Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Quantitative EEG Assessment of Brain Injury and Hypothermic Neuroprotection after Cardiac Arrest

Hyun-Chool Shin*, Shanbao Tong, Soichiro Yamashita, Xiaofeng Jia,
Romergryko G. Geocadin and Nitish V. Thakor

Abstract— **In this paper we provide a quantitative electroencephalogram (EEG) analysis to study the effect of hypothermia on the neurological recovery of brain after cardiac arrest. We hypothesize that the brain injury results in a reduction in information of the brain rhythm. To measure the information content of the EEG a new measure called *information quantity* (IQ), which is the Shannon entropy of decorrelated EEG signals, is developed. For decorrelating EEG signals, we use the discrete wavelet transform (DWT) which is known to have good decorrelating properties and to show a good match to the standard clinical bands in EEG. In simulation for measuring the amount of information, the IQ shows better tracking capability for dynamic amplitude change and frequency component change than conventional entropy-based measures. Experiments are carried out in rodents to monitor the neurological recovery after cardiac arrest. In addition, EEG signal recovery under normothermic ($37^{\circ}C$) and hypothermic ($33^{\circ}C$) resuscitation following 5, 7 and 9 minutes of cardiac arrest is recorded and analyzed. Experimental results show that the IQ is higher for hypothermic than normothermic rats. The results quantitatively support the hypothesis that hypothermia accelerates the recovery of brain injury after cardiac arrest.**

I. INTRODUCTION

The development of quantitative electroencephalogram (EEG) analysis was motivated by the need for objective measures as well as some degree of automation [1]. Quantitative EEG analysis shows promising results as a tool for diagnostic monitoring of brain injury such as after resuscitation from cardiac arrest [2]-[4].

Recently the relation between hypothermia and EEG has been reported by [5][6]. These results may support the hypothesis that therapeutic hypothermia, which is to lower the body's temperature after cardiac arrest, dramatically increases the chances of recovery and improves the neurological outcome [7]–[9].

However, most of results have been based on subjective and qualitative observation and not a quantitative EEG-based analysis of the effect of therapeutic hypothermia after cardiac arrest. Here we provide a quantitative, entropy or information based, analysis of EEG for studying the effect of the therapeutic hypothermia on neurological recovery after cardiac arrest. We hypothesize that brain injury results in a reduction in information content of the brain rhythm. Further we test the hypothesis that the neurological recovery in the brain is reflected in the information content in EEG signals. From the perspective of the information theory, the information contained in a signal can be physically quantified by calculating the entropy [10].

The EEG as a physical signal can be divided into its predictable component and the uncertain component, and the amount of information contained in the signal is more related to the uncertain parts. Thus for an accurate information measurement, the predictable component, which is called the information redundancy, need to be removed as much as possible. Conventionally the information in EEG signals was measured without removing the information redundancy. To remove redundancy in EEG signals we use the discrete wavelet transform (DWT) for two reasons. One is that theoretical and experimental results show that correlations between values after DWT are extremely small. This means that DWT does a very good job in removing redundancy [11]–[12]. The other reason is that the multiresolution decomposition of DWT results in a good match to the standard clinical bands of interest: Gamma, Beta, Alpha, Theta and Delta (in accordance of the sampling rate of 250 Hz) [4]. Next we use the Shannon entropy (SE) to measure the uncertainty. In short, we measure the Shannon entropy of decorrelated EEG signals. To distinguish the new wavelet based measure from the conventional SE, we will call it as the information quantity (IQ).

II. INFORMATION QUANTITY (IQ)

Quantitative analysis offers two major advantages over traditional visual analysis. First, it is objective and highly reproducible. Second, it is able to extract information which is not readily apparent upon visual inspection.

A. Entropy-based qEEG Analysis

We have recently developed the entropy-based EEG analysis methods which have been validated and have shown promising results in objectively tracking the EEG recovery after cardiac arrest [2]–[3]. Entropy is a method to quantify the order/disorder of a time series. It is calculated from the distribution of one of the signal parameters, such as amplitude, power, or time-frequency representation. The Shannon entropy (SE) gives a useful criterion for analyzing and comparing probability distribution and provides a good measure of the information [10]. The classical Shannon

This work was supported by the NIH under Grant HL71568 and Grant NS42640.

H. Shin, S. Tong, X. Jia and N. V. Thakor are with the Department of Biomedical Engineering, Johns Hopkins School of Medicine, Baltimore, MD 21205. hshin13@bme.jhu.edu

S. Yamashita is with the Department of Anesthesiology, Tsukuba University, Japan.

R. Geocadin are with the Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD 21205.

entropy is expressed in

$$\text{SE} = -\sum_{m=1}^{M} p(m)\log_2 p(m) \tag{1}$$

where $p(m)$ is the probability of finding the system in the m^{th} microstate with $0 \le p(m) \le 1$ and $\sum_{m=1}^{M} p(m) = 1$. To analyze nonstationary EEG signals, we need to calculate the temporal evolution of SE. To do this an alternative time dependent SE measure based on sliding temporal window technique is applied. Let $\{s(i) : i = 1, \cdots, N\}$ denote the raw sampled signal. Now we define a sliding temporal window $w \le N$, and the sliding step $\Delta \le w$. Then sliding windows are defined by

$$W(n; w; \Delta) = \{s(i), i = 1 + n\Delta, \cdots, w + n\Delta\}$$

where $n = 0, 1, \cdots, [n/\Delta] - w + 1$ and $[x]$ denotes the integer part of x. To calculate the probability, $p_n(m)$ within each window $W(n; w; \Delta)$, we introduce intervals such that

$$W(n; w; \Delta) = \cup_{m=1}^{M} I_m \tag{2}$$

Then the probability $p_n(m)$ that the sampled signal belongs to the interval I_m is the ratio between the number of the samples found within interval I_m and the total number of samples in $W(n; w; \Delta)$. Using $p_n(m)$, SE(n) is defined as

$$\text{SE}(n) = -\sum_{m=1}^{M} p_n(m)\log_2(p_n(m)) \tag{3}$$

B. Information Quantity (IQ) as an Indicator of Hypothermic Neuroprotection

To track the EEG recovery under hypothermia and normothermia, we need to measure the signal entropy accurately. The EEG as a physical signal can be divided into the predictable parts and the uncertain parts and also the amount of information is related more likely to the uncertain parts. The predictable parts, which are called the information redundancy, need to be removed as much as possible. To remove redundancy in EEG signals we use the discrete wavelet transform (DWT) which does a very good job at removing redundancy [11]. To distinguish the new measure from the conventional SE, we will call it as the information quantity (IQ).

Based on the above arguments, we can define the information quantity (IQ). First the DWT coefficients within each window are obtained as

$$WC(r; n; w; \Delta) = \text{DWT}[W(n; w; \Delta)] \tag{4}$$

Then to calculate $p(m)$ within each transformed window $WC(r; n; w; \Delta)$, intervals in (2) are modified

$$WC(r; n; w; \Delta) = \cup_{m=1}^{M} I_m \tag{5}$$

Similar with $p_n(m)$ in SE, the probability, $p_n^{wc}(m)$ within each window $WC(r; n; w; \Delta)$ is calculated using (5) instead of (2). Finally IQ is defined as

$$\text{IQ}(n) = -\sum_{m=1}^{M} p_n^{wc}(m)\log_2(p_n^{wc}(m)) \tag{6}$$

Thus we can explore the IQ evolution of the whole data $\{s(i) : i = 1, \cdots, N\}$ with (6).

C. Comparing IQ with Conventional Wavelet Entropy (WE)

It is worth relating the IQ in (6) with the conventional wavelet entropy (WE) in [4]. In the WE the probability is calculated as the relative wavelet energy, i.e.,

$$p_n^{we}(m) = \frac{E_n(m)}{E_n} \tag{7}$$

where $E_n(m)$ is the energy of the DWT coefficients in m subband and $E_n = \sum_{m=1}^{M} E_n(m)$. Then the WE is defined as

$$\text{WE}(n) = -\sum_{m=1}^{M} p_n^{we}(m)\log_2(p_n^{we}(m)) \tag{8}$$

Thus WE measures how spread the DWT coefficients are in different subbands. The WE provides a good way to analyze short duration EEG signals. But it may show ambiguous results for signals with large dynamic amplitude range in time domain. This is because the WE is based on the normalized relative wavelet energy, not absolute energy. More substantive comparison will be shown in Sec. III for simulated signals.

III. Simulation Results

To see the time evolution of IQ, other simulated signal with multiple sinusoidal components and Gaussian distribution is used in Fig. 1. The number of sinusoids is time-dependent, systematically increasing for the first 12 seconds. After that, the signal has Gaussian distribution with increasing value of standard deviation. Fig. 2(a) shows the simulated signal in time domain. It starts with single sinusoid and after 4, 6, 8, and 10 sec., one more sinusoid is added until 12 sec. Then from 10 to 12 sec., it consists of 5 sinusoids whose frequencies are 1, 5, 10, 20 and 40 Hz. Here we can anticipate that the amount of information or entropy increases with time until 12 seconds, after that it will show a large decease due to the small magnitude around zero until 13 seconds, and it will increase continually. Fig. 2(b) shows the plots for SE, WE and IQ. From 0 to 12 sec., the SE without removing redundancy is almost constant regardless of the number of sinusoidal components but IQ and WE increase in accordance with the increase of sinusoidal components. From 12 to 13 sec., SE and IQ show a large decrease as expected but WE keeps constant without any responsivity to the signal change. From 13 sec. IQ and WE continually increase but WE is still kept the same as before. The SE can be a good measure for observing dynamic amplitude change but may not be for frequency component change. Interestingly the WE has the opposite property to that of SE, it is good for frequency change and not good for amplitude. The proposed IQ is shown to be a good measure for both.

IV. Experimental Results

Here we firstly describe rodent cardiac arrest and hypothermia model. Then we provide experimental and clinical results based on qEEG analysis explained in previous section.

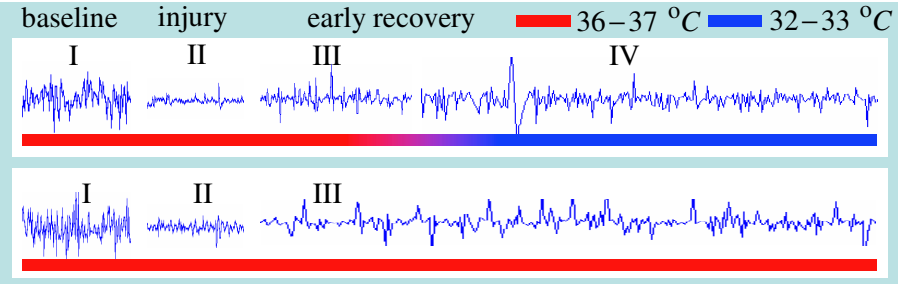
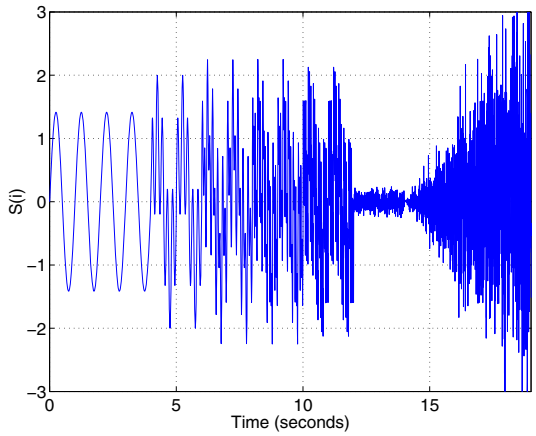
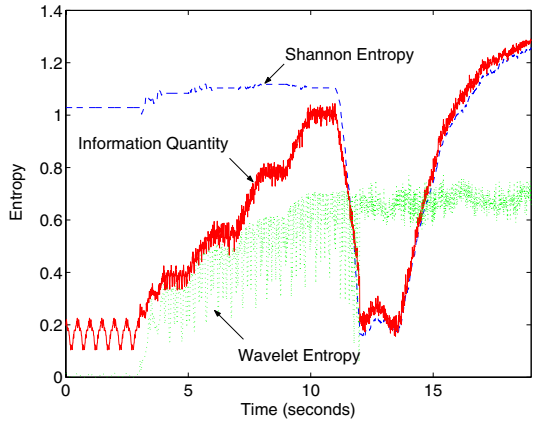


Fig. 1. Real EEG data for rat under hypothermia (top trace) and normothermia (bottom trace) after asphyxic cardiac arrest.



(a)



(b)

Fig. 2. Time evolution of SE, WE and IQ for signal with time-varying frequency components and Gaussian distribution. (a) time domain representation. (b) comparison of SE, WE and IQ.

A. Rodent Cardiac Arrest and Hypothermia Model

We have adopted an experimental design that has been modelled as closely as possible to the actual clinical situation. This brain injury model has been approved by the animal Care and Use Committee of the Johns Hopkins Medical Institutions. Asphyxic cardiac arrest and resuscitation protocol was performed as modified from Katz and colleagues [2][13].

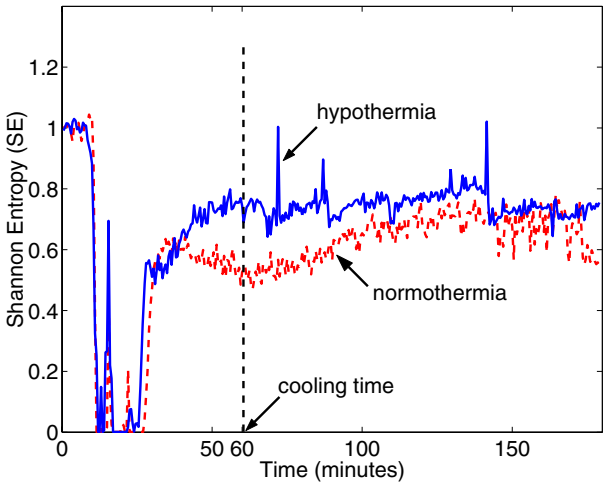
The experimental protocol is as follows. The animal studies were done in rodents. Cranial screw EEG electrodes and subdermal ECG electrodes were inserted. Following stabilization from surgery, baseline EEG and blood gas recordings were taken. This was followed by induction of global hypoxic-ischemic injury using asphyxia by clamping the endotracheal tube and disconnection from ventilator. After a predetermined period (i.e. 5, 7 or 9 minutes) of asphyxia induced cardiac arrest, the animal was resuscitated with resumption of ventilation, chest compression and use of epinephrine. Forty five minutes after successful resuscitation, hypothermia was induced and maintained for 12 hours. The 45 minute delay is modelled after the clinical delay of taking the patient from the resuscitation area to the intensive care unit where hypothermia may be initiated. Hypothermia was maintained for 12 hours. The duration of 12 hours is based on the actual human studies which showed the enhanced recovery [7]. The animal was then be gradually rewarmed, monitored for competency in ventilation and weaned off the ventilator. Continuous EEG recording was maintained throughout this period.

B. Experimental Results with Rats

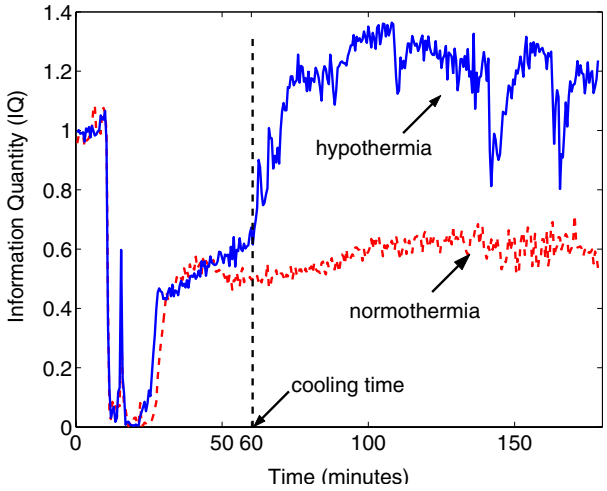
To quantitatively demonstrate the effect of hypothermia on neurological recovery, we calculated SE and IQ for EEG data obtained from Wistar rat. Rats are randomly divided into two groups: hypothermia (32-33$°C$) and normothermia (36-37$°C$) groups.

Fig. 1 illustrates EEG recordings under normothermia and hypothermia. The EEG recording under hypothermia is divided into four phases: (I) baseline, (II) 5 min asphyxic cardiac arrest, (III) early recovery under normothermia and (IV) early recovery under hypothermia. The EEG recording under normothermia is divided into three different phases: (I) min baseline, (II) 5 min asphyxic cardiac arrest and (III) early recovery under normothermia. We observed that after cardiac arrest EEG signal amplitude is highly suppressed and then gradually activated with time. However, the difference between the two EEG signals in Fig. 1 was not readily discerned from visualizing the wavefront itself; i.e., the effect of hypothermia on the EEG signal recovery was not evident without quantitative analysis.

Fig. 3 compares IQ and SE for real EEG data measured under hypothermia and normothermia after 5 min asphyxic cardiac arrest. During the early recovery phase



(a)



(b)

Fig. 3. SE and IQ for experimental EEG data for rats under normothermia and hypothermia after 5 min asphyxic cardiac arrest. (a) SE (b) IQ.

before temperature change at 60 min, we observe an increase in both SE and IQ. After the temperature decreases, the IQ under hypothermia becomes apparently higher than that under normothermia, which is shown in Fig. 3 (b). But the difference in SE is not so noticeable (Fig. 3 (a)). These results reinforce the idea that hypothermia accelerates the neurological EEG signal recovery after cardiac arrest.

V. Discussion and Conclusions

We have presented quantitative results to support the idea that hypothermia related changes in brain's electrical activity can be objectively tracked in real time by qEEG. This presents the potential for qEEG as a real time monitoring technique to evaluate hypothermia therapy for brain injury. We also present the potential ability of qEEG to provide an objective estimation of injury and recovery which may be used to stratify the degree of injury sustained by the brain. This estimation may also be used to provide prognostication of functional recovery. The use of IQ in the preliminary work presented here showed that the qEEG measure indicates that EEG data under hypothermia contained more information than those under normothermia. We will need to correlate the qEEG signal measures to neurological outcome and survival. This will require extensive investigations with a pool of subjects and more complete clinical examination.

We believe that development and validation of a robust objective measure of brain injury and recovery will contribute greatly to the advancement and understanding of the process of injury and recovery, as well as influence further development of hypothermia as a therapy. Our qEEG tool can also be used to help advance hypothermia technologies. In the longer term, we hope that our technology may be useful in the intensive care setting as a simple and easy to interpret measure that will enhance bedside care, akin to monitoring the ECG after a heart attack or monitoring the blood-pressure in a shock-trauma victim.

References

[1] N. V. Thakor and S. Tong, "Advances in quantitative electroencephalogram analysis methods," *Annu. Rev. Biomed. Eng.*, vol. 6, pp. 453-495, 2004.

[2] S. Tong, A. Bezerianos, A. Malhotra, Y. Zhu and N. V. Thakor, "Parameterized entropy analysis of EEG following hypoxic-ischemic brain injury," *Physics Letters A*, vol. 314, pp. 354–361, 2003.

[3] A. Bezerianos, S. Tong and N. V. Thakor, "Time-dependent entropy estimation of EEG rhythm changes following brain ischemia," *Annals of Biomedical Enginnering*, vol. 31, pp. 221–232, 2003.

[4] O. A. Rosso, S. Blanco, J. Yordanova, V. Kolev, A. Figliola, M. Schürmann and E. Başar, "Wavelet entropy: a new tool for analysis of short duration brain electrical signals," *Journal of neuroscience methods*, vol. 105, pp. 65–75, 2001.

[5] H. Fritz, R. Bauer, B. Walter, O. Schlonski, D. Hoyer, U. Zwiener, K. Reinhart, "Hypothermia related changes in electrocortical activity at stepwise increase of intracranial pressure in piglets," *Exp. Toxicol. Pathol.*, vol. 51, pp. 163–71, 1999.

[6] R. Burger, M. Zuechner, M. Bendszus, GH. Vince, K. Roosen, "Moderate hypothermia improves neurobehavioral deficits after an epidural focal mass lesion in rodents," *J. Neurotrauma.*, vol. 20, pp. 543-58, 2003.

[7] S. A. Bernard, B. M. Jones and M. K. Home, "Clinical trial of induced hypothermia in comatose survivors of out-of-hospotal cardiac arrest," *Ann Emerg Med.*, vol. 30, pp. 146–153, 1997.

[8] H. a. C. A. S. Group, "Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest," *N Engl J Med*, vol. 346, pp. 549-56, 2002.

[9] J. P. Nolan, P. T. Morley, T. L. Vanden Hoek and R. W. Hickey, "Therapeutic hypothermia after cardiac arrest," *Circulation*, vol. 108, pp. 118–121, 2003.

[10] C. E., Shannon, "A mathematical theory of communication," *Bell Syst. Tech. Journal*, vol. 27, pp. 623–656, 1948.

[11] S. Mallat, "Theory for Multiresolution Signal Decomposition: The Wavelet Representation," *IEEE Pat. Anal. Mach. Intell.*, vol. 11, pp. 674-693, July 1989.

[12] M. Antonini, M. Barladu, P. Mathieu, and I. Daubechies, "Image Coding Using Wavelet Transform," *IEEE Trans. on Image Proc.*, vol. 1, pp. 205-220, April 1992.

[13] L. Katz, U. Ebmeyer, P. Safar and A. Radovsky, "Outcome model of asphyxial cardiac arrest in rats," *J. Cereb. Blood Flow Metab.*, vol. 15, pp. 1032–1039, 1995.