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Novel Early EEG Measures Predicting Brain Recovery after Cardiac Arrest

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Abstract: In this paper, we propose novel quantitative electroencephalogram (qEEG) measures by exploiting three critical and distinct phases (isoelectric, fast progression, and slow progression) of qEEG time evolution. Critical time points where the phase transition occurs are calculated. Most conventional measures have two major disadvantages. Firstly, to obtain meaningful time-evolution over raw electroencephalogram (EEG), these measures require baseline EEG activities before the subject's injury. Secondly, conventional qEEG measures need at least 2∼3 h recording of EEG signals to predict meaningful long-term neurological outcomes. Unlike the conventional qEEG measures, the two measures do not require the baseline EEG information before injury and furthermore can be calculated only with the EEG data of 20∼30 min after cardiopulmonary resuscitation (CPR).

Keywords: quantitative EEG; ischemic brain injury; cardiac arrest; entropy

1. Introduction

Cardiac arrest (CA), which affects 200,000∼375,000 people annually, is a significant cause of death in the United States. Most of the patients that are successfully resuscitated undergo prolonged coma and only 10∼20% survive to hospital discharge. Among the survivors, neurological complications and cognitive deficits are the major cause of morbidity and continued disability [1–7].

To non-invasively monitor and predict critical brain injury after cardiac arrest, quantitative electroencephalogram (qEEG) analysis has been developed and has shown promising results for early prognostication. Most qEEG measures are based on the hypothesis that critical information about brain injury and recovery is embedded in neurological activity in electroencephalogram (EEG) signals. The time dependent entropy (TDE) measure has been used to study EEG during recovery from asphyxic cardiac arrest injury [8,9]. Also, a quantitative metric called Information Quantity (IQ) has been introduced to measure the effects of the therapeutic hypothermia on brain recovery [10,11]. An alternative measure, subband IQ (SIQ) [12], has been developed to account for the behavior of the single, clinical EEG bands such as Delta, Theta, Alpha, Beta, and Gamma [13,14].

Such qEEG measures offer two major advantages. First, they are able to extract quantitative information which is not readily apparent upon visual inspection. Second, the measures can be potentially useful in measuring and titrating different grades of cardiac arrest injuries and hypothermic treatments. However, most conventional measures have two major disadvantages. Firstly, to obtain meaningful time-evolution over raw EEG, these measures require baseline EEG activities before the subject's injury. The baseline EEG signals are required for calibrating the qEEG measures. Secondly, conventional qEEG measures need at least 2∼3 h recording of EEG signals to predict meaningful long-term neurological outcomes. In some sense, 2∼3 h can be thought of as a short period.

However, considering that patient's initial severity after cardiac arrest is highly related to long-term outcomes [15,16], a measure able to predict long-term outcomes at the very early stage after injury is definitely necessary and useful.

The qEEG time evolution shows three distinct phases: isoelectric period, fast progression, and slow progression. In this paper, we propose novel quantitative EEG measures by exploiting critical time points in EEG time evolution. The first new measure is the critical time point, t_{iso}, which is a critical transition time from an isoelectric period after cardiopulmonary resuscitation (CPR) to sudden and fast progression. We hypothesize that t_{iso} is the time index bearing neurologically significant change after CPR. Our expected result is that the short duration of isoelectric phase after CPR, i.e., shorter t_{iso} results in the better neurological recovery. The second measure is related to the slope of the EEG progression. During the fast progression period, the slope of SIQ suddenly increases and the slope change then becomes steady during the slow progression. As the second measure, we choose the time duration, t_{fast}, where the slope is maximized after t_{iso}. t_{fast} is the time duration from t_{iso} to the time point where EEG starts to be highly "activated" through bursting and burst suppression periods compared with the isoelectric period. We expect that the longer t_{fast} leads to a better outcome. Unlike the conventional qEEG measures, the two measures do not require the baseline EEG information before injury and furthermore can be calculated only with the EEG data of 20∼30 min after CPR while conventional measures require an EEG recording for more than 3 h. In the experiments, we will demonstrate the usefulness of the proposed measures in terms of how well the measures predict actual neurological outcomes observed after 72 h.

2. Quantitative EEG Predicting Long-Term Brain Injury after CA

qEEG plays a significant role in EEG-based clinical diagnosis and studies of brain function. In [9], a detail review of the advances in qEEG researches is provided. Among them, the widely used quantitative and statistical measures are based on the information entropy of EEG signals. In the entropy based qEEG measures, it is hypothesized that brain injury results in a reduction in information content of the brain rhythm and the neurological recovery in the brain is reflected in EEG signals. In this section, we briefly review some specific approaches and their variations of Shannon entropy (SE) based qEEG measures.

2.1. Review of Shannon Entropy Based qEEG Measures

The traditional Shannon entropy is defined as

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

where $p(m)$ is the probability of finding the system in the mth microstate with $0 \leq p(m) \leq 1$ and $\sum_{m=1}^{M} p(m) = 1$ [17].

To analyze nonstationary signals, a temporal evolution of SE is needed. To do this, an alternative time dependent SE measure based on sliding temporal window technique is introduced [8,9]. Let $\{s(i) : i = 1, ..., N\}$ denote the raw sampled signal. Also we define a sliding temporal window size $w \leq N$, and the sliding step $\Delta \leq w$. Then sliding windows are defined by $W(n; w; \Delta) = \{s(i), i = 1 + n\Delta, ..., w + n\Delta\}$ where $n = 0, 1, ..., [n/\Delta] - w + 1$ and $[x]$ denotes the integer part of x. To calculate the probability, $p_n(m)$ within each window $W(n; w; \Delta)$, intervals such that $W(n; w; \Delta) = \bigcup_{m=1}^{M} I_m$ is defined. Then the probability $p_n(m)$ that the sampled signal belongs to the interval I_m is calculated as 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 $p_n(m)$, a time-dependent Shannon entropy, $\mathrm{SE}(n)$ is defined as

$$\mathrm{SE}(n) = -\sum_{m=1}^{M} p_n(m) \log_2 p_n(m) \tag{2}$$

To get the accurate $\mathrm{SE}(n)$, it is required to estimate $p_n(m)$ correctly. But $p_n(m)$ may vary depending on the parameter selection of M and the maximum value of $W(n;w;\Delta)$. The conventional measure uses the baseline data to set up those parameters. Furthermore, $\mathrm{SE}(n)$ is normalized by the averaged $\mathrm{SE}(n)$ calculated in the baseline period.

Also, by removing the redundancy in EEG signals for better quantification, IQ has been developed [10]. First the discrete wavelet transform (DWT) coefficients within each window are obtained as $WC(r;n;w;\Delta) = DWT[W(n;w;\Delta)]$. r is the decomposition level of DWT. Then to calculate $p_n^{wc}(m)$ within each transformed window $WC(r;n;w;\Delta)$, intervals in $W(n;w;\Delta)$ are modified $WC(r;n;w;\Delta) = \bigcup_{m=1}^{M} I_m^{wc}$. Similar with $p_n(m)$ in $\mathrm{SE}(n)$, the probability, $p_n^{wc}(m)$ within each window $WC(r;n;w;\Delta)$ is calculated.

Finally IQ is defined as

$$\mathrm{IQ}(n) = -\sum_{m=1}^{M} p_n^{wc}(m) \log_2 p_n^{wc}(m) \tag{3}$$

Although IQ is a good measure of wide band EEG signals, it has a limitation that EEG recovery in each of the clinical bands (delta, theta, alpha, beta, and gamma) is hardly characterized. To overcome this limitation, SIQ has been developed [12] which is separately estimated in each subband. The probability $p_n^k(m)$ in kth subband that the sampled EEG 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 kth subband. Using $p_n^k(m)$, $\mathrm{SIQ}^k(n)$ in kth subband in defined as

$$\mathrm{SIQ}^k(n) = -\sum_{m=1}^{M} p_n^k(m) \log_2 p_n^k(m) \tag{4}$$

Finally SIQ is obtained by averaging $\mathrm{SIQ}^k(n)$ over 5 subbands :

$$\mathrm{SIQ}(n) = \sum_{k=1}^{5} \mathrm{SIQ}^k(n) \tag{5}$$

Estimation of SIQ entails the selection of a certain number of parameters such as selection of wavelet function, the partitioning levels to estimate entropy and the sliding window length.

Figure 1 shows the raw EEG signals and the SIQ evolution of two animals which resulted in a low and a high neurological deficit score (NDS) after 72 h. NDS accounts for several cognitive and behavioral parameters including reflexes, autonomic, motor, and sensory function by assessing neurological performance quantitatively, on a scale of 0 (brain dead) to 80 (best) [18]. The low NDS score indicates the poor outcome and vice versa. From a typical time evolution of SIQ we can see three distinct phases: isoelectric period, fast progression, and slow progression phases. Clearly, even from the visual inspection, the rat with a higher NDS shows a higher value of SIQ. Moreover, the rat exhibiting low NDS shows a sparse EEG signal but the rat with high NDS shows energetic EEG in this early period. This visual finding is consistent with SIQ during isoelectric and fast progression periods.

However, previous studies using IQ or SIQ [10,12] require the baseline EEG information prior to injury for calibration and furthermore need an EEG recording for more than 3 h for meaningful results.

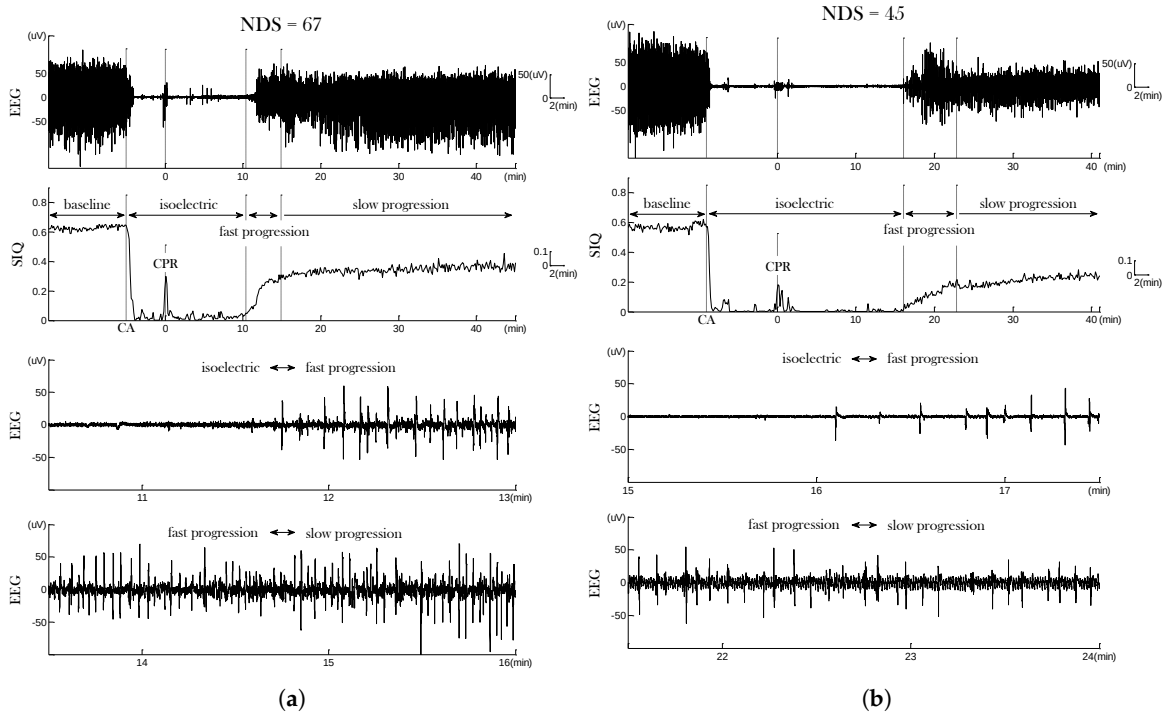

Figure 1. Electroencephalogram (EEG) signals and typical time evolution of subband IQ (SIQ). (**a**) Progression of SIQ for the high neurological deficit score (NDS) (67), 5 min cardiac arrest (CA) and (**b**) evolution of SIQ for the low NDS (45), 9 min CA.

2.2. Novel qEEG Measures Exploiting Critical Transition in EEG

Here, we explain two novel quantitative measures that are the critical time durations in EEG signals. These are based on SIQ temporal evolution. The rat with the low NDS score shows a longer isoelectric period and slower increase of SIQ than the rat with good outcome. Motivated by this finding, the measures demarcate the transition periods of isoelectric, fast progression, and slow progression.

Figure 2 shows the contrasting SIQ evolutions where critical time points are marked. Note that the origin time is the CPR time in Figure 2. To calculate these points, we first define the slope of the SIQ evolution as

$$\Delta_s(t) = \begin{cases} \dfrac{\mathrm{SIQ}(t) - \mathrm{SIQ}_{iso}}{t - t_0}, & \mathrm{SIQ}(t) > \mathrm{SIQ}_{iso} \\ \Delta_s(t) = 0 \text{ and } \Delta_s(t') = 0 \text{ for } 0 \le t' < t \end{cases} \tag{6}$$

where SIQ_{iso} is the average of $\mathrm{SIQ}(t)$ for $t_0 - \varepsilon \le t \le t_0 + \varepsilon$ and t_0 is arbitrarily selected in the isoelectric period.

In the first measure, we calculate the time point where the slope starts to increase continuously. By choosing the maximum time such that $\Delta_s(t)$ is equal to zero, we can overcome and isolate the fluctuation of SIQ during the isoelectric period. The resulting formula for the transition time from isoelectric to fast progression is given by

$$t_{iso} = \arg_t\{\max(\Delta_s(t) = 0)\} \tag{7}$$

t_{iso} is the duration of the isoelectric phase from CPR, not from the start of the isoelectric phase. In Figure 2 (below), all the $\Delta_s(t)$ prior to time point t_{iso} were marked as zero. Since in some situation, it is hard to know the time when CA occurs and the total duration of the isoelectric phase is not always available, the proposed t_{iso} is more practical. But t_{iso} might be not directly related with common physiology. Here, we assume that longer CA, i.e., longer duration from CA to CPR leads to a longer

isoelectric period after CPR. With the assumption, t_{iso} can be proportional to the total isoelectric duration. The assumption is not clearly validated in the paper. However, the experimental data analysis supports the assumption.

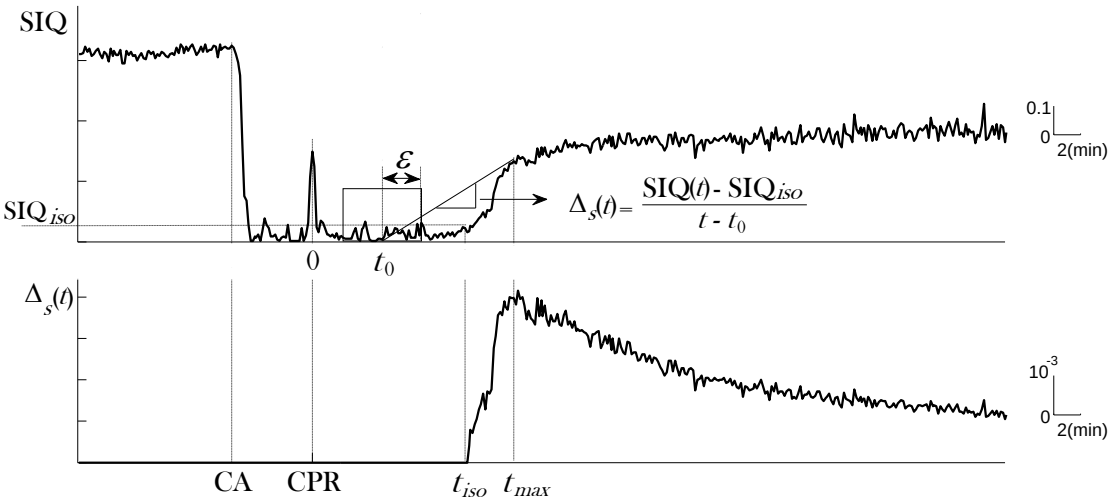

Figure 2. Slope, $\Delta_s(t)$, of typical quantitative electroencephalogram (qEEG) evolution.

The second measure is the time point where the transition from fast progression to slow progression occurs. Using the slope in Equation (6), the transition point t_{fast} is calculated by

$$t_{max} = \arg_t\{\max(\Delta_s(t))\} \tag{8}$$

$$t_{fast} = t_{max} - t_{iso} \tag{9}$$

t_0 is a certain time point in the isoelectric phase and affects SIQ_{iso}. During this phase, EEG signals keep steady in very low levels. Thus once t_0 is uniformly selected within the isoelectric phase after CA and SIQ_{iso} is calculated by averaging over a certain window, SIQ_{iso} is not very sensitive to the selection of t_0. The role of ε is to determine the window size for averaging in the isoelectric phase. Also according to the section of t_0, $\Delta_s(t)$ in Equation (6) changes. For a given t, the less value of t_{iso} results in less $\Delta_s(t)$ and vice versa. But the proposed measures do not use $\Delta_s(t)$ itself. As in Equations (6) and (7), the proposed measures use the time points when the transition from isoelectric to fast progression and from fast to slow progression occur, respectively. Although $\Delta_s(t)$ can vary according to the selection of t_0 and ε, the overall shape of $\Delta_s(t)$ is not very sensitive and therefore the transition time, t_{iso} and t_{max} are not so dependent on t_0 and ε.

Figure 3 shows an example of EEG signals and their respective $\Delta_s(t)$ for various NDSs. After CPR, $\Delta_s(t)$ remains at zero for a while. It then shows a relatively rapid increase, then slows down at a critical point, t_{max}. As expected, t_{iso} and t_{fast} are correlated with NDS. For the high NDS, t_{iso} and t_{max} are marked at a comparatively early instant of time and vice versa for low NDS.

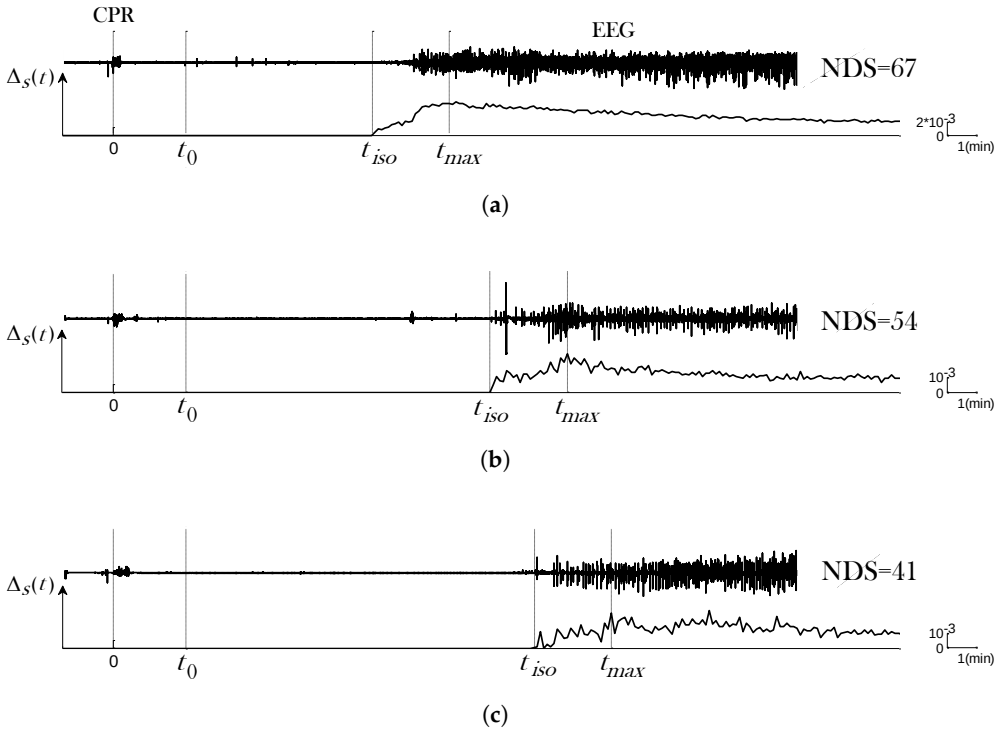

Figure 3. Novel qEEG measures, t_{iso} and t_{max}, of various NDS classes (high, middle, and low). (**a**) time evolution of $\Delta_s(t)$ during high NDS (67); (**b**) time evolution of $\Delta_s(t)$ during middle NDS (54); (**c**) time evolution of $\Delta_s(t)$ during low NDS (41).

3. Experimental Methods

We obtained EEG recordings from 19 rats during experiments designated to study the information evolution in brain rhythms following asphyxic cardiac arrest. Two channels of EEG using sub-dermal needle electrodes (Grass Instruments, Quincy, MA, USA) were inserted in the right and left parietal areas, and we used the EEG signal from right parietal area. One channel of ECG and one channel of arterial pressure were recorded continuously before the insult, during the insult, and through 3 h of recovery. The signals were digitized using the data acquisition package CODAS (DATAQ Instruments INC., Akron, OH, USA). Sampling frequency of 250 Hz and 12 bit A/D conversion were used for ECG and arterial pressure. EEG data are sampled at 1 kHz with an anti-aliasing filter (<500 Hz). This brain injury study was 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 et al. [19].

Wistar rats (300 ± 25 g) were used in the experiments. The initial anesthesia was induced with 4% halothane and 50:50% nitrous oxide:oxygen. Baseline recording for 10 min was done after 5 min washout to ensure that halothane did not have a significant effect on EEG. After washout, asphyxia was induced by stopping and disconnecting the ventilator and clamping the tracheal tube. CA was confirmed by observing the drop of mean arterial blood pressure (MABP) <10 mmHg. Surgical graded asphyxia of 5, 7, and 9 min followed. Note that respiratory to cardiac arrest model may be different in both outcomes and EEG signals than primary cardiac arrest. Resuscitation was performed by chest compression until return of spontaneous circulation (ROCS) (i.e., achieving spontaneous MABP $<$ 60 mmHg). For ten of the 19 rats, clinical hypothermia was applied. Clinical hypothermia was applied using cooling mist as described in [10,11].

All surviving rats underwent comprehensive behavioral testing by an independent observer 72 h from the start of the recovery period. NDS was chosen as the basis for these studies because it accounts

for several behavioral parameters, including motor and sensory functions [18]. Furthermore, NDS is an appropriate means of associating qEEG to graded neurological outcome.

4. Results

For the data analysis, the sliding window, w and the sliding step, Δ are set to 8 s, and 1 s, respectively. To calculate $p_n^k(m)$ in Equation (4), the total number of bins, M is set to 20 and each bin is equally arranged in the range of ± 50. Also 5 level DWT is used using 5-tap Daubechy filter. To get the proposed measures in Equations (6) and (9), t_0 and ε are set to 3.5 min and 64 s for all rats, respectively.

To determine whether the results shown in Figure 3 help over 19 rats, the averaged results of were provided in Figure 4. It is observed that t_{iso} and t_{max} become increased as the CA durations are increased. But t_{fast}, which is the difference of t_{max} and t_{iso}, are not so significantly related with the CA durations.

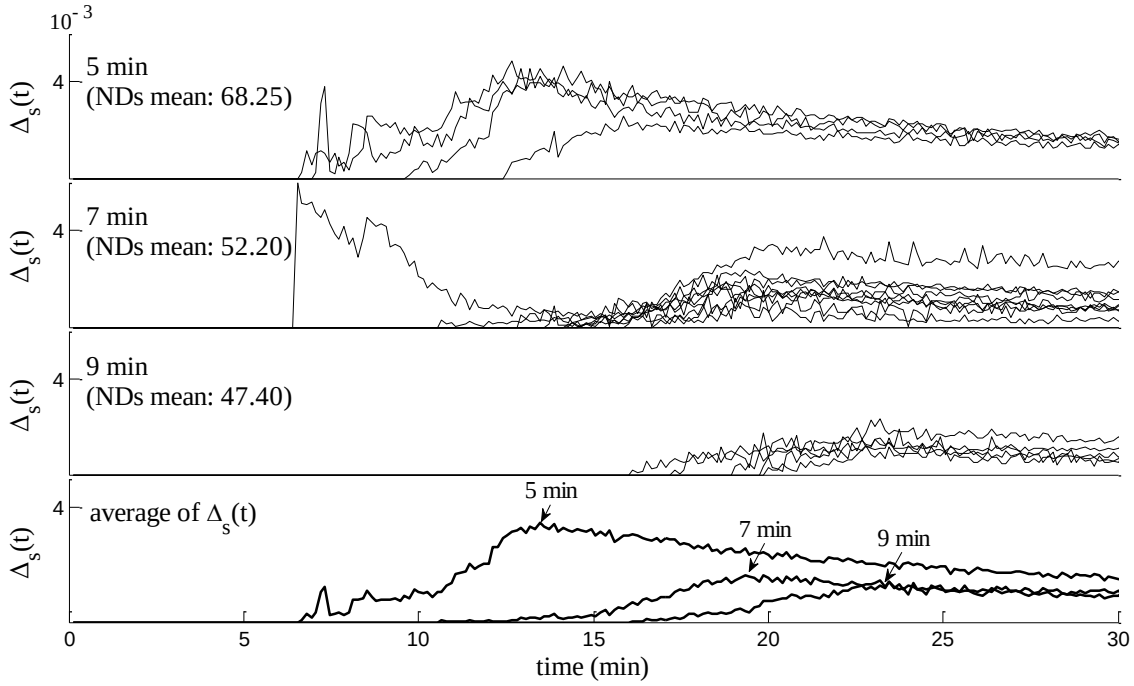

Figure 4. The time evolution of $\Delta_s(t)$ with three graded NDS over 19 rats.

Correlation coefficients of various measures with NDS are summarized in Table 1. In addition to t_{iso} and t_{fast}, t_{iso} + asphyxia is also investigate. t_{iso} + asphyxia means the total duration of the isoelectric phase. μ_{SIQ} is the averaged SIQ over all intervals for 100 min to 150 min. As can be seen in Table 1, t_{iso} shows the highest correlation. But unlike the expection, t_{fast} does not show a significant correlation with NDS. Also note that t_{iso} and t_{iso} + asphyxia are closely related. This experimentally implies that the duration of the isoelectric phase from CPR can be used as an estimate of the total duration of the isoelectric phase. This experimentally suports the assumption in Section 2.2.

Table 1. Outcomes of the various measures for the whole data set. Bold indicates the rats applied clinical hypothermia.

Rat Num.	Asphyxia (min)	NDS	t_{iso} (min)	t_{iso} + Asphyxia	t_{fast} (min)	μ_{SIQ}
1	**5**	**75**	**6.73**	**11.73**	**6.27**	**1.1920**
2	**5**	**71**	**6.33**	**11.33**	**6.14**	**1.0245**
3	5	67	9.40	14.40	4.13	0.7412
4	5	60	11.98	16.98	3.47	0.6222
correlation coefficient			−0.9470	−0.9470	0.9358	0.9622
p-value			0.0530	0.0530	0.0642	0.0378
5	**7**	**70**	**5.35**	**12.35**	**2.67**	**1.0121**
6	**7**	**65**	**10.33**	**17.33**	**11.07**	**0.8879**
7	**7**	**60**	**14.97**	**21.97**	**11.06**	**0.5869**
8	7	54	14.58	21.58	3.60	0.9063
9	7	51	12.60	19.60	7.07	0.5117
10	**7**	**50**	**16.47**	**23.47**	**5.20**	**0.8929**
11	**7**	**47**	**14.20**	**21.20**	**4.80**	**0.6859**
12	7	45	13.98	20.98	9.34	0.5716
13	**7**	**41**	**13.93**	**20.93**	**5.20**	**0.5619**
14	7	39	15.67	22.67	2.93	0.5647
correlation coefficient			−0.7376	−0.7376	0.2497	0.6806
p-value			0.0149	0.0149	0.4866	0.0303
15	9	52	19.62	28.62	2.93	0.4707
16	9	50	18.80	27.80	1.87	0.5584
17	**9**	**49**	**19.32**	**28.32**	**3.46**	**0.6547**
18	**9**	**45**	**16.10**	**25.10**	**6.27**	**0.7770**
19	9	41	16.87	25.87	3.20	0.6253
correlation coefficient			0.8524	0.8524	−0.4047	−0.6004
p-value			0.0666	0.0666	0.4991	0.2843
Total correlation coefficient			−0.7888	−0.7849	0.2025	0.7085
p-value			0.0001	0.0001	0.4058	0.001

To see the parameter dependency of the proposed measures, Figure 5 shows t_{iso} and t_{max} for various ε and t_0. SIQ_{iso}, t_{iso} and t_{max} are the plots of all 19 rats according to ε and t_0 and $\Delta_s(t)$ is the plot of the rat #3 or #10. As shown in Figure 5, $\Delta_s(t)$ is not so sensitive to ε and t_0 for a certain range of the parameters. For t_{iso} and t_{max}, the values keep steady for each rat.

The proposed measures and conventional μ_{SIQ} were analyzed with respect to NDS through two bivariate statistical methods. Pearson correlation coefficients were used to assess the joint relationship between the measures and NDS. A higher correlation was observed between the proposed measures and NDS than between μ_{SIQ} and NDS. Hypothesis testing was then conducted to determine the significance of the measures as a predictor of NDS using Student's *t*-test ($n = 19$). Our findings from these results reveal that the proposed measures are useful in predicting long-term NDS. The findings are apparent when either metric is plotted against NDS, as shown in Figure 6, where there is a more discernible linear relation between the proposed measures and NDS. Analogous measures can also be applied to show changes in entropy when the EEG assumes a normal or quasi-normal character later when bursting and volatile EEG can no longer characterize the animal's recovery.

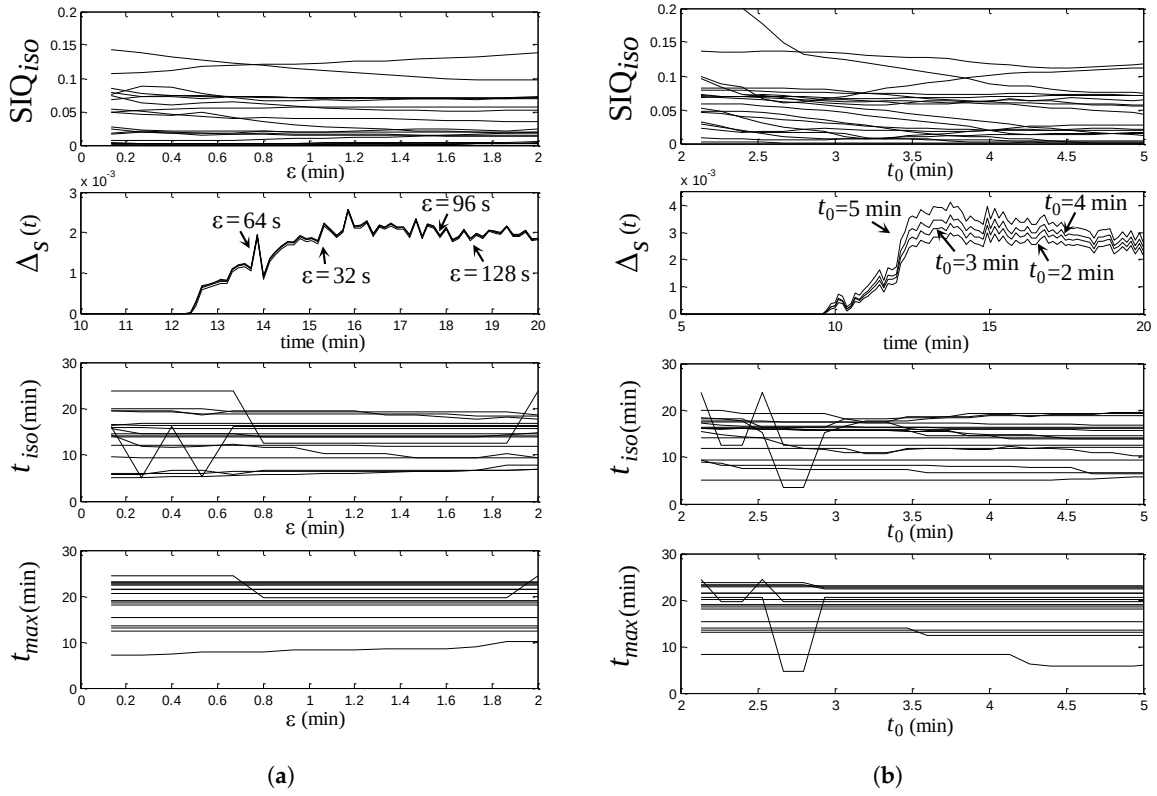

Figure 5. t_{iso} and t_{max} according to ε and t_0. (**a**) variation of ε (**b**) variation of t_0.

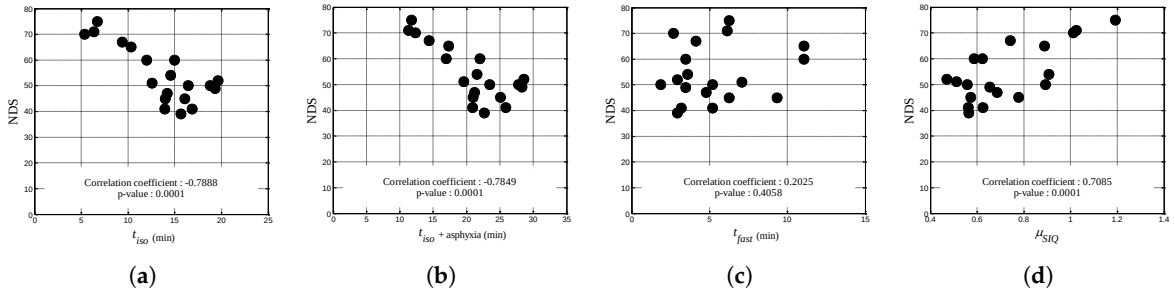

Figure 6. Correlation coefficients of various measures with NDS. (**a**) t_{iso} vs. NDS (**b**) (t_{iso}+asphyxia) vs. NDS (**c**) t_{fast} vs. NDS; and (**d**) μ_{SIQ} vs. NDS.

5. Conclusions

We proposed qEEG measures to predict long-term brain recovery by exploiting three distinct phases of qEEG time evolution including isoelectric, fast progression, and slow progression. Critical time points where the phase transition occurs were calculated. The proposed measures, t_{iso} and t_{fast}, are the duration of the isoelectric phase and the duration of the fast progression, after CPR respectively. While the proposed measures are correlated with the neurological recovery, they do not need the baseline EEG recording before CA injury and they can also be calculated with 20∼30 min EEG data.

We believe that the newly developed measures can be applied to the qEEG analysis of neurological injury and recovery and can also be combined with conventional measures for a more thorough prediction of brain recovery. Although the proposed measures do not need the baseline EEG signals, the time information of CA and CPR are needed. This might be a limitation in clinical application and

remains to be studied. Also, in case of sudden CA patients, EEG may not be available just after CPR and the isoelectric or transition phases of EEG could not be detected. Unless these phases return or persist in some ways over post arrest, then the clinically utility of the proposed measures would be limited. Related to this, further work needs to be done to see if these phases occur at a later time point.

Future work will involve the use of these measures with different drug interventions that enable an animal's arousal. We will also chart the restoration of separate subband activities through t_{iso} and t_{fast}. This will enable a finer discrimination of good vs. poor outcome for animals.

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Conflicts of Interest: The authors declare no conflict of interest.

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