# Automated EEG entropy measurements in coma, vegetative state/unresponsive wakefulness syndrome and minimally conscious state

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## Summary

**Monitoring the level of consciousness in brain injured patients with disorders of consciousness is crucial as it provides diagnostic and prognostic information. Behavioral assessment remains the gold standard for assessing consciousness but previous studies have shown a high rate of misdiagnosis. This study aimed to investigate the usefulness of electroencephalography (EEG) entropy measurements in differentiating unconscious (coma or vegetative) from minimally conscious patients.**

**Left fronto-temporal EEG recordings (10-minute resting state epochs) were prospectively obtained in 56 patients and 16 age-matched healthy volunteers. Patients were assessed in the acute (≤1 month post-injury; n=29) or chronic (>1 month post-injury; n=27) stage. The etiology was traumatic in 23 patients. Automated online EEG entropy calculations (providing an arbitrary value ranging from 0 to 91) were compared with behavioral assessments (Coma Recovery Scale-Revised) and outcome.**

**EEG entropy correlated with Coma Recovery Scale total scores (r=0.49). Mean EEG entropy values were higher in minimally conscious (73±19; mean and standard deviation) than in vegetative/unresponsive wakefulness syndrome patients (45±28). Receiver operating characteristic analysis revealed an entropy cut-off value of 52 differentiating acute unconscious from minimally conscious patients (sensitivity 89% and specificity 90%). In chronic patients, entropy measurements offered no reliable diagnostic information. EEG entropy measurements did not allow prediction of outcome.**

**User-independent time-frequency balanced spectral EEG entropy measurements seem to constitute an interesting diagnostic – albeit not prognostic – tool for assessing neural network complexity in disorders of consciousness in the acute setting. Future studies are needed before using this tool in routine clinical practice, and these should seek to improve automated EEG quantification paradigms in order to reduce the remaining false negative and false positive findings.**

*KEY WORDS: coma, EEG entropy, electroencephalography, minimally conscious state, unresponsive wakefulness syndrome, vegetative state*

## Introduction

Distinguishing, after a severe acquired brain injury, between unconscious comatose or vegetative state/unresponsive wakefulness syndrome (VS/UWS) patients and conscious or minimally conscious state (MCS) patients [1] remains extremely challenging. Coma is defined by the absence of both arousal (i.e., absence of eye opening) and awareness (i.e., absence of voluntary or non-reflex movements) [2]. VS/UWS is characterized by the return of arousal without recovery of awareness. The MCS is defined by the presence of inconsistent but reproducible goal-directed behaviors (e.g., response to command, visual pursuit, localization of noxious stimulations or contingent behavior in response to specific emotional stimuli) [3]. Patients with such disorders of consciousness (DOC) who remain unable to communicate represent a major diagnostic challenge [4]. Assessing the level and content of consciousness is indeed intrinsically difficult. Voluntary movements are easily misinterpreted as reflex activity and motor responses may be very limited or easily exhausted due to fluctuating vigilance [5]. Studies have shown that up to 40% of patients diagnosed as unconscious or vegetative may show signs of consciousness when assessed with standardized behavioral scales [6-9]. The Coma Recovery Scale-Revised (CRS-R) has been developed specifically to differentiate MCS from VS/UWS patients [10]. However, these evaluations require time and trained, experienced

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assessors. The aim of this study was to investigate the usefulness of automated electroencephalography (EEG) entropy measurements in the differential diagnosis of DOC.

The EEG is an objective tool that permits continuous and online monitoring of brain function. Since interpretation of the raw EEG signal requires considerable expertise and specialized training, simpler and more standardized measures of brain function are desired [11]. Originating from thermodynamics, EEG entropy is a measure of disorder that describes the irregularity, complexity, or unpredictability of a stochastic EEG signal [12]. A regular EEG signal, such as the one recorded in slow wave sleep or deep anesthesia, has very low entropy while the multitude of brain activities of an awake subject generates a more complex signal (i.e., with high entropy). Entropy is known to be independent of absolute scales such as the amplitude or the frequency of the signal [13] and can be calculated in several ways. Approximate entropy [14,15] or Shannon entropy [16,17] analyses the time domain, whereas spectral entropy [18,19] assesses the frequency domain. Here we used an automated time-frequency balanced spectral entropy device previously validated for monitoring the level of general anesthesia in patients undergoing surgery [20-22]. To date, however, no studies have assessed its sensitivity and specificity in the diagnosis and prognosis of DOC.

## Materials and methods

This multicentric study was prospectively performed in 56 patients with DOC who were comatose on admission (aged 54±19 years; 37 males) and in 16 age-matched healthy participants without a neurological or neurosurgical history (50±17 years; 9 males). Inclusion criteria for patients included: age over 18 years; no neurological or neurosurgical history other than the brain injury; absence of centrally-acting drugs or neuromuscular function blockers; diagnosis, according to the international criteria, of: coma [2], VS/UWS [1,23] or MCS [3] caused by acute acquired brain damage (traumatic or non-traumatic). Assessment of functional outcome was performed at one-year follow up. The study was approved by the ethics committees of the Faculties of Medicine of the Universities of Liège and Brussels. Written informed consent was obtained from all the control subjects and from the patients' legal surrogates.

Behavioral measurements of consciousness were obtained by trained, experienced neuropsychologists using the French adaptation of the Coma Recovery Scale-Revised (CRS-R) [10,24]. The CRS-R consists of six subscales: auditory, visual, motor and oromotor/verbal functions as well as communication and level of arousal. The 23 items are ordered according to their degree of complexity; the lowest item on each subscale represents reflexive activity while the highest item represents behaviors that are cognitively mediated. Scoring is based on the presence or absence of operationally-defined behavioral responses to specific sensory stimuli (e.g. if visual pursuit of a mirror is present at least twice in the same direction, the patient is considered to be in the MCS).

EEG recordings (10-minute epochs) during the resting state were obtained following the arousal facilitation protocol as defined in the CRS-R manual [10,24]. After skin preparation with isopropyl alcohol, specific entropy sensors (Datex-Ohmeda S/5, GE Healthcare, Datex-Ohmeda Division, Helsinki, Finland), composed of self-adhering flexible bands holding three electrodes, were placed on the forehead and temple. Impedances were kept $<5\ k\Omega$ and data were sampled at 400Hz. Online state entropy and response entropy were recorded on a portable computer using the Datex-Ohmeda Collect S/5 software. The monitor automatically recorded two kinds of entropy: state entropy (only cortical EEG) and response entropy (also including frontal electromyogram). The difference between state and response entropy is that the latter is more influenced by the contribution from the electromyography-dominated high-frequency band [25]. State entropy was calculated over the EEG dominant frequency range from 0.8 to 32Hz and response entropy was measured over the complete range of frequencies from 0.8 to 47Hz. Note that state entropy parameters can vary from 0 (suppression of EEG) to 91 (alertness), whereas response entropy ranges from 0 to 100.

The basis of the Datex-Ohmeda entropy algorithm is *time-frequency balanced spectral entropy* which is computed from a time-frequency decomposition of the signal. The signal is decomposed in its different frequencies and each frequency is computed not once but with a sliding window whose size depends on the frequency. The decomposition is dependent on the frequency of the signal: low frequency (needing more signal) will be assessed using a larger window as compared to high frequency. For each time interval (i.e., 1 second) a spectral entropy is automatically computed [21].

Statistical analyses were performed using STATA software (Stata Statistical Software; Release 11. College Station, TX: StataCorp LP 2009). Correlation analysis between behavioral scales (CRS-R total score) and EEG entropy was performed using Spearman testing. Non-parametric tests were used for univariate analysis (Wilcoxon rank sum/Mann-Whitney test and Kruskal-Wallis test) to test whether EEG entropy differed i) between diagnostic groups, ii) between acute and chronic patients, and iii) according to etiology (traumatic vs non-traumatic). Multivariate analyses were also performed using the logistic regression model. Receiver operating characteristic (ROC) analysis [26] was used to identify a cut-off value differentiating conscious (MCS) from unconscious (coma or VS/UWS) patients and to differentiate good (i.e., recovery of functional communication) from bad outcome. Results were considered significant at $p<0.05$.

## Results

Fifty-six patients and 16 age-matched healthy volunteers were enrolled in this study. Etiology was traumatic in 23 patients; the non-traumatic cases (n=33) comprised patients with post-anoxic-ischemic encephalopathy (n=16), ischemic or hemorrhagic stroke (n=10), subarachnoid hemorrhage (n=3), encephalitis (n=2) and metabolic encephalopathies (n=2). Patients were assessed in the acute (≤1 month post-injury; n=29) or chronic (>1 month post-injury; n=27) stages. The acute patients had the following clinical diagnoses: coma (n=6; mean CRS-R total score of 1±1); VS/UWS (n=14;

CRS-R total score of 4±1) and MCS (n=9; CRS-R total score of 11±3); the chronic patients were diagnosed with: VS/UWS (n=10; CRS-R total score of 5±1) and MCS (n=17; CRS-R total score of 11±4).

In the 56 patients with DOC, mean resting state EEG entropy measurements showed a positive linear correlation with CRS-R total scores (r=0.49; p<0.001) (Fig. 1). The patients' mean EEG entropy values differed between diagnostic groups (35±28 in coma; 45±28 in VS/UWS and 73±19 in MCS; $Chi^2$ = 31.97; p<0.001). The healthy controls showed mean entropy values of 89±1. The MCS patients showed higher EEG entropy values than the VS/UWS patients (Z=-2.95; p=0.003). EEG entropy values also differed between acute and chronic patients (43±24 versus 73±25 respectively; Z=-4.2; p<0.001). No differences were observed between traumatic and non-traumatic etiology (61±28 versus 54±28 respectively; Z=-0.84; p=0.4). Figure 2 shows the entropy values in acute (coma, VS/UWS, MCS) and chronic (VS/UWS, MCS) patients, and in healthy volunteers.

ROC analysis revealed an entropy cut-off value of 67 differentiating unconscious (coma, VS/UWS) from conscious patients (MCS), with a sensitivity and a specificity of 77% (area under the curve 0.8; 95% confidence interval 0.6-0.9). Likewise, in the acute patients, ROC analysis identified a cut-off value of 52 differentiating unconscious from conscious patients, giving a sensitivity of 89% and a specificity of 90% (area under the curve 0.9; 95% confidence interval 0.8-1.00). In the chronic patients, on the other hand, the sensitivity and specificity of the ROC analysis was too low to allow reliable conclusions to be drawn (area under the curve 0.5; 95% confidence interval 0.3-0.8).

At one-year follow up it was found that of the 56 studied patients, 24 had died, five were still classifiable as VS/UWS, 17 showed a severe disability, three showed a moderate disability, and four had returned to independent living (missing data: n=2). Initial EEG entropy values did not predict patients with good or poor outcome (57±29 versus 57±25 respectively; p=0.72). In the acute setting, ROC analysis differentiating poor from good outcome identified a cut-off entropy value of 57 with a specificity of 78% and a sensitivity of 60% (area under the curve 0.70; 95% confidence interval 0.4-0.9). The observed area under the ROC curve (0.70) is considered to reflect a moderate discrimination capacity and means that in patients with an entropy value above 57, the test will correctly recognize 60% of those who will recover and 78% of those who will not recover functional communication (i.e., emerge from MCS) one year later. For chronic patients, the prognostic value of the entropy measurements was shown to be of even lower than for acute patients.

Similar results were obtained for all reported analyses when using response entropy variables as opposed to the reported state entropy variables.

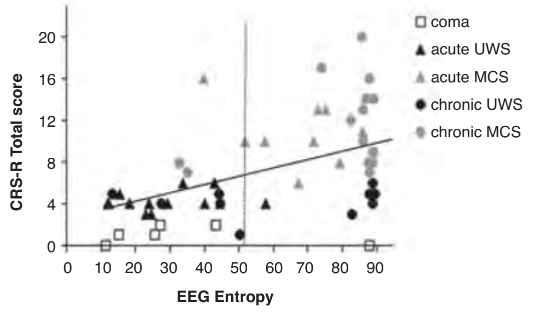

Figure 1 - Correlation between EEG entropy and Coma Recovery Scale–Revised (CRS-R) behavioral assessments in coma (white squares), acute unresponsive wakefulness syndrome (UWS; black triangles), chronic UWS (black circles), acute minimally conscious state (MCS; grey triangles) and chronic MCS (grey circles). The dashed line shows the EEG entropy cut-off value of 52, separating conscious from unconscious patients. Note that a positive linear correlation between EEG entropy and CRS-R total scores was observed: the higher the EEG entropy value, the higher the level of consciousness. Note also that false positives occurred mainly in chronic cases.

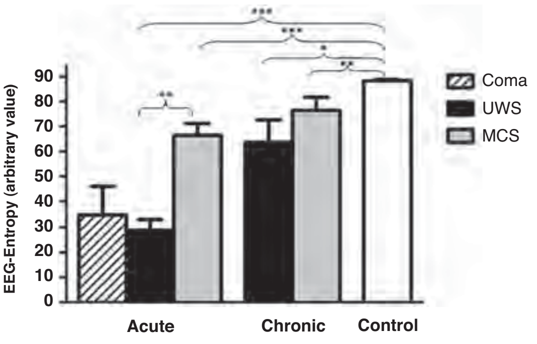

Figure 2 - EEG entropy values in acute and chronic disorders of consciousness, and healthy volunteers. (*=p<0.05; **=p<0.001; ***p<0.0001). Mean EEG entropy values are different between groups. In the acute group, MCS patients showed higher EEG entropy values than VS/UWS patients.

## Discussion

Electroencephalography can be used to assess thalamocortical function in severe brain damage and can help to establish the prognosis of patients still in the acute stage, especially those in anoxic comatose states [11,27-29]. The diagnostic use of EEG in DOC, on the other hand, is less documented [30]. Previous studies employing automated user-independent EEG quantification correlated the EEG bispectral index (BIS) with clinical assessment and outcome [31-33]. Similar to EEG entropy calculation, the EEG BIS is primarily used and validated as a means of monitoring the degree of sedation during anesthesia [34,35] and it ranges from 0 (death) to 100 (fully awake) [36]. A disadvantage of bispectral monitoring is that the calculation parameters used (i.e., frequency analysis or the ratio of the power in the high and low beta ranges; bispectral analysis or the ratio of the bicoherence in fast and slower frequencies; and time domain analysis or burst suppression ratio) remain hidden, which makes it a "black box", not appreciated by electrophysiologists and neurologists, and not acceptable for scientific measurements. In this study, we therefore focused on EEG entropy measurements as a means of assessing the level of consciousness in DOC. The automated time-frequency balanced spectral entropy measurements used in this study (combining both time and frequency domains) were shown to correlate with behavioral assessments of consciousness as measured by the CRS-R total score. This finding extends preliminary data showing a correlation between EEG approximate entropy offline calculations and the less sensitive Glasgow Coma Scale in coma survivors [37]. The online-calculated state entropy values of our VS/UWS and MCS patients were 49% and 18% lower respectively, than those of normal age-matched healthy controls, indicating that the complexity of various brain oscillations varies according to the level of consciousness (i.e., the unconscious brain-damaged patients showed a less complex EEG signal). These results corroborate our previous findings [32,38] in which the EEG BIS values of 13 VS/UWS and 30 MCS patients were 30% and 11% lower respectively than those of conscious brain-damaged controls. Similar results were also obtained in two recent studies using offline EEG entropy calculations in DOC patients. Sarà and Pistoia reported results for approximate entropy in 10 VS/UWS patients that were 33% lower than those recorded in 10 healthy controls [39]. Similarly, Wu and colleagues reported results for cross approximate entropy in 21 VS/UWS patients (studied <6 months) and in 16 MCS patients that were 27% and 8% lower respectively than those of 30 conscious but brain-damaged patients [40]. The latter study showed no difference at the group level between VS/UWS and MCS.

We here observed a reliable difference in entropy measurements between VS/UWS and MCS in the acute setting. A mean EEG entropy cut-off value of 52 in a 10-minute resting state epoch allowed us to distinguish between unconscious (coma, VS/UWS) and conscious (MCS) patients in the acute stage. The sensitivity and specificity of entropy recordings in distinguishing unconscious from minimally conscious patients were even better than the values previously reported using bispectral index measurements in VS/UWS and MCS patients studied within 11 weeks of the insult (sensitivity of 89% and specificity of 90% for EEG entropy versus sensitivity and specificity of 75% for BIS) [32]. Moreover, the bispectral monitor is a commercial tool that employs hidden mathematical algorithms not acceptable for scientific purposes. The EEG entropy measurement used in this study is therefore a surprisingly reliable (and easy-to-administer) tool that could assist clinical diagnosis in the early stage.

In chronic patients, VS/UWS patients showed no significant difference in entropy compared to MCS patients. This may reflect genuine time-dependent cortical reorganization and plasticity [41] or it could be related to (muscle) artifacts due to increasing spasticity over time. The importance of contamination by high-frequency muscle artifacts in the entropy calculation we employed is clearly illustrated in figure 3. Neuromuscular blocking (1mg/kg of intravenous rucuronium administered for clinical reasons independent of the present study 11 days after cardiac arrest) instantly reduced entropy measurements in one clinically comatose patient. This observation is in line with previous studies showing non-zero EEG entropy and BIS values due to muscle artifacts in patients with the clinical diagnosis of brain death [42,43].

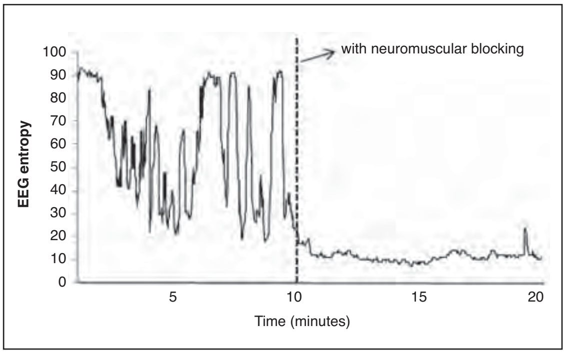

Figure 3 - Neuromuscular blocking reduces EEG entropy in a case of post-anoxic encephalopathy.

EEG entropy values were not found to differ according to etiology, suggesting that the technique can be used in both traumatic and in non-traumatic brain injured patients. In contrast to previous studies showing the prognostic value of the EEG BIS (at group level, [32]), we here failed to show any difference in initial entropy values between patients with good (i.e., recovery of functional communication) versus bad outcome at one-year follow up.

Finally, no difference was found between state entropy (designed to include only cortical EEG) and response entropy (also including frontal electromyogram) measurements. It should be stressed that the latter is developed merely to assess EEG reactivity to pain in general anesthesia settings [44] but seems less useful in the present context which assesses resting state EEG in DOC. Note that noxious stimulation did not significantly increase response entropy in a subgroup of 12 MCS, 12 VS/UWS and six comatose patients in the present cohort.

In conclusion, we here showed decreased complexity of neural networks, as measured by time-frequency balanced spectral entropy measurements in severely brain injured patients. User-independent EEG entropy measurements allowed us to distinguish unconscious (coma or VS/UWS) from minimally conscious patients in the acute stage with a sensitivity and a specificity superior to those previously reported for BIS measurements [38]. The automated entropy calculation paradigms employed should, however, be improved through future studies (e.g., multiresolution entropy [45] or Lempel-Ziv complexity [40]) in order to reduce artifacts such as those due to muscle spasticity. This could open the way for validating clinically user-independent EEG quantification in the specific context of disorders of consciousness. Other investigations should also be performed to verify the prognostic potential of the technique. Continuous online fronto-temporal EEG entropy monitoring, easily accessible at the bedside, may therefore constitute an additional method helping clinicians in the differential diagnosis of unsedated severely brain-injured patients recovering from coma. The current challenge is to document how these EEG and functional neuroimaging studies can improve our assessment and rehabilitation planning [46-48] in patients with disorders of consciousness.

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