Combined nonlinear metrics to evaluate spontaneous EEG recordings from chronic spinal cord injury in a rat model: a pilot study

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Abstract Spinal cord injury (SCI) is a high-cost disability and may cause permanent loss of movement and sensation below the injury location. The chance of cure in human after SCI is extremely limited. Instead, neural regeneration could have been seen in animals after SCI, and such regeneration could be retarded by blocking neural plasticity pathways, showing the importance of neural plasticity in functional recovery. As an indicator of nonlinear dynamics in the brain, sample entropy was used here in combination with detrended fluctuation analysis (DFA) and Kolmogorov complexity to quantify functional plasticity changes in spontaneous EEG recordings of rats before and after SCI. The results showed that the sample entropy values were decreased at the first day following injury then gradually increased during recovery. DFA and Kolmogorov complexity results were in consistent with sample entropy, showing the complexity of the EEG time series was lost after injury and partially regained in 1 week. The tendency to regain complexity is in line with the observation of behavioral rehabilitation. A critical time point was found during the recovery process after SCI. Our preliminary results suggested that the combined use of these nonlinear dynamical metrics could provide a quantitative and predictive way to assess the change of neural plasticity in a spinal cord injury rat model.

Keywords Spinal cord injury (SCI) · Sample entropy · Nonlinear · Complex system · Firing pattern · EEG

Introduction

A spinal cord injury (SCI) often causes permanent changes to patients with loss in motor control, sensation and other body functions below the damage site. Clinicians face huge challenges to manage the loss of neural functions in patients with SCI (Burns and O'Connell 2012; Eng et al. 2007). Unfortunately, there is little evidence to provide strong support for successful neural regeneration following spinal cord injury in human. Disruption of motor and sensory afferents caused by SCI often results in significant neuroanatomical changes in the brain (Hou et al. 2014). Recent findings indicate that these changes in the brain may be closely related to the recovering process of sensorimotor functions in SCI patients (Freund et al. 2013). Therefore, deeper understanding and monitoring of structural and functional changes undergoing in the brain may shed new light on SCI treatment.

Interestingly, recovery of locomotor function after spinal cord injury could be seen in animals. It prompts that the neural plasticity would play a major role in functional recovery after spinal cord injury in animals (Edgerton and Roy 2009; Jurkiewicz et al. 2007; Schwab 2002). In human, it has been already reported that complex cortical functional reorganizations could be identified in spinal cord injured patients, which indicates that ongoing cortical plasticity is also the key to successful rehabilitation in human subjects (Zhou et al. 2014). Therefore, neural plasticity is expected to be a promising approach to help the recovery of neurological loss (Dietz 2006; Edgerton and Roy 2009). However, how neural plasticity changes after SCI is still unclear and needs further investigations.

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To address this issue, previous studies have used EEG and multiple spatial–temporal methods to evaluate the changes in neural plasticity, their results indicate that frequencies and amplitudes of EEG signals acquired from somatosensory cortex are changing significantly while the cortex is undergoing functional reorganization after SCI (Nardone et al. 2013). However, due to the complex nature of the brain, mere changes happened during early functional recovery are hard to be identified (Bullmore and Sporns 2012; Koch and Laurent 1999; Tononi et al. 1994). Therefore, it is still unclear what is going on during early recovery process which is rather important for clinical treatment. Similar situations are likewise in other electrophysiological fields. To solve this problem, researchers have introduced entropies and other nonlinear complex metrics which are good at unveiling hidden characteristics of physiological processes that are hard to be identified using traditional waveform/frequency metrics (Gosseries et al. 2011; Linkenkaer-Hansen et al. 2001; Pincus 1991; Toutounji and Pipa 2014).

With the hypothesis that nonlinear dynamical metrics may help to reveal mere changes in neural firing patterns during early recovery, here we propose a pilot study to monitor the brain activity in spinal cord injured rats using EEG technology, and evaluate the complex changes in neural plasticity by using nonlinear dynamical analysis. To extract dynamical features and to assess the degree of complexity of the EEG time series, sample entropy (SampEn), detrended fluctuation analysis (DFA), and Kolmogorov complexity (KC) are applied here as indicators to quantitatively measure the neural plasticity changes following spinal cord injury in rats.

Materials and methods

Animals

Fifteen Wistar rats (weight: 270–285 g) were used in this study. All experimental procedures were approved by the Research Ethics Committee of the Authors' institutes. To produce chronic compression, a trained spine surgeon performed the operations under microscopy using an established surgical protocol for implantation of water-absorbing materials (Hu et al. 2011; Pu et al. 2016; Long et al. 2013). During the surgery, the water-absorbing polymer was then carefully inserted into the upper side of the rat spinal canal at the C5 level. This polymer can absorb liquid in the spinal canal to expand its volume seven-fold in 2 h and remain at the maximal volume for 6 months. Thereafter, it could produce a chronic course of compression on the cervical spinal cord in the rat. After implantation, the incision site was closed by layers and the

animals were allowed back to the cage until fully recovering from the surgery on a heating bed.

EEG recordings and dataset size

The cortical EEG was recorded from the forelimb region of the rat primary somatosensory cortex via skull screws. The signal was amplified 100,000 times with band-pass filtering between 1 and 100 Hz. All EEG signals were acquired with a sampling rate of 50,000 Hz, then downsampled to 1000 Hz. Each recording session was 400 s, and we recorded the signals of each rat at day 0 (the day before the surgery), day 1–7. Therefore, there were 15 datasets from 15 rats. In each dataset, there were eight recordings (Day 0–7). In each session, there were 400,000 data points. All the following signal processing programs were developed in the MATLAB environment (version 8.0, Mathworks, MA, USA) using a Dell Precision Workstation with Intel Xeon platform (4 cores, 3.2 GHz, 16 Gbytes RAM).

Data analysis

Band filtering and data pre-processing were performed using EEGLAB (Delorme and Makeig 2004). Sample entropy and detrended fluctuation analysis were performed using PhysioToolkit (Goldberger et al. 2000). Kolmogorov complexity was also calculated in MATLAB using the algorithm described in (Kaspar and Schuster 1987). Statistical analysis was performed using one-way ANOVA (MATLAB built-in command `anova1.m`, power calculation was performed using `sampsizepwr.m`). Spearman rank correlation analysis between the specific nonlinear metric (e.g. sample entropy, DFA, Kolmogorov complexity) and the BBB score at each day was calculated using MATLAB built-in command (`corr.m`).

Behavior analysis

Motor dysfunction due to spinal cord compression was evaluated using the Basso Beattie Bresnahan (BBB) score (Scheff et al. 2002). The BBB scores were evaluated each day before the EEG recording session.

Results

Spontaneous EEG signals from 15 Wistar rats were recorded before and after injury. Figure 1 shows the example original EEG recordings of rats 1 and 2. The original EEG recordings contained 2×10^7 data points in the time span of 400 s. In two rats, the EEG recordings at Day 0 generally shows less fluctuations than Day 1, 3, 5, and 7.

Fig. 1 Spontaneous EEG recordings of Rat 1 and 2 at Day 0–7. The recording time span is 400 s

Then, we evaluated the sample entropy of the spontaneous EEG recordings. The EEG data were first down-sampled to 1000 Hz and filtered using a 1–100 Hz bandpass filter. Figure 2 shows the sample entropy of EEG recordings at Day 0–7 from left/right side of primary somatosensory cortex region respectively. The results show that the sample entropy decreased immediately after injury, then gradually increased during the following week.

Fig. 2 Sample entropy of spontaneous EEG recordings of Wistar rats (*left/right* side of primary somatosensory cortex region). * $p < 0.01$, one-way ANOVA, the red color emphasizes the comparison between day 2 and 3. (Color figure online)

Generally, an increasing tendency could be found from Day 1–7, fluctuations were found in the data. At Day 3, a significant increase in the entropy value could be identified. ($p < 0.01$, one-way ANOVA). Similar tendency could be found on both sides of brain regions.

In order to study the fluctuations in spontaneous EEG recordings and assess the correlation properties of the data, we performed detrended fluctuation analysis (DFA) on EEG time series. Figure 3 shows the results of DFA scaling exponent. After injury, a clear increase was observed. The scaling exponent increased around 0.5 at Day 1, then dropped back fast at Day 2 and 3. After Day 3, the scaling exponent gradually decreased to the range of 0.3–0.35. Similar tendency could be found on both sides of brain regions. Compared with sample entropy results, a similar significant change could be found between Day 2 and 3 ($p < 0.01$, one-way ANOVA).

To investigate the complexity nature of EEG signals before and after injury, the time series of EEG recordings were assessed by Kolmogorov method. Kolmogorov complexity index results were shown in Fig. 4. The injured spinal cord caused a sharp drop in Kolmogorov complexity index at Day 1, then gradually increased afterwards. Interestingly, in this result, we also found a significant change between Day 2 and 3 on both sides ($p < 0.01$, one-way ANOVA).

BBB scores were used to evaluate the level of motor dysfunction of injured rats. From Day 1–7, the BBB scores kept increasing after injury (Fig. 5). To study the sequence of locomotor recovery patterns, BBB scores can be evaluated into three phases: early (0–7), intermediate (8–13) and late phases (14–21) of recovery. In our results, we can see the early and intermediate phase of recovery after injury. Interestingly, there were significant differences between Day 3 and 4, Day 5 and 6, Day 6 and 7. The BBB

Fig. 3 The scaling exponent result from detrended fluctuation analysis (DFA) of spontaneous EEG recordings of Wistar rats (*left/right* side of primary somatosensory cortex region). $*p < 0.01$, one-way ANOVA, the *red color* emphasizes the comparison between day 2 and 3. (Color figure online)

Fig. 4 The result from Kolmogorov complexity assessment of spontaneous EEG recordings of Wistar rats (*left/right* side of primary somatosensory cortex region). $*p < 0.01$, one-way ANOVA, the *red color* emphasizes the comparison between Day 2 and 3. (Color figure online)

Fig. 5 The Basso Beattie Bresnahan (BBB) scores for locomotor recovery assessment Wistar rats. $*p < 0.01$, one-way ANOVA, the *red color* emphasizes the comparison between Day 3 and 4. (Color figure online)

scores of rats at Day 4, 6 and 7 were notably higher than at Day 3, 5 and 6, respectively.

We performed correlation analysis between BBB scores and various nonlinear dynamical metrics. Table 1 shows the correlation coefficients and corresponding p values between BBB scores and nonlinear dynamic metrics by Spearman's rank correlation.

Discussion and conclusions

The objective of this pilot study is to investigate whether and how the nonlinear dynamics is changed after chronic spinal cord injury in a rat model. In the present study, we have recorded the EEG spontaneous activity from somatosensory region of 15 Wistar rats, analyzed the electrical recordings with nonlinear dynamics measurements: sample entropy, DFA scaling exponent and Kolmogorov complexity index, and explored the correlation

Table 1 The correlation between BBB and nonlinear dynamical metrics

Metrics	SampEn left	SampEn right	DFA left	DFA right	KC left	KC right
BBB versus	0.70	0.74	−0.76	−0.72	0.62	0.59
<i>p</i> value	0.02	0.08	0.07	0.03	0.08	0.04

between behavioral BBB evaluation and these nonlinear indices. Sample entropy, Kolmogorov complexity index and DFA scaling exponent provide insights of firing patterns in the EEG recording. In our preliminary results, it is suggested that these nonlinear metrics could be used as a convenient way to quantify the dynamics of neural functional recovery after chronic injury to the spinal cord.

SCI could cause severe deficits of sensory and motor functions. There is increasing evidence from animal models that structural and functional changes took place in sensorimotor areas of the brain after spinal cord injury (Freund et al. 2011; Hains et al. 2003; Jurkiewicz et al. 2006, 2007). To investigate these changes, EEG signals provides a useful way to quickly evaluate specific brain functions by analyzing EEG data acquired from selected cortical regions. In previous studies, quantifying nonlinear dynamics in the temporal pattern of the EEG signal gives more insights into the characteristics and behavior of the underlying neural plasticity processes and mechanisms (Capano et al. 2015; Escudero et al. 2015; Pu et al. 2013; Stepp et al. 2015). In the information aspect, entropy is a measure of unpredictability of time series, and has been widely used, improved and proven valid in quantification of a variety of physiological data (Ahmed and Mandic 2011; Liang et al. 2015; Richman and Moorman 2000). As an embedding entropy metric, sample entropy provides a generalized and improved metric for assessing complexity and irregularity in EEG time series. In the context of sample entropy, the complexity is reflected by the probability distributions of averaged uncertainty. Lower values of sample entropy indicate more self-similarity in data set, while increasing values correspond to intuitively increasing process complexity. In our results, though it is hard to tell the differences directly from the recording EEG waveforms of different days (Fig. 1), the curve of sample entropy values shows a clear drop after injury at Day 1 (the first day after SCI) (Fig. 2), which could be explained by the fact that the complex brain dynamics was disrupted and became less complex after the afferent pathways had been retarded by chronic injury. Interestingly, the recovery tendency of sample entropy shows close correlation with BBB scores. At the second day after SCI, sample entropy stayed at the lowest level and then gradually increased to the level of normal status as the value before injury. Meanwhile, the BBB score were also gradually returned during recovery process. These results from rats are consistent with the hypothesis in earlier clinical research that healthy neural

systems are more complex than abnormal neural systems. For example, AD (Alzheimer's disease) patients generally had significantly lower sample entropy values in the background EEG recordings than normal people (Abásolo et al. 2006), which suggests that brains affected by AD showed a more regular and less complex dynamical behavior in parts of regions. Previously, sample entropy has been applied to analyze heart rate data from spinal cord injury patients (Serra-Añó et al. 2014). To our knowledge, few studies have explored SCI-related changes by applying sample entropy to EEG data. The present study proved that sample entropy have the potential to be a dynamical marker to quantify functional plasticity changes in spontaneous EEG recordings of rats before and after SCI.

When researchers apply nonlinear metrics, they usually use more than one metric to get the whole picture of data because that each method has its own pros and cons. As sample entropy cannot capture all details of neurodynamics, detrended fluctuation analysis (DFA) was applied to the same data. DFA is a method for determining the statistical self-affinity of a time series, it is widely used to evaluate the degree of complexity of electrophysiological signals by detecting long range correlations embedded in a nonstationary time series (Lee et al. 2004, 2007). DFA needs longer data length, but is good at analyze fluctuations from local trends, therefore it can avoid artifacts from apparent long range correlations (Cirugeda-Roldan et al. 2014). When interpreting DFA results, DFA exponent = 0.5 means the time series is uncorrelated with itself, <0.5 means anti-correlated, and >0.5 means correlated. In our results, the DFA scaling exponent values were below 0.5 at the majority of time. Before injury, the exponent was smaller than 0.3, indicating long-range negative correlation in signal fluctuations. In contrast to sample entropy, we found a climb-up (closed to 0.5) in the DFA exponent values after injury at Day 1, indicating the absence of long-range correlations. Afterwards, DFA dropped back from Day 2–7 while the sample entropy increased. In the present study, the results from sample entropy and detrended fluctuation analysis were consistent, indicating not only the loss of complexity due to SCI, but also the restoring of complexity during the recovery process of motor ability after SCI.

Our initial hypothesis is further supported by the result of Kolmogorov complexity evaluation. Kolmogorov complexity is conceptually different from entropy measures, as it measures the amount of information by description length (size) (Teixeira et al. 2011). In recent years,

Kolmogorov complexity has been widely used in biomedical applications to estimate the temporal complexity of neurophysiological time series (Gao and Hu 2011; Gao et al. 2013; Ibáñez-Molina et al. 2015; Xiong et al. 2013). A time series with complex temporal patterns tends to have a large value of Kolmogorov complexity. In the present study, the index of Kolmogorov complexity reached the lowest point between Day 1 and 2, which shows a latency or less sensitive than previous two metrics which immediately changed at Day 1 after SCI. But the later changes which showed gradual restoring of complexity were still in consistency with sample entropy, DFA and BBB scores. All of three nonlinear metrics show similar implications in complexity theory: (1) The complexity of the rat neural system dropped immediately after SCI. (2) The complexity could restore gradually during the recovery process. Accordingly, the motor ability of rats was at the worst level immediately after SCI and then gradually recovered from Day 1–7 showing that they were regaining the motor ability. As previous findings have suggested that neural system at normal and healthy state will be more complex than at abnormal state, e.g. epilepsy and aging, these results further support our hypothesis that the loss and recovery of complexity due to SCI can be reflected and quantitatively assessed by the combined use of nonlinear dynamical metrics.

Interestingly, we also found that the changing of three dynamical metrics may have some critical point during the recovery after SCI. There were significant changes between Day 2 and 3 in sample entropy, DFA, and Kolmogorov complexity index. For sample entropy and Kolmogorov complexity index, the values climbed up rapidly from Day 2 to 3. For DFA scaling exponent, the tendency changed from steep decreasing to a gentler manner. These results could suggest that there may be a critical time point between Day 2 and 3 in rats. In this period, critical transitions may occur in the dynamical system. To test this hypothesis, we first thought we could also find a critical point between Day 2 and 3 in the BBB scores. Then we found an interesting latency that the expected significant difference was seen between Day 3 and 4 which was approximately a day later. These results may indicate that the dynamical metrics could somehow predict the behavioral change in motor ability 1 day earlier. Although the present study is based on SCI in rats, the underlying dynamical mechanisms are transferable to clinical applications in human. The changes in Day 1 and 2 after SCI in rat can be interpreted as the early stage of acute SCI in human. Therefore, this study proved that sample entropy as well as other dynamical metrics may have the potential to be a marker of neural plasticity for early and timely interventions after SCI, as well as an objective and quantitative evaluation of the recovery process of SCI in clinical practice.

Some limitations of our present study merit consideration. Here, the combination of sample entropy, DFA scaling exponent, and Kolmogorov complexity index show potential use as an index of spinal cord injury rehabilitation, but caution should be applied due to the preliminary nature of the present study. As seeing is believing, a combined fMRI data set will further support our hypothesis by showing how functional connectivity changes inside and between the brain and the spinal cord after the injury incident. Most importantly, similar studies should be conducted in human subjects for directly clinical implications.

In summary, the nonlinear and complexity metrics and the combined use of them on spontaneous EEG data could provide a quantitative and predictive measure for analyzing the neural plasticity changes of the brain after chronic spinal cord injury in rats. Our preliminary results demonstrate the potential dynamical approach to evaluate neural plastic changes in a rat model of chronic spinal cord injury.

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