconscious and diagnosed with Unresponsive Wakefulness Syndrome (UWS, i.e. Vegetative State (VS)). On the neurophysiological level the correlates of these subjective experiences, however, are difficult to disentangle. It is assumed that a functional correlate of unconsciousness is, besides other neuronal correlates, a disintegration of neuronal networks, meaning a cessation of information exchange across distant cortical and subcortical areas as well as a reduction of information capacity (Dehaene et al., 2006; Alkire et al., 2008; Boveroux et al., 2010; King et al., 2013). In particular, the disintegration of long-range connections seems to result in an impaired ability to process information and, consequently, the lapse of consciousness (Boly et al., 2011; Jordan et al., 2013; Ku et al., 2011; Lee et al., 2013). Still, the leading processes to the emergence or the loss of consciousness are largely unknown and remain a major field of research in neuroscience.

Especially the discrimination between various Disorders of Consciousness (DOC) in severely brain-damaged patients remains a highly challenging task. Clinical diagnosis, at least partly, requires patients to behaviorally respond to the examiner, often to an extent that is beyond the patient's capabilities. Nonetheless, clinical unresponsiveness, which is the absence of behavioral response to external stimulation, does not necessarily imply unconsciousness (Alkire et al., 2008). Especially motor disabilities, such as Broca's aphasia or anarthria in the presence of quadriplegia and ocular palsy can hinder the clinical testing procedure. Therefore, clinical testing is at times insufficient and leads to a considerable rate of misdiagnosis (Andrews et al., 1996; Childs et al., 1993; Schnakers et al., 2009). More sophisticated diagnostics of DOC include functional imaging and electrophysiological methods, which circumvent the need for obvious behavioral responses by directly tracking correlates of neuronal activity within the patient's brain, which can be understood as surrogate parameters for information processing. However, hemodynamic functional imaging in particular is accompanied by large efforts in handling the severely disabled patients. Electrophysiological measures, in contrast, offer the opportunity of bedside testing and are therefore promising for routine clinical application.

Classical EEG parameters, such as spectral power, are useful to indicate the condition (e.g. wakefulness, NREM-sleep) and certain cognitive processes (e.g. evoked potentials) in a human's brain. New approaches to specify information processing capabilities in terms of EEG activity include non-linear analysis, such as DCM (Boly et al., 2011) or entropy measures (Jordan et al., 2008), which have already yielded relevant diagnostic information in DOC, such as a correlation of entropy values with the clinical assessment by means of the CRS-R (Gosseries et al., 2011) and a distinction of clinically diagnosed DOC patient groups (King et al., 2013). The main principle of entropy measures based on Shannon's information theory is the quantification of information in a given signal as the probability of the occurrence of specific patterns in a finite set of possible patterns, e.g. EEG time series (approximate entropy (Bruhn et al., 2000), Shannon entropy (Bruhn et al., 2001) or permutation entropy (Bandt and Pompe, 2002)) or its spectral composition (spectral entropy (Inouye et al., 1991)). As more different messages can be conveyed in a signal, the entropy of the signal increases, and so does the information content of a specific message. Entropies therefore allow for a quantification of the information conveyed in the EEG. Generally, more stochastic signals yield higher entropy values, e.g. the EEG of a wakeful brain, which is processing and integrating sensory input, shows a more irregular pattern than compared to the EEG signal during anesthesia or deep NREM sleep. This may be correlated with changes of neuronal information processes, regarding information capacity and information transfer (Inouye et al., 1991; Thomeer et al., 1994; Wheeler et al., 2005; Alkire et al., 2008; Jordan et al., 2013).

To differentiate DOC patients we chose two independent entropy measures that rely on symbolization of signal patterns and that were shown to generate robust findings on noisy real world data (Bandt and Pompe, 2002; Staniek and Lehnertz, 2008). As a univariate measure permutation entropy (PeEn) quantifies the probability of specific amplitude order patterns in a signal and is a surrogate measure of "information processing" in the generating system (Bandt and Pompe, 2002). Symbolic transfer entropy (STEn), on the other hand, is a robust multivariate measure that also relies on symbolization of order patterns to evaluate directed interaction between two systems. STEn serves as a surrogate to quantify "information flow" between driving and responding systems, e.g. parts of the brain (Staniek and Lehnertz, 2008).

Based on the results of general anesthesia, where changes of STEn were suggested as a loss of fronto-parietal information flow (cortical feedback) (Jordan et al., 2013), we hypothesized that entropy measures could be able to identify states of minimal consciousness and residual abilities of instruction following in patients with DOC. Specifically, the entropy parameters were used with regard to the expected gradual differences between Unresponsive Wakefulness Syndrome (UWS)/Vegetative State (VS), Minimally Conscious State (MCS) and controls. Specifically, in DOC patients we expected that PeEn values varied as a function of the level of consciousness with controls showing the highest and UWS/VS patients the lowest PeEn values. Furthermore, these differences should be pronounced in higher cognitive areas such as the frontal lobe, but less evident in earlier areas of auditory processing such as the temporal lobe. Furthermore, using other measures of directional information flow it has been shown that especially feedback connectivity seems to be impaired in DOC (Boly et al., 2011). We sought to retrace these findings by using STEn as a measure of directional connectivity. We expected to find a gradual decrease in feedback information flow from healthy participants over MCS to UWS/VS patients. Furthermore, we were interested in how task demands shape information processing. Here we expected an increase of frontal and temporal PeEn and fronto-temporal as well as fronto-posterior STEn towards specific stimuli.

To test our hypotheses we applied an auditory paradigm during EEG recording. The so called own name paradigm has been introduced into DOC research several years ago (Schnakers et al., 2008), after it has been shown to elicit differential cortical responses even in NREM sleep (Perrin et al., 1999). In our study, we decided to choose an active version of the own name paradigm, because the passive listening condition has been criticized to indicate mere automatic processing due to the strong saliency of the own first name (Schnakers et al., 2008; Perrin et al., 2005). A differential response to an active task demand, i.e. counting a target name, should, however, reflect purposeful conscious information processing.