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Use of Telemetric EEG in Brain Injury

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1. Introduction

Telemetry technology allows remote measurement and recording of signals such as biopotentials. This technology offers the advantage of long-term EEG recordings without causing unnecessary distress, as happens in EEG systems where implanted leads connect to the recording device through a cable. The EEG recordings can be used to detect changes in the brain activity after a traumatic event. The use of telemetry for EEG acquisition is the most reliable option in experimental studies due to the reduction of animal stress. Besides its current disadvantages, such as a reduced number of channels when compared to tethered EEG, telemetry can allow us to distinguish oscillatory brain patterns that become pathological after a neurological injury. Normal brain oscillatory synchronization can be correlated with cognitive function and behavioral state. However, abnormal brain oscillations can be caused by pathologies characterized by dysfunction of the cholinergic system and trauma, leading to epilepsy. This phenomenon is the result of abnormal hypersynchronous firing in certain neuronal populations in the brain. Although not all kinds of brain injury can induce epilepsy, the spike/wave activity present during epileptic seizures is of special relevance, because severe brain injury can, in most cases, induce epilepsy.

The combination of EEG acquired through telemetry and video is widely used for assessment of epileptic focus, to distinguish epileptic seizures from psychogenic non-epileptic seizures, re-assessment for potential surgery to treat epilepsy and to study animal models. Nevertheless, the assessment of the long-term EEG changes that occur after brain injury is a challenge, because a large amount of data is accumulated. Reducing the sampling rate and/or the recording schedule is not an option since each subject may respond differently to the injury and treatment. Furthermore, seizure-like events do not occur in pre-determined periods, therefore arbitrary sampling would compromise acquisition and analysis. In order to acquire reliable results, one requires a good estimation of duration and frequency of seizures and/or the duration of sleep stages. Several studies have addressed the need for analytical tools capable of optimally performing spectral analyses and, in this chapter, we evaluate the advantages and disadvantages of some available tools. The reduction and removal of artifacts in the acquired data, spectral decomposition of the signal using fast Fourier and wavelet transforms, and batch-processing will also be discussed. We will provide a view of the role of telemetric EEG technology in neuroscience, focusing on the study of brain injury induced by chemical means. Approaches to assess long-term EEG changes, choices of acquisition parameters, and tools to analyze the EEG data will be introduced.

2. Uses of telemetry technology

The advance of remote recording of physiological data, such as biopotentials, by radio (Holter and Generelli, 1949) was a great advancement in the field of physiology. Telemetry has been used to assess physiological measures through the recording of biopotentials of subjects in remote locations for decades (Fischler & Frei, 1963; Hambrecht *et al*, 1963; Lee *et al*, 1964; Vreeland *et al*., 1963). The aerospace industry, NASA and the former USSR used telemetry to record electrocardiogram (ECG), electroencephalogram (EEG) and electromyogram (EMG) during different missions (Akulinichev & Baevskii, 1964; Blanc, Gravier, & Geier, 1967; Caldwell & Lewis, 1995; Frostjr *et al*, 1975; Helvey *et al*, 1964) with the objective to monitor pilots/astronauts, collecting information regarding changes in physiological parameters.

The technologies for recording of biopotentials remotely have been improving in parallel with different technologies. For example, the development of the transistor made possible the design of small and relatively power-efficient circuits, allowing small devices to be implanted (Jacobson and Mackay, 1957). Kamp (1984) described the use of a miniaturized 8-channel EEG amplifier combined with a standard radio transmitter/receiver system to record long-term EEG at the patient's residence. Van der Weide and Kamp (1984) created a system to record long-term home EEG in epileptic patients using radio telemetry transmitted over a regular telephone line. Wroe and co-workers (1987) combined telemetry and recording using a standard cassette system, allowing monitoring of epileptic patients in the clinic. Peng and colleagues (2001) used a regular telephone network to send data from a 20-channel EEG system to a monitoring center where the data could be stored and analyzed. Frequency resolution is very important when acquiring EEG signals and the use of frequency modulation (FM) technology allowed a higher sampling rate. Neihart & Harrison (2004) created an FM transmitter (433 MHz) powered by an inductive link (transcutaneous) to send biopotential data to a monopole antenna. A wireless multichannel recording system was designed by Mohseni and colleagues (2005) and featured integrated circuit AC amplification, DC input stabilization, time-division-multiplexing (each signal has a "timeslot") and wireless FM transmission (0.05-6 kHz). Rizk and co-workers (2007) designed and implemented a single-chip to function as a 96-channel, brain-machine interface. The interface uses bidirectional communication, sampling the signals at 31.25 kHz and digitally suiting it for transmission, fulfilling the requirements for an implantable system. However, the newest existing techniques to implement brain-computer interfaces still face problems such as gliosis surrounding the implant and biocompatibility. Visual and auditory replacements and hand and limb prosthetics could revolutionize medicine, but there is still a long way to go (Rothschild, 2010). Finally, optical technology can potentially be used to transmit local field potential data (LFP) more accurately. Wei & Ziaie (2009) accomplished it designing a system composed of a printed circuit board (2.2 x 2.2 cm) to accommodate 4 amplifiers, 16 light-emitting diodes (LED) and a CCD camera to record the signal coming from the LED at 30 frames per second allowing reconstruction of a simulated LFP.

2.1 The use of EEG telemetry to detect clinical seizures in patients

The choice of what telemetry system to use in the clinic must be made according to the physician's expectations and requirements for an EEG system. The physician will determine the level of sophistication required for their EEG system (Schomer, 2006). In any case, although controversial, the EEG can be a potential marker to help in the diagnosis and

classification of seizures if monitored continuously. Meierkord (1992) used video-EEG telemetry to identify frontal lobe epilepsy and differentiate it from pseudo-seizures in patients. Overall, the seizure duration was short (up to 60 sec) and inter-ictal epileptiform EEG activity was identified as well as ictal abnormalities. In a similar effort, Raymond and colleagues (1999) were able to distinguish epileptic seizures from "non-epileptic" seizures. They described that even though it is unusual, some patients may display both epileptic seizures and "non-epileptic" seizures. They combined video-EEG telemetry and MRI (not simultaneous) to help in diagnosis and, interestingly, in 12 of 14 patients, the first seizure was "non-epileptic", suggesting that long-term monitoring is necessary to avoid pitfalls in the diagnosis. Moreover, there are situations when patients do not show structural anomalies in the MRI (Scott *et al*., 1999) but the EEG reveals epileptiform patterns. In these specific cases, although the telemetric EEG does not show a clear cut identification of the epileptogenic site (due to the spatial resolution limitation), it is still a valuable tool. In an attempt to increase the spatial resolution of the EEG, Gross and co-workers (2000) used closely spaced electrodes to study frontal lobe epilepsy (32-64 channels) and found abnormalities that were apparent with 10-20 electrodes. Nevertheless, independent of the number of channels, it is very important to precisely evaluate the video-EEG recordings and, if necessary, review it. In a re-assessment of data collected during 17 months from 121 patients (video-EEG telemetry), Alsaadi and colleagues (2004) changed the diagnosis of 24% of the patients after re-analyzing the data.

2.2 The use of EEG telemetry to study behavior and detect seizures in animal models

Telemetry has been shown to be extremely useful in animal models, allowing approaches that could be considered non-ethical in humans. Several studies were conducted specifically to verify the efficacy of new technologies that allow miniaturization of the telemetry system. Both the study of normal physiological events such as thermoregulation, sleep and circadian cycle (Herold *et al*., 1998) and the mechanisms of different neuropathologies can be explored through the use of telemetric EEG in animal models. Dimpfel and colleagues (1988) performed the implantation of bipolar electrodes in cortical and sub-cortical structures of rats to allow long-term recording of EEG after different drug treatments, such as amitriptyline, imipramine, amitriptylinoxide, amphetamine, diazepam, haloperidol and LSD. Cotugno and co-workers (1996) described a method to surgically implant telemetry transmitters in rats and record the EEG. The transmitter is implanted in a dorsal subcutaneous pocket and two stainless steel electrodes placed in the skull are connected to the transmitter through a subcutaneous tunnel. The EEG is then collected by an antenna located in a receiver positioned under the animal.

Fitzgerald and colleagues (2003) adapted a method to record EEG in rats through telemetry and perform real-time fast Fourier transform. They used a Data Sciences International system (DSI; St. Paul, Minn.) to send raw EEG of rats injected with atropine, caffeine, ketamine or pentobarbarbital to an oscilloscope (DataSys 7200, Gould Instrument Systems, Valley View, Ohio) with storage, fast Fourier transform (FFT) and averaging features. Then, they calculated the relative power peaks for atropine (< or =5 Hz), caffeine (7.5 Hz) and ketamine (induced a shift from 5 to 10 Hz to < 5 Hz). Bastlund and co-workers (2004) used telemetry to record cortical EEG, EMG, and temperature for long-term monitoring (5-8 weeks) of epileptiform activity in rats injected with either pentylenetetrazole or kainic acid. Weiergräber and colleagues (2005) while studying transgenic mouse models of epilepsy and sleep disorders, used EEG recorded through telemetry playing a crucial role in the

neurological characterization of various transgenic mouse models and giving valuable information about epilepsies and sleep disorders in humans. They emphasized that without restraint from tethered EEG systems, the subjects can be observed without interference in their physiology.

Williams and co-workers (2006) used a three EEG channel system (DSI; St. Paul, Minn.) to record interictal spikes and epileptiform activity in the cortex and hippocampus of rats. They studied the model of kainic acid-induced seizures and long-term telemetric EEG recording to investigate epileptogenesis. According to them, although the chance to perform prolonged recordings is a great advantage, the cost, surgical complexity and frequency resolution of the system are listed as disadvantages. Obviously, collecting the data is just the first step, and throughout the use of the same system, White and colleagues (2006) tested different algorithms to process very large EEG data files acquired over 13 days. They concluded that the quality of the EEG and the type of analysis method employed can affect the positive predictive value (PPV, or true positives divided by the sum of true positives and false positives) and sensitivity (true positives divided by the sum of true positives and false negatives). In that sense, both implantation surgery accuracy and telemetry device integrity may be very important factors.

Lapray and colleagues (2008) presented a cost-effective and reusable telemetry system to record EEG in rats. The system allows a sampling rate of 500 Hz (bi-directional) and a range of up to 3 meters. The data transmission rate is roughly 115 kbps and the receiver connected to a computer through the USB port. The software developed by the group allows the recording of simultaneous video, opening the possibility to efficiently correlate behavior and EEG patterns. Finally, the study not only of EEG, but also action potentials during normal behavior, can be benefited by telemetry. It is known that the activity of place cells is highly correlated with the animal's spatial position (O'Keefe and Speakman, 1987; O'Keefe *et al*., 1998). A very innovative system was created by Chen and co-workers (2008) that used telemetry to record brain potentials in 3D mazes to investigate the role of hippocampal place cells in rats. The wireless technology used was Bluetooth which allowed a range of 5 meters and sampling at up to 10 kHZ, drastically increasing the frequency resolution and satisfying the conditions to have single unit recordings.

3. Distinguishing pathological from normal oscillatory brain patterns

The identification of physiologically relevant brain wave patterns is indispensable when doing EEG studies. In essence, oscillatory brain patterns can be classified as normal (non-pathological) or abnormal (pathological) brain oscillations. For example, normal brain oscillatory synchronization is highly correlated with mental process, perception, memory and behavioral states, such as sleep (Singer, 1999; Engel *et al*., 2001; Pareti and De Palma, 2004; Gross *et al*., 2004; Cantero and Atienza, 2005; Schnitzler and Gross, 2005). By comparison, abnormal brain oscillations are usually associated with dysfunctions, such as, cholinergic system imbalances and epilepsy (Traub, 2003; Timofeev and Steriade, 2004; Schnitzler and Gross, 2005). When spike/wave activity is present in the EEG, it is defined as an epileptiform pattern. It might not necessarily mean that the subject developed epilepsy, since this pathology is characterized by spontaneous recurrent seizures (SRS). The spike/wave activity occurs due to hypersynchronous firing in certain regions of the brain that are then called an "epileptic focus" (Engel, 1993). Depending on the affected area, the manifestations can be sensory, motor, or cognitive. The limbic regions are the most

frequently affected areas, including the hippocampus, amygdala, pyriform cortex, and cortex (Turski *et al*., 1983b; Carpentier *et al*., 1990; Petras, 1994; Scremin *et al*., 1998; Shih *et al*., 2003). The situation becomes critical if the seizure is sustained for a prolonged period without significant interruption or recovery. When such an event takes place, the subject is experiencing *status epilepticus* (SE) and can years later display SRS. Under these circumstances, appropriate treatment is anticonvulsant therapy and monitoring (*i.e*. continuous video-EEG) in order to try to interrupt the process of epileptogenesis.

3.1 Normal brain oscillatory synchronization

Various types of brain oscillations can be identified during the circadian cycle. A simplification of these types is exemplified in Fig. 1. Among normal function during the circadian cycle, sleep is of great importance and, obviously, sleep scoring or staging is fundamental as a tool in understanding normal and pathological situations. Gottesmann, (1992) described seven sleep-waking stages in the rat: 1 - attentive walking with dorsal hippocampus theta; 2 - quiet waking without theta pattern; 3 - sleep with cortical slow waves of increasing amplitude; 4 - deeper sleep with cortical spindles that progressively increase in number and amplitude; 5 - pre-paradoxal sleep events with high amplitude spindles that occur in parallel with thalamic sensory transmission to cortex; 6 - paradoxical sleep (eye movements are absent); 7 - paradoxical sleep with the characteristic rapid eye movements (REM). Since manual sleep scoring is laborious and time-consuming, several attempts have been made to automate this process. Gross and co-workers (2009) designed a MATLAB toolbox to perform semi-automated sleep scoring. The system is able to distinguish the states of waking, non-REM (NREM), transition-to-REM, and REM sleep if EEG and EMG are recorded simultaneously. Methods describing details for optimal EEG acquisition calibration, electrode application, signal filtering and power spectral analysis for sleep research were described by Campbell (2009).

The search for the substrates of normal brain oscillations and its correlation with cognitive function, neurochemistry and behavioral states has been studied for several decades. Graf & Kastin, (1984) pointed that peptides can play a role, for example, in sleep, EEG and circadian patterns. Neurons that secrete orexins (excitatory neuropeptide hormones) are likely to be very important in promoting wakefulness during the circadian cycle and in controlling the transition to REM sleep. Also, hormones, like estradiol, can decrease sleep and increase locomotion (Mong *et al*., 2003). Among the neuroanatomical areas that play a role on sleep, the locus coeruleus is very important, generating brain states such as alertness. Its activation changes the EEG activity from typical non-alert patterns to alert patterns. The locus coeruleus also has a role in attention processes by changing the sensory responses of neocortical neurons and participating in orienting responses occurring in the forebrain that are closely linked to event-related potentials (Foote *et al*., 1991). EEG studies indicated that the noradrenergic connections from the locus coeruleus excite the upper brain areas, while activation of serotonergic pathways inhibits the same areas. A population of cholinergic neurons can induce and maintain paradoxical sleep and also induce a rapid and transient elevation of alertness (Kayama and Koyama, 1998). In other words projections from the locus coeruleus work as the arousal system. The suprachiasmatic nucleus located in the hypothalamus can also modulate sleep (Dijk and Duffy, 1999). The hypothalamic ventrolateral preoptic area and pons/basal forebrain can play a role on both arousing and sleep-inducing neuronal networks. The mentioned structures could play a role as an ON/OFF switch or transition from sleep to awake state and vice-versa. During sleep, one

subpopulation of pontine neurons discharges during REM stage exclusively and another subpopulation stops its firing activity during REM (Sinton and McCarley, 2004). Finally, the so-called sleep spindles occur due to cyclical interactions between thalamo-cortical and thalamo-reticular neurons (McCormick and Bal, 1997).

Several authors investigated the relationship between normal oscillations with cognitive function and behavioral states. The importance of "naps" is very well recognized in certain cultures and, indeed, brief periods of sleep (5-15 min) can improve cognitive performance. However, side naps that last longer than 30 min can result in a short period of impairment but produce better cognitive performance over longer periods. Early afternoon naps are most effective and can result in performance improvement revealing that the circadian time within which the nap occurs is very important (Lovato and Lack, 2010). Buzsáki, (1991) elaborated a model of memory trace formation based on neocortical–hippocampal interactions, proposing that during exploratory behavior, information is transmitted from neocortex to hippocampus through fast-firing granule cells projections to a specific population of CA3 pyramidal neurons. In fact, during the acquisition of memories (spatial and episodic), the hippocampus is initially engaged, but later the memory traces are migrated to the neocortex (Ribeiro *et al*., 2007). Indeed, the immediate early genes expression is upregulated during REM sleep in cortical areas but not in the hippocampus (Ribeiro *et al*., 2007). O'Neill and co-workers (2010) investigated the role of the hippocampus in episodic and spatial memories. The hippocampus is able to not only encode this type of memory, but also to consolidate it throughout interactions with the cortex during "reactivation" of the original network firing patterns during sleep and rest. These interactions could be coordinated by sharp wave/ripple events occurring in the hippocampus. There is a close relationship between sleep mechanisms and memory processes. During REM sleep, there is an increase on the transcription of genes linked to plasticity phenomena, allowing the occurrence of both long-term potentiation (LTP) and depotentiation in areas such as the hippocampus. Sleep spindles would be related to plasticity in the cortex, due to specific reactivation of hippocampal and cortical neuronal circuits. Interestingly, when there is a predominance of delta waves, a neuronal reactivation (in phase with delta activity) concomitant with high protein synthesis levels may have a crucial role to play in a long-lasting LTP (Poe *et al*, 2010).

Other authors have been investigating the sleep/awake EEG patterns during several types of situations. Miller (1995) studied EEG data acquired from truck drivers during sleep and wake period (driving) with the purpose of creating a database available internationally. Pavy Le-Traon & Roussel (1993) reviewed several studies about sleep during manned space flights and found that the most important disturbances occur because of changes in phase due to tasks that are required during the flight. The authors consider that environmental factors, such as microgravity, light-dark cycles and psychological elements, play a role and must be studied. Using an interesting approach to investigate the link between genetics and neurophysiology, Linkowski (1999) studied sleep in twins. Recording EEG during three consecutive nights using a small sample of both monozygotic and dizygotic young male twins, they found out that the twins had a variance in sleep stages that could be genetically determined. However, REM sleep variances apparently did not have a relationship with genetics. Teenagers have peculiar sleep schedules that are likely linked to brain "maturation". According to Feinberg & Campbell, (2010) the power on the delta (1-4 Hz) band declines between ages 11 and 12 years and falls by 65% by age 17 years. Theta power during NREM is reduced earlier. The group hypothesizes that during adolescence, the

reorganization in the human brain, particularly frontal cortex, may contribute to these EEG changes. As this period is crucial, errors in brain plasticity may induce mental illness, such as schizophrenia.

Several investigators have focused on the study of sleep patterns in different species. Immediately prior to hibernation, REM sleep is not present if temperature is below 25ºC and during deep hibernation animals are preferentially in NREM sleep. The hibernation is not homogenous through time and the power of the signal in the delta band is higher after arousal from hibernation and then reduced over time (Canguilhem & Boissin, 1996). Birds are frequently used to investigate auditory processing through the analysis of multiunit electrophysiological responses (Terleph *et al*., 2006), but little is known about the occurrence of sleep in flying birds. Circumstantial evidence of sleep during flight indicates that similar to mammals, birds can exhibit slow-wave and REM sleep. Interestingly, slow wave sleep can occur in one or both hemispheres at a single time and REM sleep occurs only simultaneously in both hemispheres of the brain. Since the eye connected to the "awake" hemisphere remains open, it allows the bird to have navigation information during most of time during a flight (Rattenborg, 2006). In sum, the study of EEG sleep pattern in different species could one day allow a better understanding of sleep disturbances.

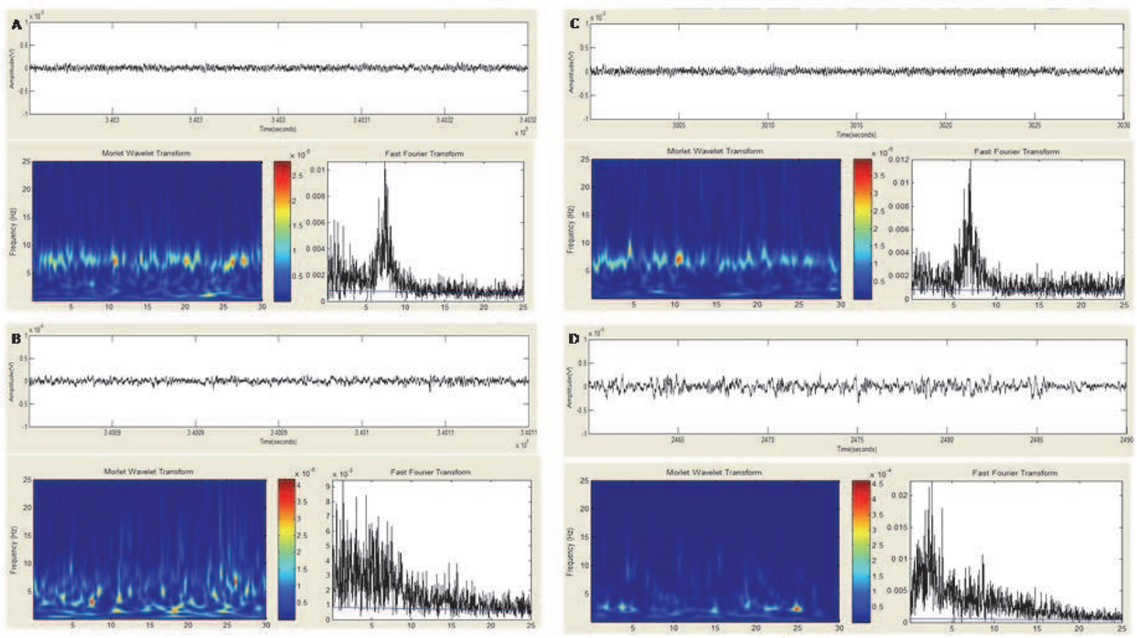

Fig. 1. Cortical electrocorticograms showing baseline electrical activity in Sprague-Dawley rats. The raw EEG (top), Morlet wavelet transform (bottom left), and FFT (bottom right) are being represented during the states of awake alert (exploratory behavior - A), awake non-alert (B - resting), REM sleep (C) and non-REM sleep (D). Note the sustained frequency on the theta band (4.1-8.0 Hz) during awake alert (scanning) and REM sleep. The dominant frequencies are shifted to the left during awake non-alert and much more during non-REM sleep.

3.2 Abnormal brain oscillatory synchronization

The abnormal changes found in EEG oscillations are highly linked to sleep disturbances, cognitive performance and syndromes like epilepsy. It is very important to keep regular

sleep periods and a reduction of as little as 1.3 hrs may result in reductions in alertness (Bonnet and Arand, 1995). According to Newmark & Clayton, (1995), headaches and sleep problems are probably overlooked during medical evaluations during active duty. Sleep disturbances can be associated with depression (Vanbemmel, 1997) and interestingly, sleep deprivation can function as an antidepressant treatment in 40-60% of patients that suffer from depression (Hemmeter *et al*., 2010). Although the mechanisms are still unclear, this phenomenon may help on the development of new antidepressants.

Among all situations that cause alterations of brain oscillatory patterns, brain damage is the most critical, leading to seizures and sleep disturbances. Shouse, da Silva, & Sammaritano (1996) pinpointed that seizures and inter-ictal events have circadian distribution, indicating that some arousal and sleep states are seizure-prone, while others are seizure resistant, both modulating seizure occurrence. Kotagal & Yardi (2008) pointed out that seizures during the sleep state are reported in approximately one third of epileptic patients. Both normal sleep pattern and sleep deprivation modulate the frequency of epileptiform discharges observed in the EEG and behavioral seizures do occur more frequently during NREM sleep.

Brain damage can be caused mechanically, chemically or even influenced by genetic factors. Blast is currently the major cause of battlefield injuries and death. Blast overpressure waves affect organs such the brain, auditory system, the gastrointestinal tract, and predominantly the lungs (Wightman and Gladish, 2001; DePalma *et al*, 2005; Garner and Brett, 2007; and Long *et al*, 2009). Unfortunately, there are no currently approved neuroprotective agents for use in ischemic stroke or traumatic brain injury. Recently, Vespa and co-workers (2010) showed that TBI can lead to electrographic SE, a state in which prolonged and uninterrupted seizures occur without recovery, for a period of 30 min or more. The identification of SE is essential in avoiding the development of epilepsy. Seizures are clinical manifestations of hypersynchronous and hyperexcitatory neuronal activity in a given neuronal network and can lead to brain damage and further "rewiring" that causes a chronic epileptic state, characterized by SRS (Shorvon, 2000). It is known that patients that suffer TBI may, at some point, develop SRS and latency to SRS is dependent on the degree of damage (Salazar *et al*., 1995; Chen *et al*., 2009; Lowenstein, 2009). It is very important to distinguish EEG traces characteristic of each state from seizures and seizure-like events. The clear identification of electrographic SE is essential to interfere and attempt to avoid the development of epilepsy.

Exposure to certain compounds can also induce SE and lead to brain damage. Exposure to organophosphorus agents (OP) can cause signs of seizures such as myoclonic movements, respiratory distress, and death (Engel, 1993; McDonough & Shih, 1997). OP compounds inhibit the enzyme acetylcholinesterase that normally degrades the neurotransmitter acetylcholine. When acetylcholinesterase is inhibited, the result is a cholinergic hyperactivation in brain areas such as piriform cortex and the medial septal area leading to increased glutamatergic drive in the piriform, entorhinal, and perirhinal cortices and the hippocampus, causing the expression of motor seizures and SE (Myhrer, 2007). This excessive glutamatergic drive can cause neuroexcitotoxicity (Wasterlain and Shirasaka, 1994). The overactivation of N-methyl-D-aspartate (NMDA; a type of glutamatergic receptor) immediately induces an influx of Ca^{2+}, leading to a series of molecular events that ultimately cause cell death (Delorenzo *et al*., 2005). As one of the results of brain damage caused by SE, certain brain areas display neuroplastic changes (like axonal sprouting) in neuronal circuitry. The axonal sprouting in the hippocampus is hypothesized in the literature as one of the causes of epilepsy (Mello *et al*., 1993; Okazaki *et al*., 1995).

Although prolonged seizures lasting 30 min or more are characterized as SE (Sloviter, 1999), recently, Chen and Wasterlain (2006) proposed the term ''impending status epilepticus'' for seizures that last at least 5 min, pointing out such seizures should be treated immediately.

The use of animal models of SE is an excellent tool to study SE and its consequences. Approaches such as telemetry have greatly reduced the number of animals used and greatly refined such studies. Models such as seizures induced by systemic and intra-hippocampal pilocarpine (Turski *et al*., 1983a; Cavalheiro *et al*., 1991; Furtado *et al*., 2002; Furtado *et al*., 2011; Castro *et al*., 2011), soman (McDonough *et al*., 1986; Carpentier *et al*., 1990; Petras, 1994; Shih and McDonough, 1997; Myhrer, 2007; de Araujo Furtado *et al*., 2010; Figueiredo *et al*., 2011), kainic acid (Ben-Ari *et al*., 1979; Williams *et al*., 2007) and electrical stimulation of the amygdala (Nissinen *et al*., 2000) have brought answers to fundamental questions about the mechanisms of seizures and treatment options. SRS was found in animals experiencing SE induced by pilocarpine (Leite *et al*., 1990; Mello *et al*., 1993) and kainic acid (Pisa *et al*., 1980; Cronin and Dudek, 1988; Hellier and Dudek, 1999) after a latent period. Also, self-sustaining SE and SRS can be provoked by uninterrupted electrical hippocampal stimulation (Lothman *et al*., 1989; 1990), perforant path stimulation (Mazarati *et al*., 1998; Mazarati *et al*., 2002) and electrical stimulation of the amygdala (Nissinen *et al*., 2000). Brain damage caused by OP (such as soman) can also lead to SRS. There are reports in the literature implying the occurrence of recurrent seizures in rats (McDonough *et al*., 1986b) and a full characterization of soman-induced SRS is described by de Araujo Furtado *et al*., (2010) using long-term EEG recording through telemetry.

Regardless of the fact that the discussion continues as to which brain changes lead to SRS, the occurrence of an initial insult may likely induce SRS (Sloviter, 1999). However, recent reports have shown that subjects that are challenged to a convulsive stimulus, but do not display SE, still have a probability of developing SRS much later (Navarro Mora *et al*., 2009; Pernot *et al*., 2009) suggesting that long-term video-EEG monitoring may be necessary in most studies in order to truly study epileptogenesis.

It is important to recognize that different patterns of seizures can be present after the brain receives a mechanical, electrical or chemical challenge. Although it is very complex, several seizure patterns have been found during the SE (Treiman *et al*., 1990). Fig. 2 shows characteristic EEG during SE and a summary of recurrent seizure patterns and SRS are presented in the next section.

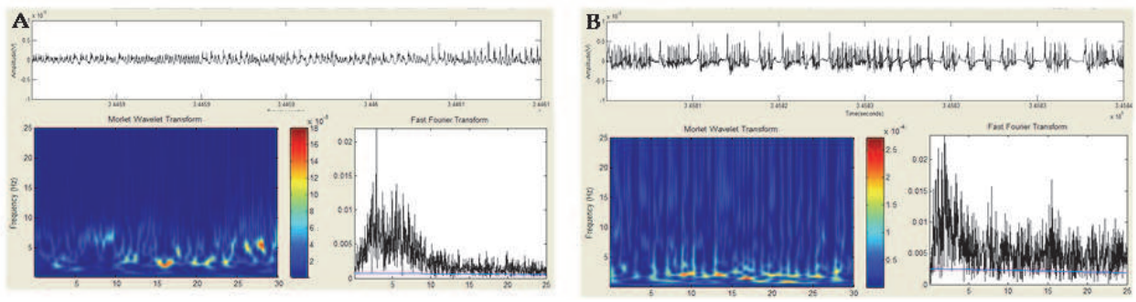

Fig. 2. Representative cortical electrocorticograms showing electrical activity during different periods after soman exposure. (A) 13 min after exposure. (B) 33 min after exposure. SE can last for several hrs and, even after treatment, recurrent seizures may occur (see next section).

3.2.1 Recurrent seizures

After the termination of SE, there is normally a period without seizures that can last from minutes to hours. Subsequently, subjects may display recurrent seizures that can induce additional brain damage. These seizures come however in different patterns, the type 1 pattern (Fig. 3A) is characterized by low frequencies between 0.8 and 1.4 Hz (delta band), with high amplitude spikes. The type 2 pattern also oscillated in the delta band, but faster than type 1, between 1.4 and 3.7. This pattern is characterized by high and low amplitude spikes (Fig. 3B). The type 3 pattern has frequencies oscillating in the theta band, between 4.8 and 5.4 Hz, with low spikes (Fig. 3C). The type 4 pattern is characterized by no spikes, but oscillates also in theta band, faster than type 3, between 5.5 and 6.5 (Fig. 3D). Long-term video-EEG monitoring may be necessary in most studies in order to detect epileptogenesis.

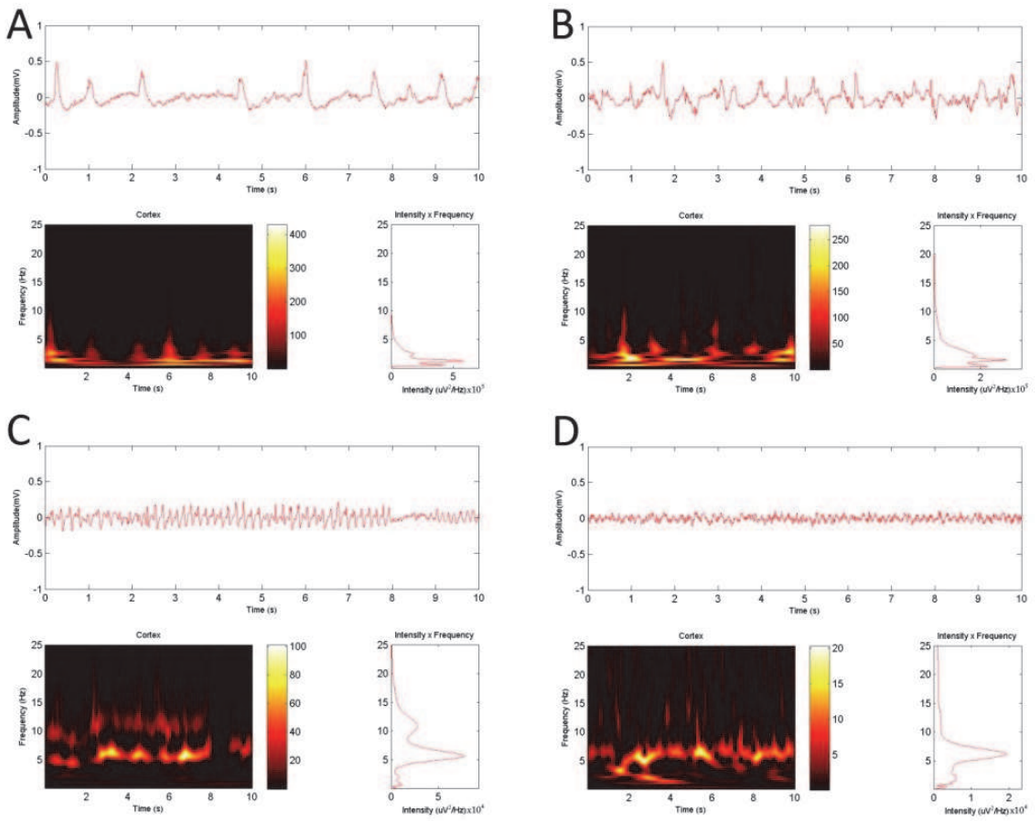

Fig. 3. Electrographic seizures patterns (10 sec) calculated and illustrated in wavelet transform analyses. A – Type 1 Pattern; B – Type 2 Pattern; C – Type 3 Pattern; D – Type 4 Pattern. The first fig (at the top) of each pattern shows the EEG (Amplitude x Time); the second fig (down left) of each pattern shows the frequencies in exact time (Frequency x Time); the third fig (down right) of each pattern shows the power of frequency (Intensity x Frequency).

3.2.2 Spontaneous recurrent seizures

Electrographic SRS are characterized by frequencies oscillating in the theta band (4.1 to 8 Hz) and are sustained during most of the duration of the seizure. From 25 sec up to 45 sec,

there also appeared to be sustained oscillation in the alpha band (8.1 to 12 Hz) but with reduced power spectrum. Dominant frequencies of the delta band (0.1 to 4 Hz) also appeared mainly at the beginning of seizures, but were not sustained in the time (Fig. 4).

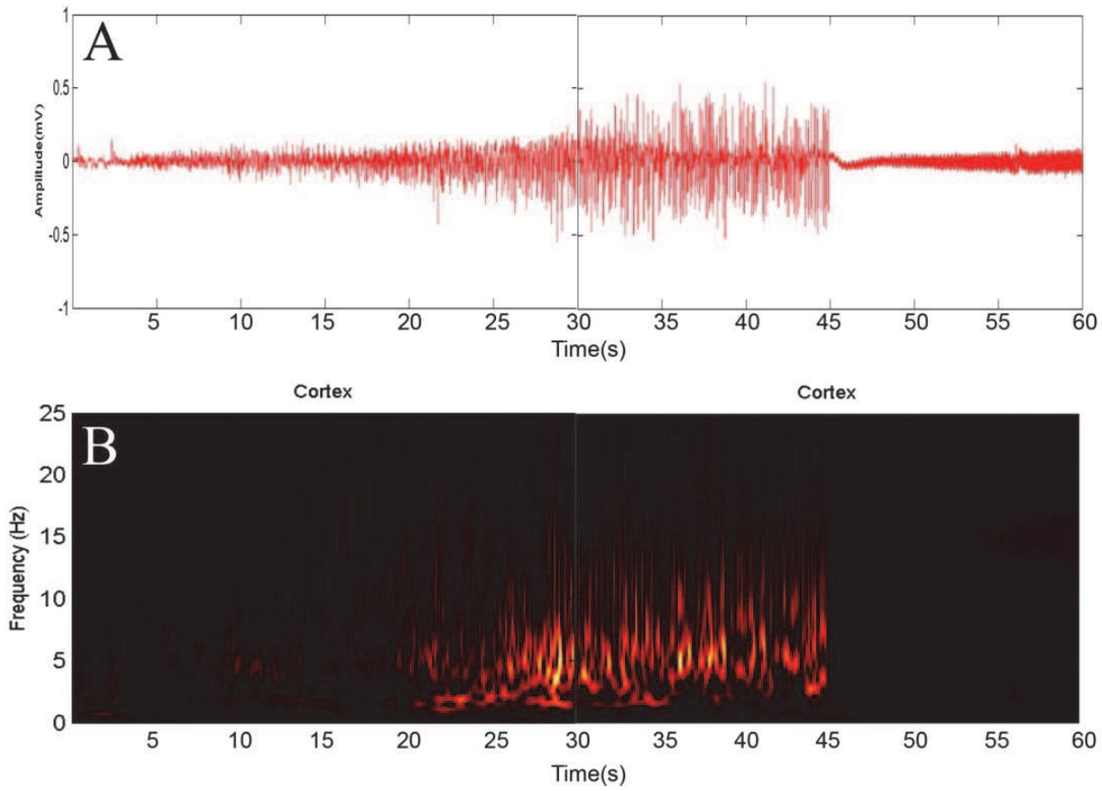

Fig. 4. Output of a representative SRS (60 sec.) wavelet transform spectral analysis. A – EEG (amplitude x time) of SRS; B – Frequency x time analyses of SRS; C- Intensity of frequencies analysis.

4. Assessment of the long-term EEG changes

The use of telemetry to capture continuous recordings has the advantage of allowing the detection of SRS and long term changes in circadian brain oscillations. However, telemetry results in a large accumulation of data. A large volume of data can result in analysis delay, frustration and poor EEG interpretation. Unique tools capable of performing efficient spectral analyses (Rossetti *et al*., 2006; Romcy-Pereira *et al*., 2008; Lehmkuhle *et al*., 2009), seizure estimation, and spike detection (Saab and Gotman, 2005; White *et al*., 2006; Casson *et al*., 2007; Jacquin *et al*., 2007; Hopfengärtner *et al*., 2007) has been used in several studies on epilepsy. Artificial neural networks have proven to be the most reliable tool (Gabor *et al*., 1996; Gabor, 1998; Nigam and Graupe, 2004; Kiymik *et al*., 2004; Tzallas *et al*., 2007; Srinivasan *et al*., 2007; Patnaik and Manyam, 2008) but require tremendous computational power in order to be time effective when analyzing large data sets. Another alternative is the use of commercial software designed for seizure detection. However, most often, this type of software is "tuned" to specific parameters for human subjects, such as sleep stages and spike and wave activity. In some cases, these parameters must be changed between

subjects, bringing bias to the analysis. Therefore, in several situations, the use of third-party software tools for the evaluation of large data sets (for example, EEG acquired during long-term pharmacological studies) may be contaminated by bias if the software was originally designed to address a dissimilar problem. However, several groups have invested time in creating tools that permit users, without previous programming experience, to run complex EEG analysis algorithms (Delorme and Makeig, 2004; Mørup *et al*., 2007; Romcy-Pereira *et al*., 2008; de Araujo Furtado *et al*., 2009). Such tools are quite reliable, and some of them are now adjusted for large data sets with multiple parameters, such as EEG, EMG, temperature and gross motor activity.

4.1 Choosing the parameters of acquisition

Prior to the start of any experiment, it is fundamental to choose the proper parameters of acquisition to optimize further analysis. The objectives, maximum frequency of interest, duration of the experiment, number of channels and available disk storage are key factors in determining the sampling rate and pre-filtering options. Obviously, according to the Nyquist Theorem, the signal must be sampled at least twice the maximum frequency of interest to extract all of the information from the bandwidth and represent the original biopotential (Drongelen, 2006). For example, in order to observe massive oscillations such as hippocampal ripples (Buzsáki *et al*., 1987; Buzsáki *et al*., 2003; ~200 Hz) a sampling rate of over 1 KHz is recommended for practical purposes. Also, if one wants to verify whether electrographic seizures have a behavioral correlate or not, synchronous video should be recorded. The use of 2 EEG channels (250 Hz each) plus temperature (250 Hz), activity (0.1 Hz) and signal strength (16 Hz) recorded in a Data Systems International system (DSI, Arden Hills, MN) results in approximately 175 MB per day. If one performs a 30-day experiment, it will be necessary to reserve approximately 5.2 GB per subject. In this particular example, the animals were placed in individual cages, each positioned on AM radio receiving pads (RPC-1; Data Systems International - DSI, Arden Hills, MN) that detect signals from an implanted transmitter (F40-EET) and send them to an input exchange matrix. Each analog input matrix is capable of receiving input from up to four receivers. A PCI-card model number CQ2240 (Data Systems International - DSI, Arden Hills, MN) receives data input from an exchange matrix. The signal is sent to a computer and telemetry data (up to 16 animals) are recorded through Dataquest ART 4.1 (Acquisition software; Data Systems International - DSI, Arden Hills, MN). The DSI transmitter uses a voltage-controlled oscillator which converts the biopotential difference into a frequency signal. The biopotential channels are encoded in pulse-to-pulse intervals that are transmitted by the F40-EET as RF waves. The relationship between the transmitted interval in microseconds and the input signal in millivolts is described by the calibration entered into the Dataquest ART 4.1 in units of microseconds per millivolts. Attenuation of the signal is very low due to the close proximity of the transmitter to the receiver. The filtering at the device level for the system (implant and acquisition system) is described as less than 3dB attenuation at 1 Hz and 50 Hz in the case of the F40-EET. The filtering within the implanted transmitter is nominally 0.6 Hz (−3dB) for the high-pass filter and 60 Hz (−3dB) for the low-pass filter. It is generated by one-pole of a high-pass filtering and one-pole of low-pass filtering. The activity of each animal is derived from the strength of the signal. When the signal strength changes by a set amount, the data exchange matrix generates an activity count. The number of counts is proportional to both distance and speed of movement. However, the activity is a relative measure, not the distance traveled (de Araujo Furtado *et al*. (2009).

Also, when dealing with prolonged EEG recordings, usually the recordings are split in several files due to the operational system file size limitation. In this case, it is important to limit the file size (for example, 100 MB), so if a data corruption/loss occurs, there is still a chance to recover some or most of the EEG epochs. However, if the file size is too small (for example 1 MB), several files will be generated making copying of files to another unit for further analysis very slow.

4.2 Choosing the tools to analyze the EEG data

The objectives of the experiment will influence the tools used for EEG analysis. Parameters, such as changes in power spectra over time, seizure duration and frequency, and number of channels recorded are very important. For example, if more than one channel is recorded, then a coherence and cross-correlation analysis may be performed (electrodes must be bipolar to run cross-correlogram).

Also, the choice of using commercial EEG software or open source software (or a combination of both) will depend on one's budget and technical background. It is common to find commercial software that allows the processing of large datasets using relatively little memory, but it is not easy to find an open source code with this feature. The graphical user interface (GUI) is another important feature to take into account. Commercial software often includes a user-friendly GUI, while the open-source software GUI is often less functional for the implementation of useful tools. For example, several functions are normally run from the command line when dealing with open source software. Also, the open-source GUI is normally just used to semi-automate the use of certain functions or to visually screen biopotential recordings, such as the EEG. Commercial code is often more stable than open-source code which is constantly aggregated with new functions and therefore, more subject to unexpected errors. Thus, open-source software is not approved for clinical use and should be used only experimentally. User support is another important factor when choosing what type of tool one may use. Commercial software has dedicated personnel for user support, while the help provided by open-source code teams is dependent on its availability.

Open source software, like the EEGLAB (Delorme and Makeig, 2004) and Chronux Analysis Software (http://chronux.org), is able to open several different file types, while commercial software is restricted to handling a small number of formats. The European data format is open and very flexible (EDF; B Kemp *et al*. 1992; Bob Kemp and Olivan 2003). In fact, EEG MATLAB toolboxes (de Araujo Furtado *et al*., 2009) can benefit from this open file format. Also, the number of functions present in open-source software is virtually unlimited, since one can always add new functions. Thus, the scientific community can always help to implement new analysis approaches. On the other hand, current commercial software is limited since the user cannot add new complex analysis options, since the source code is not available. Normally, the language adopted for open source software is MATLAB. Although it requires an initial investment in a MATLAB license, it still does not compare in terms of price to commercial code that does not have the same flexibility, and functions as MATLAB. Also, a compiled version of a MATLAB toolbox does not require MATLAB. Using MATLAB, one can test new tools that are not present yet in commercial software. Through open source software and MATLAB, one can create figures (in different formats) that are immediately suitable for publications. On the other hand, in commercial software, graphics can only be saved using specific formats. It is very clear that commercial EEG software and

open-source software have advantages and disadvantages and the software selection for EEG analysis is usually not easy.

We record EEG, activity and temperature during the entire course of an experiment and for extended periods beyond SE. A set of MATLAB algorithms was developed (de Araujo Furtado *et al*., 2009) to remove artifacts and measure the characteristics of long-term EEG recordings. The algorithms use short-time Fourier transforms to calculate the power spectrum of the signal for 2-sec intervals. The FFT can be represented by the expression:

$$X(k) = \sum_{j=1}^{N} x(j)\omega_N^{(j-1)(k-1)},$$

$$\text{where } \omega_N = e^{(2\pi i)/N}$$

The spectrum is then divided into the delta (1-4 Hz), theta (4.1-8 Hz), alpha (8.1-12 Hz), and beta (12.1-25 Hz) bands. Using the MATLAB function "robustfit.m", a linear fit to the power spectrum is used to indicate the likehood of normal EEG activity versus artifacts and high amplitude spike-wave activity. Changes in seizure frequency and duration over a prolonged period are a powerful indicator of the effects of potential neuroprotectants against seizures. The algorithm is very sensitive and, combined with further visual inspection, can give a reliable measurement of both SE duration and SRS frequency. Batch-processing is also used, which is a considerable advantage if a large number of subjects is used (such as in experimental pharmacology), because it increases the level of automation, allowing us to focus on other tasks, while the data is being processed.

Another way to evaluate spectral changes in the EEG signal is through the short-time Fourier transforms (STFT) that can be represented by the expression:

$STFT(t,w) = \int [x(\tau) - W(\tau - t)e^{-jw\tau}d\tau$, where W represents the sliding window used to divide the signal (Romcy-Pereira *et al*., 2008). Normally, when the STFT of a signal is calculated, one can represent it in a spectrogram, where the power spectrum is calculated for different times (t), segmented by the window W. In essence, a spectrogram pictures the distribution of the energy of the signal in the time and in frequency domain. However the size and type of the time window are determinants in the analysis and one must keep in mind the limitations of the STFT: as the time resolution increases (shorter window), the accuracy in which the frequency component is measured is diminished. An alternative is the use of wavelets, but it takes a longer time to process these compared to FFT.

Among the several types of wavelets, the Morlet wavelet is one of the most used to create a time frequency representation of EEG signals that may have epileptiform patterns. The Morlet wavelet is represented according to the expression:

$w(f_0,t) = A\varphi \cdot e^{-t^{2/2\sigma_t^2}} \cdot e^{i2\pi f_0 t}$, where $\sigma_t = 1/2\pi\sigma_f$ is the time of the wavelet and σ_f is its frequency (Romcy-Pereira *et al* (2008).

The GUI shown in Fig. 5 simultaneously plots the EEG in the time domain, the FFT, Morlet wavelet transform, allowing the confirmation or rejection of seizures by the user. Although many artifacts are clipped automatically, the user has the chance to verify if artifacts are still present. Gross motor activity and temperature are compared with EEG changes.

It is very important to identify and, if possible, remove artifacts in the EEG recording. Either manually or semi-automatically, artifacts should be rejected prior to any interpretation of the results. Delorme and co-workers (2007) presented an elegant method that uses independent component analysis (ICA) decomposition as a tool to isolate different artifacts from the EEG, although muscle artifact detection was not very effective.

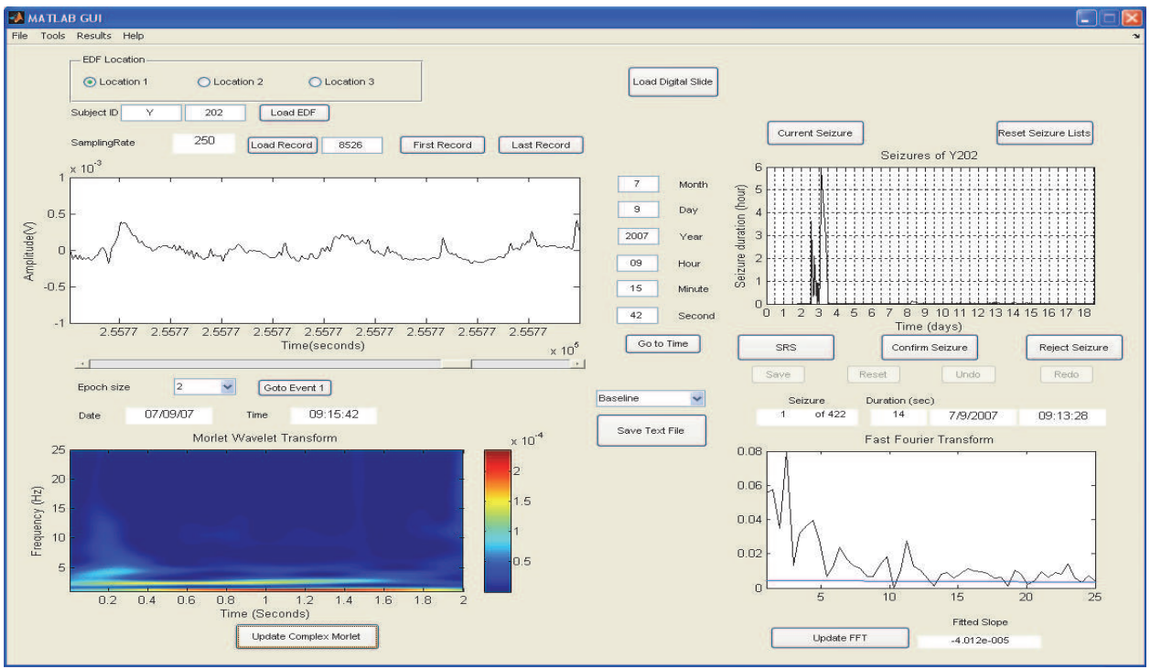

Fig. 5. Graphical user interface created using MATLAB that allows users to view various properties of EEG signal. Representative cortical electroencephalograms showing electrical activity during SE (B). Adapted from de Araujo Furtado and co-workers (2009).

As mentioned, when more than one channel is used, we can investigate the relationship between them. Connectivity between different brain circuits can be evaluated by determining the temporal relationship between brain signals from distinct brain regions. Cross-correlogram may be a better choice to analyze epileptiform patterns, when the propagation of temporal defined events has an important role. The coherence is preferred when the background activity between different areas is comparable (Drongelen, 2006).
According to Drongelen (2006), the coherence C between two different signals (x and y) can be defined as S_{xy} normalized by power spectra S_{xx} and S_{yy}, respectively. Then, in order to determine coherence, a number (without dimension) between 0 and 1, S_{xy} is squared. It can be represented by:

$$C(\omega) = \frac{|S_{xy}(\omega)^2|}{S_{xx}(\omega)S_{yy}(\omega)}$$

The cross-correlation R_{xy}, between two time series x and y, can be represented by:

$$R_{xy}(t_1 t_2 = E\{x(t_1)y(t_2)\}$$

However, the electrodes must be bipolar if ones decide to run a cross-correlogram, so the measurements on each channel will correspond to a better defined and small neuroanatomical area, something that does not happen with monopolar electrodes.
In summary, the choice of tools used for signal processing must be carefully evaluated, taking into account the goals and methodological limitations of the study. A reasonable background not only in neuroscience, but mathematics and computer programming may be necessary depending on the objectives.

5. Conclusions

The use of telemetry to record biopotentials like the EEG during long periods is fundamental to study the role of brain damage in epileptogenesis. Our group (de Araujo Furtado *et al.*, 2010) found and quantified SRS in rats exposed to the nerve agent soman, several days post-exposure. White and co-workers (2010) investigated the occurrence of spontaneous seizures in the kainate model through the use of a commercially available telemetry system (DSI). They were able to identify spikes and spike clusters, which occurred after the initial, prolonged seizure, but preceded the first spontaneous seizure, thus finding clues about the development of chronic epilepsy using the EEG as a powerful biomarker. An EEG telemetry system can allow the investigation of a phenomenon that without continuous monitoring would never be accurately studied. Still, one must be careful about the interpretation of results because the number of EEG channels limits the identification of the epileptic focus.

The identification and characterization of SRS, that occur after acute seizures induced by soman, emphasize the importance of quantifying SRS in studies where the objective is to find new therapeutics against soman-provoked seizures. It is known that exposure to soman can cause acute and chronic damage (Petras, 1994; Shih *et al.*, 2003), therefore, an ideal evaluation model must assess the neuroprotective effect of the therapeutic agent with both short-term and long-term EEG monitoring. However, it is very common to monitor the EEG for a time period of only 1–2 days post-exposure in the field of nerve agent studies. Obviously, this period is not enough to detect SRS and long-term morphological changes. Optimally, one should study the EEG changes over a period of several months (limited by the battery life of telemetry devices).

Among the limitations of telemetry, battery life is probably one of the most important. Also, an implantable telemetry system must be miniaturized in a way that the subject is not disturbed. Sealing of the transmitter plays a role, because if sealing is compromised it can ruin the device and consequentially the experiment. Several new technologies may address these limitations. New approaches that allow battery integration with the circuit/electrodes and the use of rechargeable batteries may be a great advantage (Budgett *et al.*, 2007). The lack of spatial resolution that is inherent in the EEG could be compensated by the use of arrays of multiple electrodes and the use of Bluetooth technology. Rechargeable batteries could permit one to run very long-term experiments (perhaps 1-2 years), studying epileptogenesis not only in animals that display acute seizures, but also on those that do not exhibit initial status epilepticus. Finally, the use of a semi-automated algorithm is a minimum requirement for data analysis in order to analyze continuous long-term EEG recordings in a time-efficient and accurate manner.

6. Disclosure statement

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official or as reflecting true views of the Department of the Army or Department of Defense.

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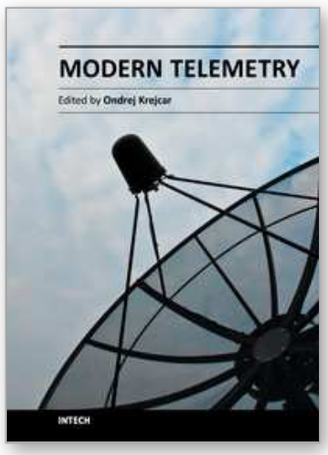

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Telemetry is based on knowledge of various disciplines like Electronics, Measurement, Control and Communication along with their combination. This fact leads to a need of studying and understanding of these principles before the usage of Telemetry on selected problem solving. Spending time is however many times returned in form of obtained data or knowledge which telemetry system can provide. Usage of telemetry can be found in many areas from military through biomedical to real medical applications. Modern way to create a wireless sensors remotely connected to central system with artificial intelligence provide many new, sometimes unusual ways to get a knowledge about remote objects behaviour. This book is intended to present some new up to date accesses to telemetry problems solving by use of new sensors conceptions, new wireless transfer or communication techniques, data collection or processing techniques as well as several real use case scenarios describing model examples. Most of book chapters deals with many real cases of telemetry issues which can be used as a cookbooks for your own telemetry related problems.

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