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Influence of Subcortical Ischemic Stroke on Cortical Neural Network

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***Abstract*—Stroke has remained as a leading cause of death and neurological disability worldwide in the past decades. Previous structural and functional studies reported little information regarding cortical neural network after stroke. Using the causality measure based on multi-channel electroencephalograph (EEG), i.e. partial directed coherence (PDC) in this paper, we investigated the different network patterns involved in pre-motor and parietal areas (F3, F4, C3, C4, P3 and P4) in three groups of patients who suffered unilateral or bilateral hemispheric stroke in basal ganglia with extension into corona radiate. Compared with the results in the control group, stroke patients showed: 1) more vulnerable long-distance intra- and inter-hemispheric interactions due to the ischemic injury; 2) strengthened short-distance interactions between the central areas in the intact hemisphere with the injured counterpart, which implied a functional compensation after unilateral stroke; 3) more suppression of cortical connections after bilateral hemispheric stroke than those with unilateral stroke. Causal interdependence by PDC analysis provides a new insight of cortical functional network following stroke.**

I. Introduction

STROKE has remained as a leading cause of death and neurological disability worldwide in the past decades. In the United States, approximate 780,000 onsets of strokes occurred with an economic burden of $65.5 billion in 2008 [1]. About 50% of the patients above 65 years old suffered hemiparesis, 46% had cognitive deficits, 19% had aphasia, and 35% had depressive symptoms six months after the ischemic stroke [2][3]. Since ischemic injury accounts for 87% of all strokes, and 85% of them occur in unilateral hemisphere, most clinical stroke studies focus the impacts on relevant brain areas after stroke.

Previous studies have shown that EEG provides abundant physiological information following stroke in the lesion site in the aspects of location, grade of damage, and physiological recovery [4][5][6]. Quantitative electroencephalography (qEEG) measures of delta (1-4Hz) power and delta/alpha ratio (DAR) have been shown to be relevant to the site of ischemic lesion, and effective in predicting the recovery of stroke as well [4][7][8]. Van Putten proposed to use brain symmetry index (BSI) to quantify the ischemic damage [5][9], which was also relevant to clinical acute ischemic hemispheric stroke. Furthermore, effectiveness of nonlinear analysis by complexity characteristic and detrended fluctuation analysis (DFA) was also reported by several studies on subcortical strokes [4][10].

By far, most researchers have focused on analyzing the EEG at isolated cortical areas without consideration of the spatiotemporal interactions between different cortical regions. Nevertheless, neural system has been considered to work with the interactive cortical networks. Therefore, investigating the cortical neural network could offer new insights into the functional change and plasticity following ischemic stroke [11]. It was reported that anomalies in the brain, e.g. Alzheimer's disease (AD) [12][13], could thus result in disorder of functional connectivity and network connections. Our hypothesis is that the interaction between different regions of the brain, or the cortical neural network should accordingly be re-organized due to the lesion of ischemic injury. For example, studies of hemispheric stroke by coherence analysis of scalp EEG signals indicated the compensation effect from the intact hemisphere [14][15], although the causality of such coherence was still not clear.

In past years, bivariate and multivariate analysis, e.g. cross correlation [16], coherence [17], mutual information[18], partial directed coherence(PDC) [19], directed transfer function and etc. [20], have been successfully implemented to analyze the interactions between two cortical areas or the cortical interactive networks. Compared with other methods, PDC analysis provides both the directionality and strength of the cortical interactions [19][21], which will be useful in characterizing cortical neural network involved in stroke and its recovery.

This present study will include our preliminary clinical results based on the data from patients with unilateral or bilateral subcortical ischemic stroke.

II. Materials and Methods

A. Subjects

We collected the data from a total of 37 right handed patients admitted to the neurology department of The Fifth People's Hospital of Shanghai. Details of the subjects are listed in Table 1. All patients were diagnosed with hemispheric ischemic stroke in basal ganglia with extension into corona radiate according to the assessment by MRI/CT. The lesion sites were left-hemispheric (n=12),

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right-hemispheric (n=13), and bilateral-hemispheric (n=12). No one had reported a history of epilepsy. CT/MRI and EEG examinations were performed within three days after the symptom onset. In order to compare the results with that of normal subjects, we also recruited healthy control subjects with matched gender and age (n=12). All control subjects had reported no history of neurological or psychological diseases.

TABLE 1: SUBJECTS SUMMARY

Group	Left Hemispheric Injury(n=12)	Right Hemispheric Injury(n=13)	Bilateral Hemispheric Injury(n=12)	Normal (n=12)
Age(yrs)	59-85	59-84	56-80	56-80
Mean ± SD	77±6.9	70±8.9	72±8.5	64±7.3
Male/Female	5/7	8/5	7/5	7/5

B. EEG Recordings

The EEG activities at 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, O1, O2, T5 and T6) were recorded with monopolar electrodes placed in accordance to the international 10-20 system referred to linked earlobes. EEG signals were amplified, filtered and digitalized by a 12-bit A/D EEG system (Sunray LQWY-N, Guangzhou, China) with sampling frequency of 100Hz. The subjects were seated in relaxation in an acoustically and electrically shielded chamber, keeping awake with eye closed throughout the experiment for 10 min. The experimental protocols were approved by the ethic committee of The Fifth People's Hospital of Shanghai.

C. PDC Method

As a frequency-domain representation of Granger causality [22], PDC analysis effectively describes the direction of interdependency among different cortical regions in pair [19][23]. Firstly, the multi-channel EEG signals are modeled with multivariate autoregressive model (MVAR). Let vector X(t) denotes N-channel EEGs (N=6 in this study) at time t,

$$X(t) = [x_1(t), x_2(t), \ldots, x_N(t)]^{'} \quad (1)$$

in which $x_n(t)$ (n=1, 2,…, N) stands for the *n*th channel EEG signal.

*p*th-order MVAR model is established as:

$$X(n) = \sum_{r=1}^{p} A(r)X(n-r) + W(n) \quad (2)$$

where A(r) (r=1, 2,...,p) is N×N coefficient matrix and W(n) is an uncorrelated white Gaussian noise. And the coefficient a_{ij}(r) in matrix A represents the contribution of the past *j*th channel x_j(n-r) to the current *i*th channel x_i. If all a_{ij}(r) (0<r≤p) are equal or close to zero, x_j does not have a direct causal interaction with x_i. Akaike's information criterion (AIC) is applied to estimate the appropriate order *p*.

Let $\overline{A}(f)$ denote the transfer function:

$$\overline{A}(f) = I - A(f) = [\overline{a}_1, \overline{a}_2, ..., \overline{a}_N] \quad (3)$$

Where $A(f) = \sum_{r=1}^{p} A(r)e^{-i2\pi fr}$ (4)

Let $\overline{a}_{ij}$ be an element of $\overline{A}(f)$, therefore, PDC at frequency f from *j*th channel to *i*th channel is defined as [23]:

$$PDC_{j\to i}(f) \stackrel{\Delta}{=} \left|\overline{a}_{ij}(f)\right| / \sqrt{\overline{a}_j(f)^H \overline{a}_j(f)} \quad (5)$$

Several existing criteria have been used to judge the significant level of such coherence [21][23]. In this study, we used the spectral causality criterion (SCC) introduced by Schnider et al. (1989). No directional information flow from *j*th to *i*th channel could be concluded if PDC (*i, j, f*) value is under a threshold of 0.1.

D. Data analysis

All EEG data were detrended for further MVAR modeling. We selected 5s representative epochs of the EEG from each subject and analyzed it with PDC after obtaining the MVAR model. The average PDC value over frequency range of 1-30Hz was used to analyze the strength and direction of the interactions. According to the coherence analysis results by Wheaton and colleagues, parietofrontal areas were supposed to be significantly involved in stroke [14]. Therefore, in this study the neural networks within pre-motor and parietal areas, i.e. six loci (F3, F4, C3, C4, P3 and P4), were analyzed with PDC.

III. STATISTICAL RESULTS

The cortical interactions in the aspects of PDC were calculated for each electrode pair. According to the cortical regions for these electrodes, the interactions can be analyzed in four types: intra-left hemispheric (LL), intra-right hemispheric (RR), left-to-right inter-hemispheric (LR), and right-to-left inter-hemispheric (RL) interactions.

In order to demonstrate cortical interdependence in frontal and parietal areas, causal networks with significant interactions (mean PDC>0.20 are highlighted) [24] were designated in Fig.1, with arrows indicating the causality. Two tailed student's t-tests were adopted to check the significance of the differences between stroke group and control group. We have some interesting findings by comparing the PDC for the normal controls with that for stroke subjects (PDC: normal vs stroke).

The left hemispheric injured group (Fig.1 (b)) indicated some significant lower or higher in aspect of average PDC values in four types of cortical interactions: i) LL interaction (P3→F3: 0.21 vs 0.19) was significantly suppressed; ii) No significant changes were found in RR interactions; iii) Two LR inter-hemispheric interactions (F3→C4: 0.19 vs 0.14; F3 →P4: 0.21 vs 0.14) were significantly suppressed, whereas C3 → C4 (0.18 vs 0.21) was enhanced; iv) Three RL inter-hemispheric interactions (F4→P3: 0.20 vs 0.14; P4→C3: 0.21 vs 0.15; P4 → P3: 0.22 vs 0.16) were significantly suppressed, whereas C4→F3 (0.17 vs 0.27) was significantly enhanced after the left- side ischemic injury. The results revealed left side injury clearly affected the intra-left hemispheric parietofrontal interactions, inter-hemispheric interactions, and the centrofrontal interactions as well.

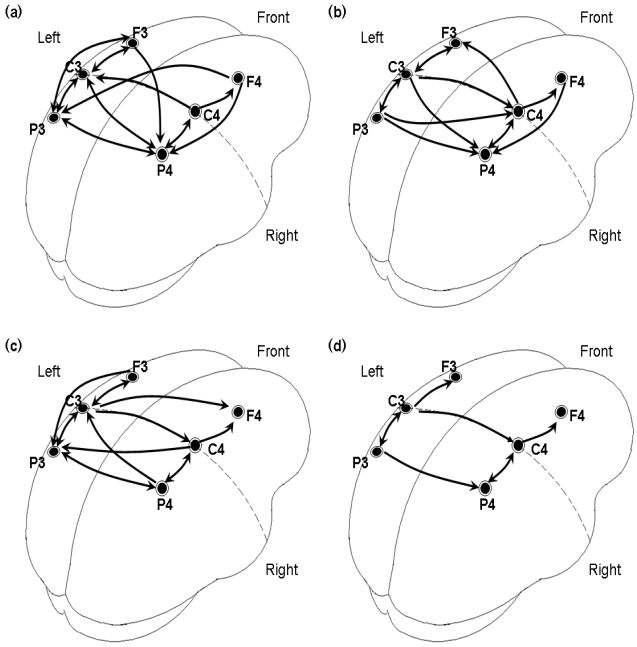

Fig.1: Different cortical neural network patterns in (a) normal controls, (b) left hemispheric stroke, (c) right hemispheric stroke and (d) bilateral hemispheric stroke

The cortical neural network pattern in the right hemispheric injury group was similar to that in left hemispheric injury group. However, compared with left hemispheric group, Fig.1(c) shows an opposite direction of the interdependence especially in the inter-hemispheric connection. The right-hemispheric injury group indicated the following significant changes in four types after stroke: i) No significant changes were found in LL interactions; ii) Two RR hemispheric interaction (F4→P4: 0.21 vs 0.17; C4→P4: 0.28 vs 0.21) were significantly suppressed; iii) LR inter-hemispheric interactions (F3→P4: 0.21 vs 0.17) was significantly suppressed , whereas (C3→F4: 0.15 vs 0.21) was significantly enhanced; iv) RL inter-hemispheric interactions (F4→P3: 0.21 vs 0.17) was significantly suppressed after the right-side ischemic injury. Less inter-hemispheric interactions were affected under right-hemispheric stroke injury compared to left-hemispheric stroke.

In accordance with the MRI examination, the bilateral stroke group presented a new pattern of neural interactive network with a wider cortical depression (Fig.1 (d)). For example, i) LL (F3→C3: 0.23 vs 0.19; P3→F3: 0.21 vs 0.19) and RR hemispheric interactions (C4→P4: 0.28 vs 0.21; F4 →P4: 0.21 vs 0.18) were significantly suppressed; ii) LR inter-hemispheric interaction (F3→P4: 0.21 vs 0.19) was significantly suppressed; iii) Three RL inter-hemispheric interactions (F4→P3: 0.20 vs 0.16; P4→C3: 0.21 vs 0.16; P4 → P3: 0.22 vs 0.17) were also suppressed. iv) The significantly strengthened interactions within the centrofrontal areas in unilateral stroke groups were not observed under bilateral ischemic stroke group, even though the interaction of C3→C4 was significant (PDC>0.20) in bilateral injury. The corresponding PDC value was comparable to that for controls.

In particular, all subjects were shown with similarly active centrofrontal and centroparietal connections.

IV. Discussion

In this paper, we investigated cortical interactive networks following three kinds of ischemic injury, i.e. left-hemispheric, right-hemispheric and bilateral-hemispheric stroke, respectively. MVAR based PDC analysis offered a new insight of the cortical functional network change after focal ischemic brain injury.

Previous studies by Molnar and colleagues showed apparent lower-dimensional complexity in the ipsilateral region after ischemic damage [4][25][26]. Besides, by conventional qEEG analysis methods, the decrease of alpha power, increase of both slow wave (delta and theta) and DAR were observed at the sites with ischemic lesion [7]. Nevertheless, these results merely reflected a characteristic of decline in neuronal survival and a trend towards pathophysiology in lesion site [27], but the intra- and inter-hemispheric functional interaction were still unknown.

In this study, we found that the focal injury, regardless of the left or right hemisphere, affected not only its own intra-hemispheric connections but also some inter-hemispheric long-distance interactions such as F3→P4 and F4→P3, which is similar to the predominant loss of long-distance cortical functional connections in patients with mild traumatic brain injury (MTBI) or Alzheimer's disease (AD) [13][28]. Besides, no significant effect was found on the intact hemisphere after the focal unilateral stroke. Therefore, we speculate that the long-distance cortical connections be more vulnerable.

In spite of the loss of functional intra- and inter-hemispheric connection after ischemic brain injury, the short-distance interactions with central cortex (C3 or C4) in the intact hemisphere were clearly strengthened after a contralateral hemispheric subcortical stroke, e.g. C3→C4, C4→F3, and C3 →F4. These inter-hemispheric interactions between central cortex (C3/C4) and the frontal area might imply alternative pathways for functional compensation. Our results are in line with that by the MRI study [29]and coherence analysis [14][15], which showed the intact hemisphere might play a compensation role in the functional rehabilitation following brain injury. Such a compensation effect in short-distance connectivity was also found following MTBI [28]. The insignificant change of cortical connections within the intact hemisphere might be attributed to the short-term injury (<3days in this study), however, Wheaton and Serrien reported significant increase of coherence in the intact hemisphere of the patients with hemispheric injury (3 months or more) during an ipsilateral motor task [14][15], which might indicate that the inter-hemispheric compensation was the ground for later recovery.

The bilateral ischemic stroke evidently caused more loss of inter- and intra-hemispheric interactions than the unilateral injury, and no significant compensation effect was found either, which implied that the functional recovery be more difficult for the patients with bilateral injury. The central cortex, which kept the similar short-distance connections with surrounding pre-motor and parietal area under three kinds of injury, can be concluded as a less affected area. It might be possibly due to its particular anatomical structure away from the lesion site, which is still unclear.

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