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Abnormal EEG Complexity and Alpha Oscillation of Resting State in Chronic Stroke Patients*

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***Abstract*— A valid evaluation of neurological functions after stroke may improve clinical decision-making. The aim of this study was to compare the performance of EEG-related indexes in differentiating stroke patients from control participants, and to investigate pathological EEG changes after chronic stroke. 20 stroke and 13 healthy participants were recruited, and spontaneous EEG signals were recorded during the resting state. EEG rhythms and complexity were calculated based on Fast Fourier Transform and the fuzzy approximate entropy (fApEn) algorithm. The results showed a significant difference of alpha rhythm (p = 0.019) and fApEn (p = 0.003) of EEG signals from brain area among ipsilesional, contralesion hemisphere of stroke patients and corresponding brain hemisphere of healthy participants. EEG fApEn had the best classification accuracy (84.85%), sensitivity (85.00%), and specificity (84.62%) among these EEG-related indexes. Our study provides a potential method to evaluate alterations in the properties of the injured brain, which help us to understand neurological change in chronic strokes.**

I. Introduction

Stroke is a leading cause of death and acquired disability in adults. Globally, 15 million people suffer from stroke every year and 5 million are left with permanently disability [1]. Stroke survivors have significantly lower performance for mental, physical, and self-rated health [2]. Intensive therapeutic interventions can help them regain their lost motor functions and facilitate their return to society, especially during chronic stage in which spontaneous recovery getting slow. Before therapeutic interventions are selected for patients after stroke, a comprehensive understanding of the neurological deficiencies in post-stroke patients will be useful for designing appropriate recovery strategies and can optimize the effectiveness of rehabilitation training. Among different neuroimaging technologies, surface Electroencephalography (EEG) is a non-invasive technology with excellent temporal resolution, low cost and no real safety restrictions. It directly measures abnormal voltage fluctuations within the impaired brain. It is widely used to diagnose cerebral dysfunctions and brain degenerative diseases. E.g. Finnigan et al. identified the slow EEG activity (delta/alpha ratio) which can most accurately discriminate between ischemic stroke patients and controls [3]. Borich et al. evaluated interhemispheric cortical connectivity between the primary motor cortices in chronic stroke patients and controls using simultaneous EEG, and found significantly increased TMS-evoked beta (15–30 Hz) imaginary phase in the stroke group [4].

Many linear signal processing methods as mentioned above have been applied in brain signal analysis and made achievements in disease diagnosing and monitoring. However, the human brain is a complex nonlinear system. Nonlinear dynamic approaches provide novel insights into brain diseases and could be a useful tool to understand the mechanisms of neuronal degeneration after injury. E.g., point correlation dimension was used for the analysis of EEG recorded in patients with unilateral stroke caused by middle cerebral artery occlusion [5]. Fuzzy approximate entropy (fApEn) was applied to monitor the motor function improvement during robot-aided rehabilitation training [6]. However, few studies have been done on evaluating and comparing the performance of these EEG indexes as bio-makers for reflecting neurological change in chronic stroke. In this study, linear and non-linear EEG-related indexes (EEG oscillation, EEG complexity) were compared between chronic stroke and healthy controls to investigate pathological changes in EEG after stroke.

II. Materials and Methods

A. Participants

Twenty stroke patients (three females and 17 males; aged 54.2 years ± 9.17) with a single unilateral brain lesion with onset at least 6 months before data collection and 13 healthy subjects (four females and nine males; aged 33.1 ± 6.60 years) were recruited for this study. The inclusion criteria of stroke subjects include (1) Sufficient cognition to follow simple instruction and understand the purpose of the experiment (MMSE>21); (2) Hemiparesis resulting from unilateral brain lesion with time since stroke more than six months before study enrolment. (3) The moderate motor function of upper limb (FMA- UL>10 and FMA-UL<50). The exclusion criteria include (1) visual field deficits. All the subjects gave their written informed consent according to the Declaration of Helsinki. Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CUHK-NTEC CREC) approved the experimental protocol (agreement #2014.705-T). This study was also registered at www.clinicaltrials.gov with study identifier NCT02323061.

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B. EEG acquisition and processing

EEG signals were referenced to a unilateral earlobe, grounded at frontal position (Fpz), and sampled at 256 Hz using a g.USBamp (g.Tec Medical Engineering GmbH, Austria) system with 16 active electrodes (g.LADYbird). The 10–20 system of electrode placement was used with electrodes placed at C3, C4, FC3, FC4, CP3, CP4, FC1, FC2, C1, C2, CP1, CP2, C5, C6, FCz, and Cz. The impedance for all electrodes were kept below 5 kΩ which was measured by passing a small current between electrodes and measuring the opposition to the flow of this current. The EEG was recorded in the resting condition with eyes open naturally in a dark sheltering room for 3 minutes, participant can blink if needed. Participant fixed his eyes at a certain position to prevent ocular contamination in EEG due to large eyeball movement. EEG signals were also online band-pass filtered from 2 to 60 Hz and notch filtered between 48-52 Hz to remove artefacts and power line interference. 30 seconds data without apparent artefacts (such as blinks, EMG, and visible drift) were selected manually from each patient's EEG recording and exported into MATLAB (The MathWorks, Natick, MA, USA) for further analysis. For offline analysis, EEG was compared from FC3, FC4, C3, C4, CP3, and CP4 between stroke patients and healthy subjects. FC-i, C-i, and CP-i were defined as FC3/FC4, C3/C4, and CP3/CP4 at the ipsilesional hemisphere while FC-c, C-c, and CP-c were defined as FC3/FC4, C3/C4, and CP3/CP4 at the contralateral hemisphere in stroke patients. FC-d, C-d, and CP-d were defined as FC3/FC4, C3/C4, and CP3/CP4 at the dominant hemisphere in stroke patients. EEG rhythms and complexity were extracted for comparison of healthy subjects and stroke patients at ipsilesional and contralateral hemispheres.

EEG rhythms

EEG rhythms have been widely used to discriminate the resting brain states of Alzheimer's, epilepsy, and mild cognitive impairment patients from those of healthy individuals [7]. In this study, four EEG rhythms (delta, theta, alpha, and beta) were compared among healthy subjects at the dominant hemisphere, and stroke patients at the ipsilesional and contralateral hemispheres. Fast Fourier Transformation (sliding windows of 2 s with 50% overlap) was used to calculate EEG frequency spectrum for the following EEG bands: delta (1 - 4 Hz), theta (4 - 8 Hz), alpha (8 - 13 Hz), and beta (13 - 30 Hz). Some of the sites that were related to motor function were used for offline analyses (left hemisphere: FC3, C3, and CP3; right hemisphere: FC4, C4, and CP4). The FC3/FC4 lay over the pre-motor cortex and the C3/C4 lay over the primary motor cortex. CP3/CP4 corresponded to the supramarginal gyrus that is part of the somatosensory association cortex.

EEG complexity

EEG complexity has been used to assess Alzheimer's disease and schizophrenia. It may reflect the condition of neuronal death, loss of synaptic connections, and the general effects of neurotransmitter deficiency [8, 9]. In this study, EEG complexity was calculated by a robust entropy-based algorithm, fApEn. Compared with other complexity algorithms for bio-signals (approximate entropy and sample-entropy), fApEn exhibits robust consistency due to its vector similarity decision rules. This study adopted the fApEn algorithm described in a previous study [6, 10-12]. To compute the fApEn of an N sample series $\{u(i): 1 \le i \le N\}$, a vector of length m could be derived from the time series:

$$X_i^m = \{u(i), \cdots, u(i+m-1)\} - \frac{1}{m}\sum_{j=0}^{m-1} u(i+j) \quad (1)$$

Where $\frac{1}{m}\sum_{j=0}^{m-1} u(i+j)$ was the baseline of the vector. The distance d_{ij}^m between X_i^m and X_j^m was defined as:

$$d_{ij}^m = \max_{k\in(0,m-1)} |w(i+k) - w_0(i) - u(j+k) + u_0(j)| \quad (2)$$

A fuzzy function $D_{ij}^m(n,r)$ was formulated to calculate the similarity degree of the two vectors X_i^m and X_j^m. where n and r were two parameters that determined the width and gradient of the boundary of the exponential function, respectively:

$$D_{ij}^m(n,r) = \exp\left(-(d_{ij}^m/r)^n\right) \quad (3)$$

The function ϕ^m then aggregated the similarity from any vector in the time series to another as follows:

$$\phi^m(n,r) = \frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m-1}\sum_{j=1,j\neq i}^{N-m} D_{ij}^m\right) \quad (4)$$

Finally, $fApEn(m,n,r,N)$ was estimated using the algorithm of the difference between the function of the length $m+1$ and m.

$$fApEn(m,n,r,N) = ln\phi^m(n,r) - ln\phi^{m+1}(n,r) \quad (5)$$

C. Statistical analysis

Statistical analysis was performed using the IBM SPSS 22 software (SPSS Inc., Chicago, Illinois, USA). For EEG rhythms (delta, theta, alpha, and beta oscillations) and EEG complexity (fApEn), repeated-measures analysis of variance (ANOVA), with group (stroke ipsilesional-hemisphere vs. healthy dominant-hemisphere and stroke contralateral hemisphere vs. healthy dominant-hemisphere) as between-subject factor and electrode (FC-i, C-i, CP-i; FC-c, C-c, CP-c; FC-d, C-d, CP-d) as within-subject factor was performed to test for group differences. The Greenhouse-Geisser adjustment was applied to the degrees of freedom for all analyses if the Mauchly's test of sphericity was significant. One-way ANOVA was also used to analyze the difference in each electrode/electrode pair if between-subject factor showed a significant effect in repeated-measures ANOVA. The significance level for all statistical analyses was set at $p < 0.05$.

III. RESULTS

A. EEG rhythms in healthy and stroke subjects

Fig. 1A depicts the comparison of alpha rhythm between stroke patents at the ipsilesional and contralateral hemispheres, and healthy subjects at the dominant hemisphere. For the electrodes at the ipsilesional hemisphere (FC-i, C-i, and CP-i), there was a significant difference between electrodes, ($F(1.208, 37.446) = 6.113$, $p = 0.014$). Furthermore, there was a significant difference between the groups ($F(1, 31) = 6.086$, $p = 0.019$). For the electrodes at the contralateral hemisphere (FC-c, C-c, and CP-c), there was no significant difference either between electrodes or between groups ($p > 0.05$). The results of one-way ANOVA revealed a significant difference between groups on electrodes FC-i ($p = 0.020$), C-i ($p = 0.027$), and CP-i ($p = 0.022$). Fig. 1B shows the scatter diagram of

stroke patients at the ipsilesional hemisphere and healthy subjects at the dominant hemisphere for alpha rhythm of the three electrodes. Linear Discriminate Analysis (LDA) was used to reduce the dimension of Fig. 1B from three-dimensional space to two-dimensional space as in Fig. 1C. A linear classifier was generated based on the datasets of two groups and LDA. Fig. 1D shows the distribution of reduced dimension datasets of the two groups, the green curve and yellow curve depict the normal distribution fitting of dataset for healthy subjects at the dominant hemisphere and stroke patients at the ipsilesional hemisphere, respectively. The classification accuracy of alpha rhythm in differentiating stroke patients from heathy participants was 69.70%. No significant difference between stroke patients and healthy subjects were observed in the EEG oscillations of delta, theta and beta (all ps > 0.05).

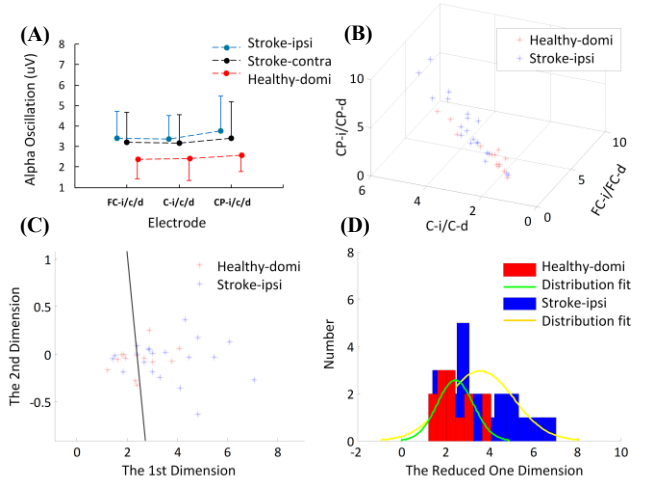

Figure 1. The performance of EEG alpha oscillation in differentiating stroke patients from healthy participants. **(A)** Comparison of alpha oscillation between stroke patients at ipsilesional and contralateral hemisphere, and healthy subjects at dominant hemisphere. **(B)** Scatter diagram of alpha oscillation in stroke-ipsilesional hemisphere and healthy-dominant hemisphere. **(C)** Linear Discriminant Analysis was used to reduce the dimension of Fig. 1B from three-dimensional space to two-dimensional space. **(D)** The distribution of dimensional reduced alpha oscillation of the healthy and stroke group; blue and yellow curve depicts normal distribution fitting of healthy and stroke groups.

B. EEG complexity in the two groups

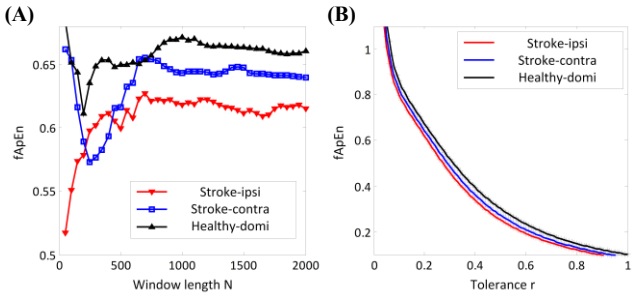

Figure 2. Change of EEG fApEn with increase of window N, and tolerance r in the ipsilesional (red line) and contralesional (blue line) brain hemisphere of a stroke patient and dominant hemisphere (black line) of a healthy subject.

Fig. 2A depicts the fApEn of the EEG with the window N increasing from 50 points to 2000 points in steps of 40 points. The EEG signal was collected on C-i and C-c from a stroke patient and C-d from a healthy subject. Fig. 2B depicts the fApEn of the same EEG with the tolerance window increased from 0.01 to 1.0 in steps of 0.01. There were only a few crossovers between the three curves when N was less than 600. No crossover was evident in the changes in the fApEn curve with r that reflected the excellent relative consistency of fApEn in short physiological signals. Combining the results of a previous study with those of the present study, N was set at 1000, and r was fixed at 0.2 [3].

Fig. 3A depicts the performance of fApEn in identifying EEG signals from stroke patients in the ipsilesional and contralateral hemispheres, and healthy subjects in the dominant hemisphere. There was no significant interaction between the group and electrode ($F(3.277, 100.036) = 1.318$, $p = 0.272$). However, there was a significant difference between healthy and stroke groups ($F(1, 31) = 10.212$, $p = 0.003$). One-way ANOVA was used to compare the difference of fApEn in each electrode. The results revealed a significant difference in FC-i ($p = 0.002$), FC-c ($p = 0.042$), C-i ($p = 0.006$), C-c ($p = 0.04$), and CP-c ($p = 0.005$). There was no significant difference in CP-i ($p = 0.11$) between the two groups. In Fig. 3B, fApEn of EEG from the three electrodes was applied to plot the scatter diagram of stroke patients at the ipsilesional hemisphere (blue points) and healthy subjects at the dominant hemisphere (red points). The dimension of the scatter diagram was reduced by LDA from 3-D to 2-D (Fig. 3C). The points from the two groups could be well separated. Fig. 3D shows the distribution of reduced dimension datasets of the stroke and healthy groups. The green and yellow curves mark the normal distribution fitting for the datasets of healthy and stroke subjects, respectively. EEG fApEn has good performance for differentiating stroke patients from healthy subjects, with a classification accuracy of 84.85%.

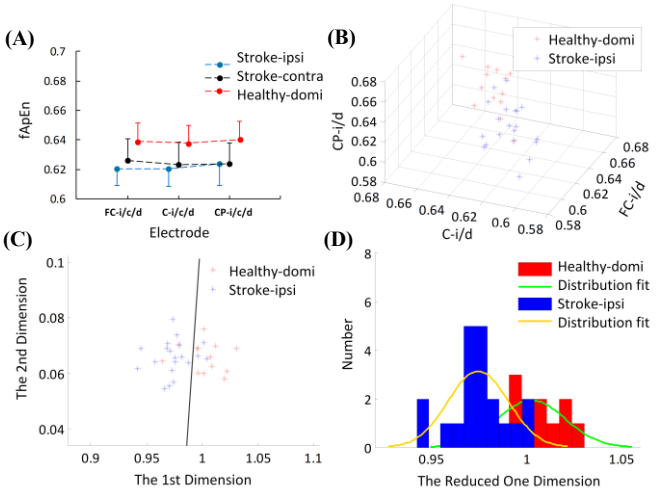

Figure 3. (A) Comparison of EEG fApEn between stroke patients at ipsilesional and contralateral hemisphere, and healthy subjects at dominant hemisphere. **(B)** Scatter diagram of EEG fApEn in stroke-ipsilesional hemisphere and healthy-dominant hemisphere. **(C)** Linear Discriminant Analysis was applied to project EEG fApEn into two-dimensional space. **(D)** The distribution and normal distribution fitting of dimensional reduced EEG fApEn of the healthy and stroke group.

IV. Discussion

Stroke-induced neuron death and changes in neural pathways affect electrophysiological signals generated from

the brain. This study investigated the changes in EEG rhythms and complexity induced by chronic stroke and the EEG index's performance in distinguishing stroke patients from healthy participants. Alpha rhythm and EEG complexity showed significant differences between stroke patients in ipsilesional hemisphere and healthy subjects in dominant hemisphere (ps < 0.05). These two indexes, especially EEG complexity, demonstrated significant discrimination ability (accuracy of 65.70% on alpha rhythm and 84.85% on EEG complexity).

A. Abnormal EEG Alpha rhythm in chronic stroke patients

In this study, stroke patients had significantly higher alpha rhythm in both ipsilesional and contralateral hemispheres. There was no significant difference in beta, delta, and theta rhythms between healthy subjects and stroke patients in both hemispheres. Numerous studies have investigated abnormal EEG rhythms in Alzheimer's disease [13], autism spectrum disorder [14], and depression [15]. Generally, these studies reported that alpha rhythm plays an important role in distinguishing patients from healthy subjects, which is similar to the results of this study. Research on stroke-related abnormalities in EEG rhythms is relatively few. Stepien et al. reported decreased ERD of alpha oscillations for the affected pericentral sensorimotor areas in acute cortical strokes compared to those of a control group [16]. In addition, within the cortical stroke group, the ipsilesional hemisphere showed a smaller alpha-ERD compared to that of the contralateral hemisphere. In contrast, EEG signals were acquired in the resting state in this study reflect the spontaneous brain state, and the stroke patients recruited in this study were all in the chronic phase. Nevertheless, our results agree with those of previous studies. Besides, it worth to note that although alpha rhythm was significantly different between stroke and healthy participants, it had poor performance on discriminating stroke patients from healthy participants, with a classification accuracy of 64.70%.

B. Abnormal EEG complexity in chronic stroke patients

fApEn, as a robust measure of signal complexity, has been applied for analyzing bio-signals, including EEG [17], EMG [6], and ECG [18]. For fApEn calculation, there are three important parameters: N, r, and m. N refers to the length of input data. A too small N value may not be sufficient for robust estimation, while too large N value may import signals without event-related information, which reduces its effectiveness in identifying the disease. Cao et al. selected N as 800 in EEG fApEn to identify Alzheimer's disease [8]. In Fig. 2A, fApEn curve varied abruptly when N was less than 600 while it trended to become stable when N was more than 600. Combined with the selection of N in previous studies and testing results in this study, N was set as 1000. For the tolerance, r, $0.1 < r < 0.25$ is recommended in many studies [6, 8, 10, 17, 18]. A series of earlier studies applied either local or global tolerance r [19]. For the resting state applied in this study, EEG amplitudes varied little over time, suggesting that the local tolerance scheme should be more suitable for static situations in this study. m refers to template length. m was 2 in this study, which is the typical choice consistently used in majority of the literature. This was also recommended by Pincus and Goldberger for approximate entropy [20] and by Yentes et al. for sample entropy [21].

For all EEG-related indexes discussed in this paper, EEG complexity generated the best performance for distinguishing stroke patients from healthy subjects with a classification accuracy of 84.85%. The EEG fApEn was significantly lower in stroke patients than healthy subjects. Entropy-related algorithms measure the amount of information produced by a stochastic source of data. Thus, the loss of entropy in EEG may be attributed to neuronal death, loss of synaptic connections, and the general effects of neurotransmitter deficiency [17]. These results also highlight the possibility that fApEn could be used as a novel evaluation tool to facilitate the evaluation of brain disorders by quantifying the complexity of brain signals.

C. Limitations and future directions

A larger sample size of chronic stroke patients should be recruited to further confirm the clinical relevance of alpha oscillation and EEG fApEn. After method validation, a user-friendly interface and easy-to-use instructions will be required to facilitate its application in the clinic.

V. CONCLUSION

In this study, EEG alpha oscillation and fApEn were significantly different between stroke patients and healthy participants (ps < 0.05). In these participants, EEG fApEn had the best performance (accuracy: 84.85%) on differentiating stroke patients from healthy participants. This study not only compared the existing measurements of neurological changes caused by stroke, but also provided a potential method to evaluate alterations in the properties of the injured brain, which may be useful for designing intervention plans in stroke rehabilitation.

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