# Electroencephalography in patients with disturbed level of consciousness

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**University of Szeged, 2021**

**Doctoral School of Clinical Medicine**

**List of scientific papers that cover the topic of the dissertation:**

I. **Bogdan Florea**, Simona Alexandra Beniczky, Helga Demény, Sándor Beniczky. Semiology of subtle motor phenomena in critically ill patients. Seizure. 2017 May;48:33-35. doi: 10.1016/j.seizure.2017.03.018. Epub 2017 Mar 30.

II. **Bogdan Florea**, Remus Orasan, Cristian Budurea, Ioan Patiu, Helga Demeny, Cosmina Ioana Bondor, László Vécsei, Sándor Beniczky. EEG spectral changes induced by hemodialysis. Clinical Neurophysiology Practice 6 (2021). doi: 10.1016/j.cnp.2021.03.006.

III. Daniel Kroeger, **Bogdan Florea**, Florin Amzica. Human brain activity patterns eyond the isoelectric line of extreme deep coma. PLoS One. 2013 Sep 18;8(9):e75257. doi: 10.1371/journal.pone.0075257. eCollection 2013.

## Abstract

**Objectives:** Our objectives were to investigate the semiology of subtle motor phenomena in critically ill patients, with or without nonconvulsive status epilepticus (NCSE), to investigate the electroencephalographic (EEG) spectral changes induced during hemodialysis in patients with chronic kidney disease, and to demonstrate the existence of a novel brain phenomenon during a coma deeper than the one reflected by the isoelectric EEG.

**Methods:** The first part of the study included 60 comatose patients with subtle motor phenomena. The semiology of these subtle phenomena was described. EEGs were classified using the Salzburg criteria for NCSE. In the second part of the study, we performed quantitative EEG spectral analysis in 56 consecutive patients. We compared EEG at the start and at the end of the hemodialysis, and we correlated the spectral changes with the biochemical and clinical characteristics of the patients. In the third part of the study, the new state was induced either by medication applied to a comatose patient or with of high doses of isoflurane in cats.

**Results:** Only 23% (14/60) of the patients had NCSE confirmed by EEG. None of the semiological features could distinguish between patients with NCSE and those without. In both groups, the following phenomena were most common: discrete myoclonic muscle twitching and discrete tonic muscle activation.

At the end of hemodialysis sessions, we found a significant increase in total EEG power, relative power in delta frequency band and the ratio of delta-theta / alpha-beta power. EEG spectral changes were associated with younger age, recent start of hemodialysis therapy, level of uremia and lower level of glycaemia.

In a state of coma beyond the isoelectric line, we identified EEG activity consisting of quasi-rhythmic sharp waves, which we called n-complexes. We demonstrated that n-complexes arise in the hippocampus and their genesis depends on hippocampal ripple activity.

**Conclusions:** In critically ill patients with subtle motor phenomena, the diagnosis of NCSE can only be confirmed by EEG, since none of the semiological features are specific. EEG spectral changes are potential biomarkers for monitoring central nervous system function during hemodialysis. The isoelectric line is not necessarily one of the ultimate signs of a dying brain.

## Introduction

Electroencephalography (EEG) is the most often used functional investigation method in neurology. Its main application is in the field of epilepsy and disturbance of consciousness, because of the cortical origin of the signals. In this PhD project, we focused on the following conditions related to disturbed level of consciousness: epilepsy/status epilepticus, uremic encephalopathy and coma.

Study 1. Subtle phenomena resembling discrete ictal manifestations, consisting of twitches of the eyelids, face, jaw, extremities or the trunk, head and/or eye deviation and peculiar automatisms have been described in patients with nonconvulsive status epilepticus (NCSE) [1,2]. These subtle motor phenomena occur when patients experience such a degree of encephalopathy that an electromechanical dissociation occurs, so that in spite of continuous ictal activity in the brain, only subtle motor phenomena are generated [3]. The diagnosis of this "subtle" status epilepticus [4,5] is challenging, since such phenomena can also occur in other pathological conditions [2]. It has been suggested that certain features of the subtle movements, like their duration or persistence can help distinguish between NCSE and other causes of these phenomena [6], but the semiology of these subtle motor phenomena has not been systematically studied yet. By using EEG as gold standard, in the first part of our study, we aimed to investigate and describe the semiological features of subtle motor phenomena that occur in critically ill patients, with and without NCSE.

Study 2. There have been controversial reports on EEG changes induced during hemodialysis in patients with chronic kidney disease (CKD), with early observational studies based on visual assessment of the recordings reporting an increase in slow EEG frequency components following hemodialysis [7,8]. However, later studies using quantitative spectral analysis methods did not confirm these observations [9-12]. EEG changes induced during hemodialysis may elucidate the pathogenic mechanisms and highlight the risk factors of a neurological complication occurring during or immediately after hemodialysis, coined dialysis disequilibrium syndrome [12-15]. Paradoxically, patients may show deterioration in their general condition toward the end of or immediately following hemodialysis, by developing symptoms such as headache, nausea and vomiting, disorientation, asterixis and involuntary jerking movements, or even psychosis, generalized tonic-clonic seizures and coma in rare cases. In the second part of our study, our goal

was to evaluate quantitative EEG changes induced during hemodialysis, using spectral analysis methods, and to identify risk factors associated with these changes.

Study 3. Coma is a state during which the brain reaches a low level of neuronal activity and metabolism. The common clinical correlate of coma is loss of consciousness and low or absent responsiveness [16]. While the initial stages (I–II) of coma are comparable to deep sleep [17], deep coma (stages III-IV) corresponds to more profound alterations of brain states, observable at the electroencephalographic (EEG) level [18,19]. Deepening of the coma beyond the BS stage leads to a flat EEG called isoelectric line, presumed to be associated with silenced activity in cortical neurons and considered as one of the limit points in establishing brain death, or even the only criterion in certain clinical conditions [20]. The activity of subcortical neurons (e.g., thalamic, hippocampal) has not been studied during the isoelectric line, but we might hypothesize both from the situation encountered during the suppression phase of the BS pattern [21] and from recordings in isolated preparations, that a rudiment of oscillatory activity might persist in subcortical neurons. In the third part of our study, we aimed to demonstrate that a novel brain phenomenon is observable in both humans and animals during a deeper coma than the one reflected by the isoelectric EEG, and that this state is characterized by brain activity generated within the hippocampus. We hypothesized that if cerebral neurons survive the deepening of coma, then network activity can revive during a deeper coma than the one accompanying the EEG isoelectric line by the change in the balance of hippocampal-neocortical interactions.

**Methods and materials**

Study 1. For the first part of our study, we prospectively recorded and described the type, location and occurrence-pattern/duration of subtle motor phenomena occurring in critically ill patients admitted to the Intensive Care Units (ICUs) of three medical centers in Cluj-Napoca, Romania. The study was approved by the Institutional Ethics Committee, and the relatives of the patients gave their informed consent. To confirm NCSE, EEG was recorded simultaneously with the subtle movements. Video footage and EEG was prospectively recorded for at least 30 minutes. Semiological features were extracted from the video recordings by three board-certified, experienced neurologists. EEG was evaluated by two board-certified clinical neurophysiologists blinded to the clinical data and scored using the Salzburg criteria for NCSE.

Study 2. In the second part of our study, we included consecutive patients with CKD, undergoing hemodialysis treatment three times per week at the Nefromed Dialysis Center in Cluj-Napoca. Patients gave their informed consent, and the study has been approved by the Ethics Committee of the Nefromed Dialysis Center. EEGs were recorded for the entire duration of the hemodialysis sessions (210–240 minutes), using scalp electrodes placed according to the international 10-20 system [22]. Artifact-free epochs of 12 s[23] recorded during awakeness were identified at the beginning and at the end of each hemodialysis session, and subsequently analyzed by two board-certified clinical neurophysiologists blinded to all clinical data. We calculated the Total Power for Delta, Theta, Alpha and Beta bands, the Relative Power for each band (ratio of the power in the frequency band and the Total Power), and the Power Ratio between the slow and the high frequency powers: (Delta+Theta)/(Alpha+Beta). For each patient, the initial and final values for the Alpha, Theta, Delta and Beta parameters were compared by calculating the difference of each data pair and comparing it to zero. End-Tidal Carbon Dioxide ($EtCO_2$), pulse, EKG, respiratory rate (RR), pulse oximetry readings, body mass, blood tests for bicarbonate ($ECO_2$), serum Na, K, Ca, serum creatinine, glucose and urea, blood pressure (BP) and pH were also recorded.

Study 3. In the third part of our study, we used EEG recordings from one comatose human patient and double simultaneous intracellular recordings in the cortex and hippocampus, combined with EEG, in cats. All experimental procedures were approved by the committee for animal care of the Laval. For the human recordings, the Committee for Ethics of the Unirea (Regina Maria) Medical Centre approved of the use of the recordings for publishing purposes; written consent was also obtained from the family.

Experiments were performed on 26 cats (2.5–4.5 kg) of both sexes. After a stable baseline EEG recording, isoflurane was increased to 4% to induce *ν*C patterns. We exposed the suprasylvian gyrus and lowered intracellular pipettes and field electrodes into the cortex and the hippocampus (aiming at the CA3 region). Neuroanatomical evidence for the placement of the recording electrodes was obtained for a few cells by staining neurons with intracellular injection of Lucifer yellow. Subsequently, brains sections of 75 μm were taken and cells were revealed.

Human EEG recordings were performed in monopolar configuration, with the reference placed on the earlobes and crosslinked. Due to the supine position of the patient, occipital electrodes were positioned more laterally, closer to the temporal ones. The analysis relied on time

relationships between the recorded voltage time series. To detect time relationships between events of similar origin recorded from different channels, crosscorrelograms were derived. The events in one channel were kept as time reference (time zero), and the time lags of the events in the other channel with respect to each event in the reference channel were plotted in a histogram.

**Results**

Study 1. In the first part of our study, 60 consecutive patients (24 female), aged 6 days to 80 years (mean: 40.7, median: 46.5 years) were analysed. The patients had a Glasgow Coma Scale between 3 and 9 (mean: 4.9; median: 5). Fourteen patients (23%) with subtle motor phenomena in the ICU had EEG-confirmed NCSE. There was no significant in demographic data, diagnosis and outcome between the two subgroups. Antiepileptic drug therapy was instituted significantly more often ($p = 0.02$) in patients with subtle convulsions and EEG-confirmed NCSE. In both subgroups, the most common phenomenon was discrete myoclonic muscle-twitching occurring almost continuously or in clusters, followed by discrete tonic muscle activation lasting 1–30 s. Subtle automatisms and eye-deviation were also identified in both subgroups. No semiological feature could distinguish between critically ill patients with NCSE and those without.

Study 2. In the second part of our study, we included 56 consecutive patients (20 female), aged between 32 and 86 years (mean: 59.82±12.76, median: 60.5 years). The patients had been receiving hemodialysis between 1 and 192 months (mean: 61.41±51.60, median: 42 months); the most frequent comorbidities were high blood pressure (50 patients; 50.0%), diabetes (18 patients; 32.1%) and hepatopathies (10 patients; 17.9%).

Hemodialysis resulted in a significant increase in Total EEG Power. Spectral analysis showed an increase in Relative Power of Delta band and an increase in the Power Ratio of the slow EEG components toward the end of hemodialysis (Table 1).

Multivariate analysis showed that EEG changes induced by hemodialysis were associated with younger age, recent start of hemodialysis, uremia and lower level of glycaemia.

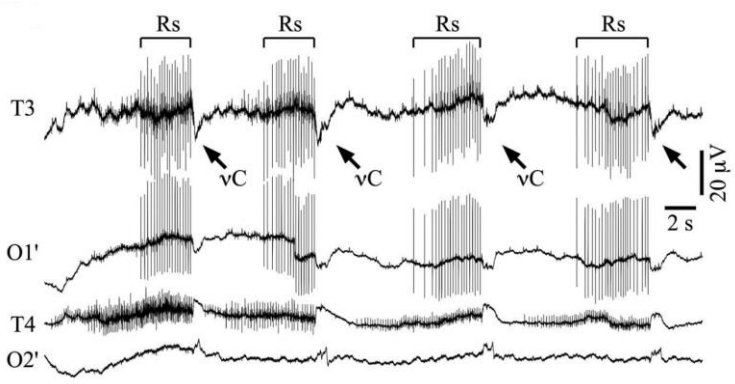
**Table 1. EEG changes during hemodialysis, demonstrated by spectral analysis**

| Parameter | Start of hemodialysis | End of hemodialysis | p |
|---|---|---|---|
| **Total Power, μV²** (mean [range]) | 14.54 (7.17, 20.7) | 19.41 (12.98, 39.29) | **<0.001*** |
| **RP Delta, %** (mean±SD) | 0.32±0.14 | 0.37±0.19 | **0.035**$^{+}$ |
| **RP Theta, %** (mean [range]) | 0.14 (0.09, 0.2) | 0.12 (0.09, 0.21) | 0.967* |
| **RP Alpha, %** (mean [range]) | 0.24 (0.14, 0.34) | 0.2 (0.13, 0.32) | 0.146$^{+}$ |
| **RP Beta, %** (mean [range]) | 0.24 (0.19, 0.38) | 0.23 (0.12, 0.32) | 0.071$^{+}$ |
| **Power Ratio** (mean [range]) | 0.94 (0.57, 1.6) | 1.08 (0.68, 2.04) | **0.033*** |

* Wilcoxon rank-sum test; + Student t test for paired samples. RP, Relative power; Power Ratio, (Delta+Theta)/(Alpha+Beta). Significant differences are marked in **bold**.

Study 3. EEG recordings of a comatose patient under antiepileptic medication revealed bursts of rhythmic spike-like discharges, similar to hippocampal ripple events (Rs), and another peculiar waveform consisting of ample and slower deflections occurring simultaneously with motor jerks (oblique arrows, Figure 1).

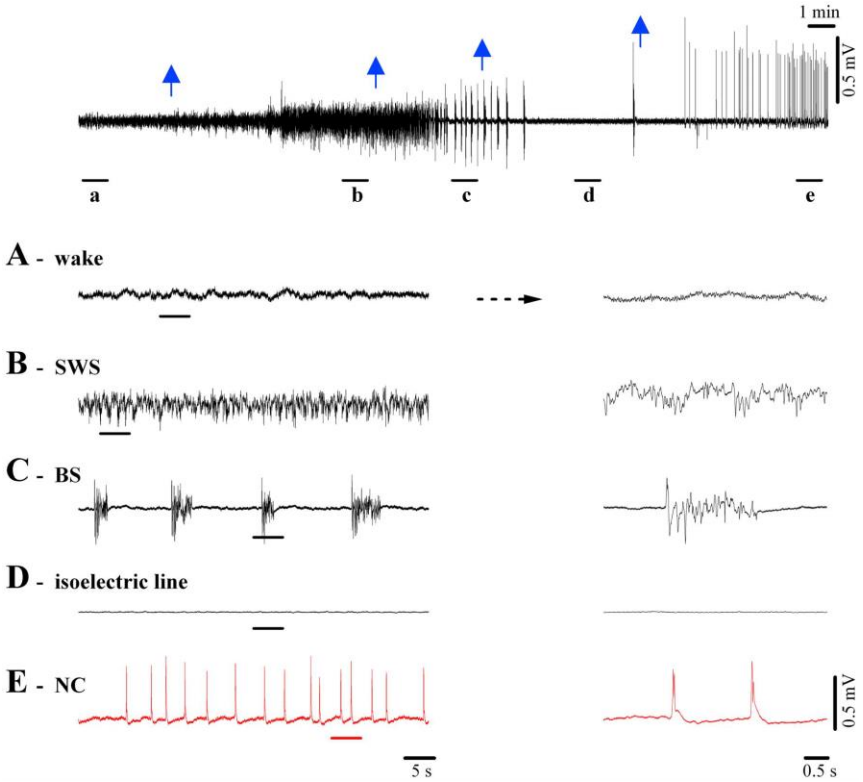
**Figure 1. Typical pattern of EEG recorded from temporal (T3 and T4) and modified occipital (O1'and O2') derivations.**




After discontinuing thiopental, a coma-deepening antiepileptic medication, the EEG passed through a period of isoelectric activity, and assumed a pattern of burst-suppression, usually present during deep coma [16]. Therefore, we hypothesized that under antiepileptic medication the patient was in a deeper state of coma, accompanied by novel EEG patterns not yet described. To elucidate the cellular mechanisms of this behavior, we recorded EEG features during progressive deepening of coma induced with isoflurane in cats (Figure 2). Slow-wave sleep (SWS)-like patterns were induced with an initial dose of isoflurane of 1% (1$^{st}$ blue arrow). The BS pattern shown in Figure 2C is associated with deep coma and can also develop during

anesthesia (in our case, isoflurane at 2%, at the 2nd arrow) [24,25]. The bursts of the anesthetic-induced BS pattern can be triggered by subliminal stimuli reaching the hyperexcitable cortex [26]. Figure 2D depicts the EEG isoelectric line following increased doses of isoflurane (3%, at the 3rd arrow) and a further deepening of the coma. Such EEG patterns are one of the hallmarks in establishing brain death [20]. By increasing the isoflurane dose beyond the induction of the isoelectric line (>3.5%) we obtained a re-vitalization of brain activity, characterized by sharp EEG waves occurring quasi-rhythmically at frequencies below 1 Hz (Figure 2E). We called this yet unknown EEG wave n-complex (Nu-complex, νC).

**Figure 2. Cat EEG recording during application of various concentrations of isoflurane**




Hippocampal νCs exhibited the greatest amplitude, and νCs from all other structures displayed a time-lag at least 10 ms after hippocampal νC events, suggesting that the hippocampus might be the key structure for generating νCs. Simultaneous cortical and hippocampal field potential recordings also revealed faster ripple oscillations from the state of BS throughout the transition to the EEG isoelectric line and νC state. Hippocampal ripple frequency slowed down continuously from the low beta range (15.8±0.9 Hz) during BS and ending within the delta range (2.2±0.7 Hz). In parallel, the amplitude of the ripples increased by an average factor of 10, suggesting a progressive synchronization within hippocampal networks. The first event after a

νC was dramatically smaller, whilst subsequent ripples displayed successively larger amplitudes. Through simultaneous intracellular recordings in the hippocampus and cortex, we determined that ripple events were exclusively recorded in hippocampal CA3, CA2, and CA1 pyramidal cells, and that intracellular νCs originating in hippocampal neurons and were relayed to cortical cells. No cortical cells displayed any activities related to ripples.

We found that during the νC state, hippocampal neurons displayed Ih type currents and bursting capabilities. When steadily depolarized, hippocampal CA3 neurons spontaneously generated rhythmic bursts, the frequency of which depended mainly on the cell's membrane potential. In addition to self-oscillating CA3–1 pyramidal cells, we recorded hippocampal neurons that displayed only minor EPSP responses during delta ripple activity, despite participating in νC events (n = 6 neurons). These neurons were situated in the dentate gyrus (DG) and were most likely granule cells, which exhibit a very high excitability threshold [27].

Synchronization is critical for the transmission of hippocampal activity towards the neocortex. We assessed synchronization by measuring the jitter of the onset of neuronal discharge with respect to the maximum of the positive field potential wave associated with delta ripples and νCs, respectively, in 39 hippocampal neurons. We obtained average jitters of 49.7 ms (±4.8) for delta ripples and 12.4 ms (±1.7) for νCs (signed-rank Wilcoxon test; $p<0.001$), indicating that hippocampal networks display greater synchronization during νCs than during delta ripples.

**Discussion**

Study 1. As demonstrated in the first part of our study, EEG remained the most robust method to diagnose NCSE. None of the semiological features could distinguish between the patients with NCSE and those without NCSE. Although it has been suggested that certain features of the subtle movements, like their duration (persistence) can help in distinguishing between NCSE and other causes of these phenomena [6], we could not confirm this in our series. Our results differ from those of a previous study which found that a combination of semiological findings (ocular movement abnormalities), remote risk factors for seizures and severely impaired mental state were seen significantly more often in the patients with NCSE [28]. A possible explanation for our diverging results might be that discrete motor phenomena, like the ones observed in subtle seizures, have also been reported as side-effects of medications typically used in the ICU, such as anesthetics (propofol, midazolam), antiemetics and corticosteroids [2]. In addition, subtle motor

phenomena, such as brainstem and spinal myoclonus, spinal reflexes, automatisms, etc. can be caused by the underlying brain insult in acutely ill patients [29].

While continuous EEG was not available in the ICUs [30,31], EEG was recorded during the subtle motor phenomena in all cases, and, when necessary, the recordings were repeated. Considering the wide variety of recorded somatotopical features, our sample-size was relatively small. Further larger-scale studies, using continuous EEG recordings are needed to fully elucidate these aspects. Nevertheless, since less than one fourth of the 60 patients with subtle convulsions had NCSE during these phenomena, it is unlikely that they were caused by epileptic activity. To the best of our knowledge, this study is the first to systematically address the semiological features of subtle motor phenomena in comatose patients, which can raise the suspicion of NCSE.

Study 2. Using EEG spectral analysis, we confirmed early observations based on visual evaluation that reported an increase in the slow EEG components at the end of hemodialysis 7,8. Previous studies using spectral analysis were not able to find such changes 9-12, possibly due to differences in methodological aspects (e.g., analyzing EEG epochs when the patients were performing mental arithmetic exercises, possibly influencing EEG background activity, or calculating the power ratio for 3–7/7–13 Hz, which does not include a significant portion of the delta band, 0.5–3 Hz).

While hemodialysis is a lifesaving treatment for patients with CKD, a paradoxical deterioration in neurological status has been observed in some patients. This deterioration consisting of headache, dizziness, nausea, vomiting, muscular cramps, tremor, convulsions, and altered states of consciousness was described as dialysis disequilibrium syndrome (DDS) [12-15]. These changes occurred especially in the first dialysis sessions and appeared when the correction of some biochemical parameters (especially urea) was too rapid. Hence, it was hypothesized that DDS was caused by cerebral edema and increased intracranial pressure, due to difference in osmolality between the rapidly dialyzed serum and the cerebrospinal fluid that was lagging behind [7,32].

We found that EEG spectral changes induced by hemodialysis were associated with younger age, recent start of hemodialysis and the level of uremia, which are similar to the risk factors for DSS [12,13]. In addition, we found that lower glycemia before hemodialysis was also associated with an increase in Delta relative power. Since hypoglycemia causes diffuse EEG slowing, lower glycaemia levels could predispose patients with CKD to spectral changes during hemodialysis.

When using modern dialysis methods, clinically manifest DDS is a rare phenomenon. Although our patients generally experienced mild symptoms, such as malaise and fatigue at the end of the dialysis sessions, these were not severe and specific enough to be considered as DDS. However, we found significant spectral changes (slowing) after hemodialysis, and these changes were associated with the same risk factors that previously were reported for DSS, suggesting that the spectral changes revealed the pathogenic mechanisms of CNS changes induced by dialysis.

Study 3. We described an active brain state that extends beyond deep coma associated with an EEG isoelectric line and potentially represents a new frontier in brain functioning. We have shown that νCs arise in the hippocampus and are subsequently transmitted to the cortex; we also proposed a scenario to explain how self-oscillations of a limited population of CA3 pyramidal cells can lead to an activity spreading all throughout the brain. The genesis of a νC depends upon another hippocampal activity, known as ripple activity, which is not overtly detectable at the cortical level. The νC state is possible due to the intense subcortical activity generated in the hippocampus under conditions where cortical spontaneous functioning is greatly reduced. Although in this study the νC state was achieved using isoflurane, the progression from wakefulness to BS and the isoelectric line is similar to other etiologies, as shown by the human data which triggered the subsequent experiments. The νC state represents the deepest form of coma obtained so far and demonstrates that the brain may remain operational beyond the EEG isoelectric line. However, in many clinical situations, the brain might cease to operate due to anoxic or toxic insults compromising neuronal integrity itself. While the isoflurane-induced νC state in our animal studies was fully reversible, other underlying etiologies may be less safe if combined with medication. The current findings should serve clinicians in their assessment of patients' depth of coma; if they encounter EEG activity patterns indicative of the νC state, it would be highly advisable to review the patient's medication-regime with regards to coma-deepening drugs. The discovery of this novel brain state and its underlying mechanisms could also revive discussions about the usefulness of depth recordings as an additional assessment criterion for brain death.

Wakefulness, as a state that hosts conscious processes and the domination of willful action is characterized by a predominance of neocortical activity. As these functions fade at the onset of unconsciousness, the orchestrating powers are relinquished to more basic structures such as the thalamus (in the case of sleep) or the limbic system (present data). When these structures are

released from neocortical influence, they begin to pursue activity patterns on their own and proceed to impose these patterns on other brain regions including the neocortex. Most of these activity patterns are already present throughout consciousness and unconsciousness. For example, hippocampal oscillations in the theta range in rodents are associated with sensory processing and the control of exploratory behaviors [33]. In our preparation, hippocampal theta oscillations were present during transient isoelectric episodes of BS. The oscillatory frequency then continuously decreased in parallel with the deepening of the coma. This was further paralleled by the slowing of intrinsically generated oscillations as a function of membrane polarization. Thus, the oscillatory frequency is not simply switched from one particular predetermined frequency band (e.g., theta) to another (e.g., delta) but rather displays a continuous evolution modulated by the depth of coma.

The presence of these oscillatory activities in the hippocampus raises some intriguing questions as to their possible involvement in mechanisms of plasticity related to learning and memory processes. The preparation itself and the easy reversibility from νC coma may prove particularly suitable for the testing of the role of hippocampal ripples either in their triggering of sharp waves as a mechanism of reinforcing memory circuits [34], or in downsizing the strength of neuronal connectivity for the purpose of synaptic homeostasis [35].

**Conclusions**

EEG is an essential tool for diagnosing and characterizing patients with disturbed level of consciousness.

By systematically addressing the semiological features of subtle motor phenomena in comatose patients, we showed that although these phenomena can raise the suspicion of NCSE, EEG is essential to confirm the diagnosis, since none of the semiological features are specific.

We also found that hemodialysis leads to slowing of the EEG background activity and to an increase in the relative power in delta frequency band. This is a potential biomarker for quantifying functional changes in the Central Nervous System during hemodialysis.

Finally, EEG was used to identify a novel rhythm in deep coma patients, originating in the hippocampus, thereby challenging the common wisdom that the isoelectric line is always associated with absent cerebral activity, and proving that the isoelectric line is not necessarily one of the ultimate signs of a dying brain.

**Acknowledgements**

I would like to thank Professor Sándor Beniczky for his constant support and high-standard supervision throughout my efforts. I would like to express my gratitude for his guidance to Professor László Vécsei, who so elegantly offers the joy of discovering the fascinating aspects of neurology to his disciples and colleagues. A special place in my academic journey belongs to Professor Florin Amzica from University of Montreal: the very long debates during the very short evenings taught me to raise questions even when everything seemed to be clear. I would like to thank the University of Szeged Doctoral School of Clinical Medicine for making this PhD project possible.

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