

# The Time-varying Networks of the Wrist Extension in Post-stroke Hemiplegic Patients

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## Research

**Keywords:** Stroke, motor dysfunction, time-varying networks, wrist extension, ipsilateral compensatory

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22 adaptive directed transfer function to investigate the dynamic motor networks in  
23 post-stroke hemiplegic patients. The corresponding time-varying networks of the  
24 wrist extension in post-stroke hemiplegic patients were constructed and then  
25 statistically explored.

26 **Results:** The results demonstrated that the effective connectivity between the stroked  
27 motor area and other areas decreased. In contrast, connectivity between non-stroked  
28 motor area and other areas was enhanced, especially the frontal and parietal-occipital  
29 lobes, to compensate for the dysfunction of the motor behaviors of the stroked  
30 patients.

31 **Conclusions:** These findings help us better understand the time-varying networks  
32 underlying the implementation of the motor behaviors of the patients with post-stroke  
33 hemiplegia and might provide a reliable biomarker to predict their future  
34 rehabilitation.

35 **Keywords:** Stroke, motor dysfunction, time-varying networks, wrist extension,  
36 ipsilateral compensatory

37

38

### 39 **Background**

40 Stroke, also known as cerebrovascular accident, is a disease of brain damage caused  
41 by the sudden burst of cerebral blood vessels or the block of blood vessels, including  
42 hemorrhagic and ischemic stroke. Stroke has high morbidity, disability, and mortality

43 rates, and 40% of stroke survivors still live with various disabilities. After a stroke,  
44 multiple functions are seriously impaired, and the most common one is post-stroke  
45 contralateral limb hemiplegia [1]. Such a wrist or upper limb dysfunction usually lasts  
46 a lifetime. Wrist extension is an essential part of hand touching object movement.  
47 Severe wrist paralysis is still a considerable challenge in clinical practice, which  
48 impacts the patients with their activities of daily living functions and the quality of  
49 life.

50 Symptoms of post-stroke limb disorders depend on the location of the brain in the  
51 left or right hemisphere. The stroke of the dominant left hemisphere may behave  
52 communication disorder and the paralysis of the right hand and foot. While lesions in  
53 the right hemisphere might lead to the impairment of perception (visual impairment)  
54 and the paralysis of the left hand and foot. Compared with the right hemisphere stroke,  
55 the dysfunction caused by the left hemisphere stroke is usually easier to be identified  
56 and diagnosed on time. In this study, we mainly took middle-aged and older people as  
57 the subjects to investigate the differences in time-varying network architectures  
58 between patients with unilateral stroke and the control group during wrist extension.

59 Currently, the studies focusing on the brain network mechanism of the post-stroke  
60 motor dysfunction have depended mainly on functional magnetic resonance imaging  
61 (fMRI). The implementations of the motor behaviors in healthy controls (HCs) are  
62 usually achieved by simultaneous activation of multiple motor-related brain regions,  
63 including supplementary motor area (SMA), sensorimotor area, primary motor area,

64 prefrontal lobe, and bilateral dorsal anterior motor area, etc. [2, 3]. The changes in the  
65 ipsilateral motor cortex of the stroked hemisphere are usually more complicated for  
66 post-stroke hemiplegic patients. For example, after analyzing the changes in the  
67 functional connectivity of bilateral primary motor areas, Li et al. found the decreased  
68 functional connectivity in stroke patients [4]. Zhao et al. used independent component  
69 analysis to explore related functional networks of stroked patients and found  
70 connectivity within and between motor-related networks were both abnormal,  
71 especially the decline in the dorsal attention network and the overcompensation of the  
72 executive control network [5]. Moreover, the increased activation of frontal and  
73 parietal regions and motor areas in stroke patients has also been found to be  
74 associated with the motor behaviors, as well as those non-motor areas such as the  
75 occipital lobe [6-8].

76 Concerning the electrophysiological characteristic, the brain activity in the  
77 sensorimotor rhythm of the 8 - 30 Hz has been widely studied, and the  
78 electroencephalogram (EEG) is thus usually used to investigate the sensorimotor  
79 rhythm related to the motor behaviors, as well as its application in stroke [9].  
80 However, recent studies have mainly concentrated on EEG oscillation related to the  
81 movement and the lateralization of the movement-related potential and the  
82 event-related desynchronization for stroke patients and HCs [10, 11], but less  
83 attention has been put on the dynamic network modalities related to the movements  
84 concerning the post-stroke hemiplegic patients.

85       The brain is a complex network, and the completion of motor execution is  
86 completed by the interaction of multiple brain regions. Stroke patients also include  
87 multiple motor and non-motor related brain regions to achieve limb movement [12].  
88 The investigation of the dynamic networks during motor execution helps understand  
89 the motor dysfunction in stroke patients. Considering the EEG has a relatively high  
90 time resolution, we can further explore the dynamic interactions among different brain  
91 regions in milliseconds. The adaptive directed transfer function (ADTF) [13] has been  
92 widely used to calculate the effective connectivity in milliseconds. It facilitates the  
93 construction of the time-varying networks on each time point, which thus provides the  
94 opportunity to estimate the directed flows among concerned brain regions and to  
95 capture the dynamic transition related to the movement effectively. For example,  
96 based on the ATDF, Li et al. have demonstrated the distinct information processing  
97 stages related to the P300 [14] and the motor imagery [15], as well.

98       To better investigate the differences in dynamic network architectures between  
99 the stroke patients and HCs during the motor execution, in our present study, we  
100 applied the ADTF in three subject groups, i.e., HCs, post-stroke hemiplegic of the left  
101 arm (PL), and post-stroke hemiplegic of the right arm (PR), to construct their  
102 time-varying networks related to the wrist extension. Thereafter, the potential  
103 differences concerning the three groups were further investigated from the perspective  
104 of the dynamic network topology and property to better understand the motor  
105 dysfunction that occurred in post-stroke hemiplegic patients.

106

107 **Methods**

108 Participants

109 The study protocol was approved by the ethics committee of the First Affiliated  
110 Hospital of Sun Yat-sen University. Twenty-seven participants were recruited in the  
111 present study, which included 9 PL patients (7 males, age  $56.1 \pm 10.7$  years), 7 PR  
112 patients (6 males, age  $55.7 \pm 8.8$  years), and 11 HCs (5 males, age  $52.8 \pm 7.6$  years).

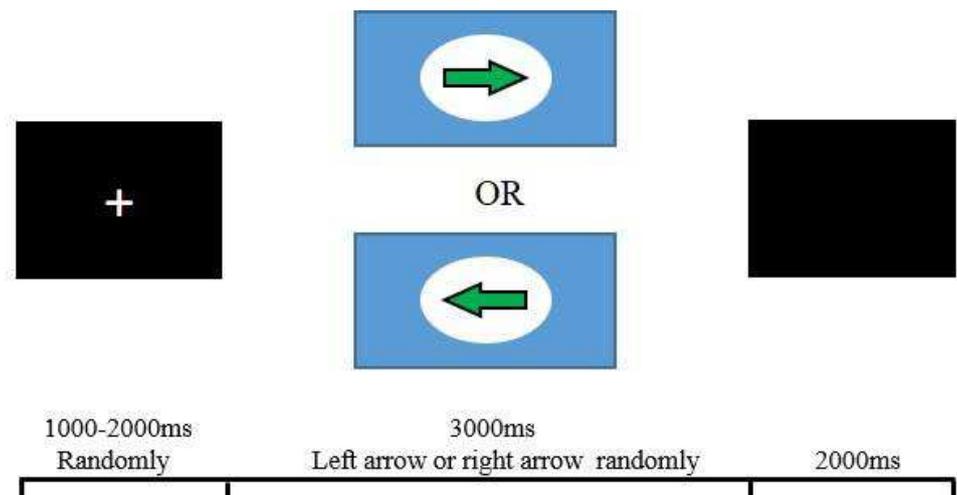
113 All participants were informed of the study protocol, along with the signed informed  
114 consent forms. Meanwhile, all subjects were self-recognized as right-handed and  
115 confirmed by the Edinburgh Handedness Inventory.

116

117 Experimental procedure

118 E-prime (Psychology Software Tools, Inc, USA) was used to present the visual  
119 directions or cues in the study. The paradigm of the Instruction Response Movement  
120 (IRM) was adopted to present a solid arrow picture pointing either to the left or the  
121 right (regarded as "GO" signals in this study). Accordingly, the subjects were  
122 requested to perform left or right wrist extension. In each IRM trial (Fig. 1), a white  
123 cross in the center of a black screen serves as an attention point, which lasted for a  
124 duration ranging from 1000 ms to 2000 ms randomly. The left or right "GO" signal  
125 then appeared randomly at the screen for a duration of 3000 ms, and the subject  
126 started to perform the required motion once for each trial when they noticed the

127 presence of the "GO" signal, which included 40 trials for each side movement. After  
128 finishing the movement, subjects rested their arms on the table, and a black screen  
129 lasting for 2000 ms was presented for a short rest. Before starting to record the EEG,  
130 subjects would also practice the required movement for 1 min to 2 mins to get  
131 familiar with our experiments.



132

133

**Fig. 1.** The experimental procedures and the timeline of a task trial.

134

135 EEG recording

136 All of the experiments were conducted in a shielded room, which provided the

137 insulation from electromagnetic signals and background noise distractions. A

138 BrainAmp 32-channel amplifier from Brain Products (Munich, Germany) was used to

139 record EEG. All of the 32 Ag/AgCl electrodes were placed according to the 10–20

140 international system. The online digital sampling rate is 1000 Hz, and electrodes FCz

141 and AFz were used as the reference and ground, respectively. Electrooculogram (EOG)

142 was measured by two extra electrodes, one above the middle point of the right brow to

143 record the EOG vertically, and the other was placed 2 cm aside from the outer corner  
144 of the right eye to record the EOG horizontally. To guarantee reliable data quality,  
145 throughout the experiment, the impedance for all electrodes was kept below 5 k $\Omega$ .

146

#### 147 EEG data analysis

148 In this study, the recorded EEG was first pre-processed to acquire the artifact-free  
149 trials and then used to construct the corresponding time-varying effective connectivity  
150 networks, which was carried out using MATLAB v2014a (The MathWorks Inc.,  
151 Natick, MA). The details were further depicted in the following sections.

152

#### 153 EEG data pre-processing

154 The EEG was first band-pass filtered with a frequency range of [1, 30] Hz, and based  
155 on the independent component analysis (ICA), the ocular was then corrected  
156 semi-automatically. Thereafter, the EEG was re-referenced to a neutral reference of  
157 the Reference Electrode Standardization Technique (REST) [16, 17]. Meanwhile,  
158 multiple procedures consisting of [-1, 000 2, 000] ms range (0 ms corresponds to the  
159 stimulus onsets) data segmentation, [-1, 000 -800] ms baseline correction, and artifact  
160 removal (using a threshold of  $\pm 75$   $\mu$ V) were also included, and the researchers further  
161 visually inspected the remaining trials to exclude those still contain residual artifacts.  
162 Afterwards, 24 canonical electrodes (i.e., Fp1/2, Fz/3/4/7/8, FC1/2, T7/8, Cz/3/4,  
163 CP1/2, Pz/3/4/7/8, and Oz/1/2) were used in the following analysis.

164

165 Power spectral density

166 For each subject, the power spectral density (PSD) of each electrode was first  
167 estimated using the pWelch at  $\alpha$  (8 - 13) and  $\beta$  (13 - 30 Hz). When exploring the  
168 group differences, the PSD of the PL, PR, and HC groups were statistically compared  
169 by using the non-parametric Wilcoxon rank-sum test, whose  $p$ -values were then  
170 multiply corrected by the false discovery rate (FDR) under a significance level of 0.05  
171 ( $p < 0.05$ ).

172

173 Time-varying network

174 To unveil the dynamic network pattern underlying the required motion, the ADTF [13]  
175 was used to construct corresponding time-varying networks of this motion, which  
176 were further statistically compared to identify the group-wise differences of dynamic  
177 network patterns between PL, PR, and HC groups. In specific, for each subject, the  
178 remaining artifact-free trials were down-sampled to 100 Hz, resulting in the 10 ms  
179 interval between two neighboring sample points, and based on the trial-by-trial ADTF,  
180 the time-varying networks were then constructed.

181

182 *1) Time-varying Multivariate Adaptive Autoregressive (tv-MVAAR) Model*

183 For each trial time series, the tv-MVAAR model was defined and then calculated with  
184 the following equation,

185 
$$X(t) = \sum_{i=1}^p A(i,t)X(t-i) + E(t) \quad (1)$$

186 where  $X(t)$  denotes the artifact-free EEG vector at time point  $t$ ,  $A(i,t)$  denotes the  
 187 matrix of the tv-MVAAR model coefficients estimated by the Kalman filter algorithm  
 188 [18],  $E(t)$  is the multivariate independent white noise, and  $p$  is the optimal model  
 189 order automatically determined by the Akaike Information Criterion [19],

190 
$$AIC(P) = \ln[\det(\Sigma)] + 2M^2P / N \quad (2)$$

191 where  $M$  is the number of EEG channels,  $P$  is the estimated tv-MVAAR model order,  
 192  $N$  is the time point, and  $\Sigma$  is the covariance matrix. The observation and state  
 193 equations were then solved by the recursive least squares algorithm with the  
 194 forgetting factor [20].

195

196 *2) Adaptive Directed Transfer Function*

197 After acquiring the time-varying tv-MVAAR model coefficient  $A(i,t)$ , its  
 198 transformation in the frequency domain,  $H(f,t)$ , would also be obtained, and the  $H_{ij}$   
 199 element of  $H(f,t)$  represents the directed information flow from the  $j$ -th to the  $i$ -th  
 200 element for each time point  $t$  at frequency  $f$ . And accordingly, Eq. (1) is then further  
 201 transfer to the frequency domain as

202 
$$A(f,t)X(f,t) = E(f,t) \quad (3)$$

203 
$$X(f,t) = A^{-1}(f,t)E(f,t) = H(f,t)E(f,t) \quad (4)$$

204 where  $A(f,t) = \sum_{k=0}^p A_k e^{-j2\pi f \Delta t k}$  with  $A_k$  being the matrix of the tv-MVAAR model

205 coefficients, and  $X(f,t)$  and  $E(f,t)$  are the transformations of  $X(t)$  and  $E(t)$  in the  
 206 frequency domain, respectively.

207 The normalized ADTF, which describes the directed information flow from the  
 208  $j$ -th node to the  $i$ -th node at frequency  $f$  and time  $t$ , is defined with a range of  $[0, 1]$  as,

$$209 \quad \gamma_{ij}^2(f,t) = \frac{|H_{ij}(f,t)|^2}{\sum_{m=1}^n |H_{im}(f,t)|^2} \quad (5)$$

210 And the integrated ADTF is finally defined as the average of the normalized  
 211 ADTF over the interested band  $[f_1, f_2]$  at time  $t$ , which was defined in a frequency  
 212 range of  $[8, 30]$  Hz in our present study.

$$213 \quad \Theta_{ij}^2(t) = \frac{\sum_{k=f_1}^{f_2} \gamma_{ij}^2(k,t)}{f_2 - f_1} \quad (6)$$

214 After acquiring the ADTF adjacency matrix for each artifact-free motion trial, the  
 215 trial-average of the ADTF matrices was obtained to define the final time-varying  
 216 networks for each subject. When exploring the group-wise differences, the  
 217 time-varying weighted networks of the PL, PR, and HC groups were first binarily  
 218 thresholded into the time-varying binary networks with a connectivity cost of 5% to  
 219 illustrate the intrinsic network architectures and were also statistically compared by  
 220 using the non-parametric Wilcoxon rank-sum test whose  $p$ -values were also multiply  
 221 corrected by FDR ( $p < 0.05$ ).

222

223 Network properties

224 Based on graph theory, the time-varying global efficiency ( $GE$ ) was calculated by  
225 using the brain connectivity toolbox (BCT, <http://www.nitrc.org/projects/bct/>) [21],  
226 which were still based on the constructed time-varying weighted networks. The  $GE$   
227 describes the ability of the time-varying networks to process information.

$$228 \quad GE = \frac{1}{n} \sum_{i \in \Psi} \frac{\sum_{j \in \Psi, j \neq i} \left( \sum_{a_{ij} \in g_{i \rightarrow j}} a_{ij} \right)^{-1}}{n-1} \quad (7)$$

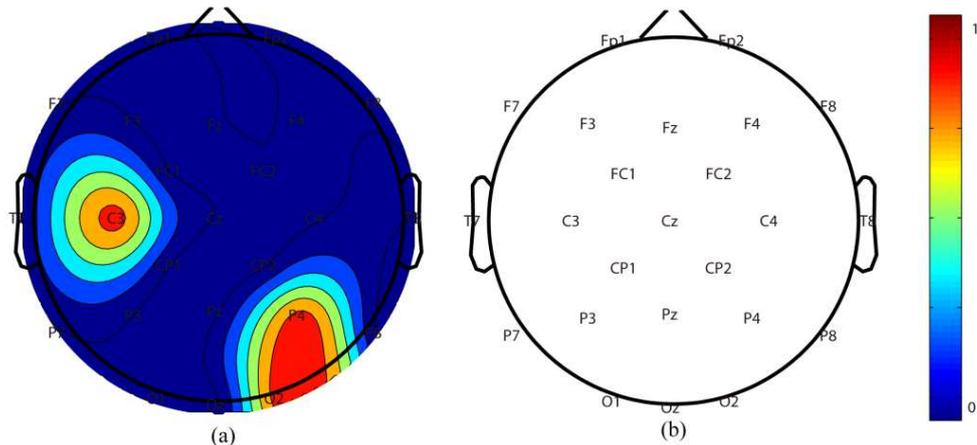
229 where  $n$  denotes the node number,  $\Psi$  denotes the set of all network nodes,  $a_{ij}$  denotes  
230 the estimated ADF connectivity strength and  $g_{i \rightarrow j}$  denotes the weighted directed  
231 shortest path from nodes  $i$ -th to  $j$ -th.

232

## 233 Results

### 234 PSD

235 The PSD of the three groups in 8 - 30 Hz was obtained, and as illustrated in Fig. 2, the  
236 electrodes whose statistical  $p$ -values passed the test were marked out. The scalp  
237 topographies exhibiting stronger PSD for the PL subjects were found to locate at the  
238 parietal and occipital areas compared to HC subjects when executing the left-hand  
239 wrist movement (Fig. 2a,  $p < 0.05$ ), while no differences were revealed between PR  
240 and HC groups when performing the right-hand wrist extension (Fig. 2b,  $p > 0.05$ ).



241

242 **Fig. 2.** Scalp PSD topographies in 8 - 30 Hz. (a) Between PL and HC groups and (b)

243 Between PR and HC groups. The regions printed with deep red color denote the PSD

244 of the PL/PR group is significantly greater than the HC group, and the blue denotes

245 the opposite.

246

247 Differential time-varying network patterns

248 To investigate the time-varying patterns of brain networks in HC, PL, and PR groups

249 during wrist extension, the effective connectivity at each time point was averaged

250 across subjects and then sparsed with 5% sparseness (i.e., the connection edge with

251 the strongest weight remaining 5%) to display the transient network topology. As

252 displayed in Fig. 3, for the HC subjects (Fig. 3a), the electrodes C3 or C4 served as

253 the crucial hub to control the right or left-hand wrist extension at first, which then

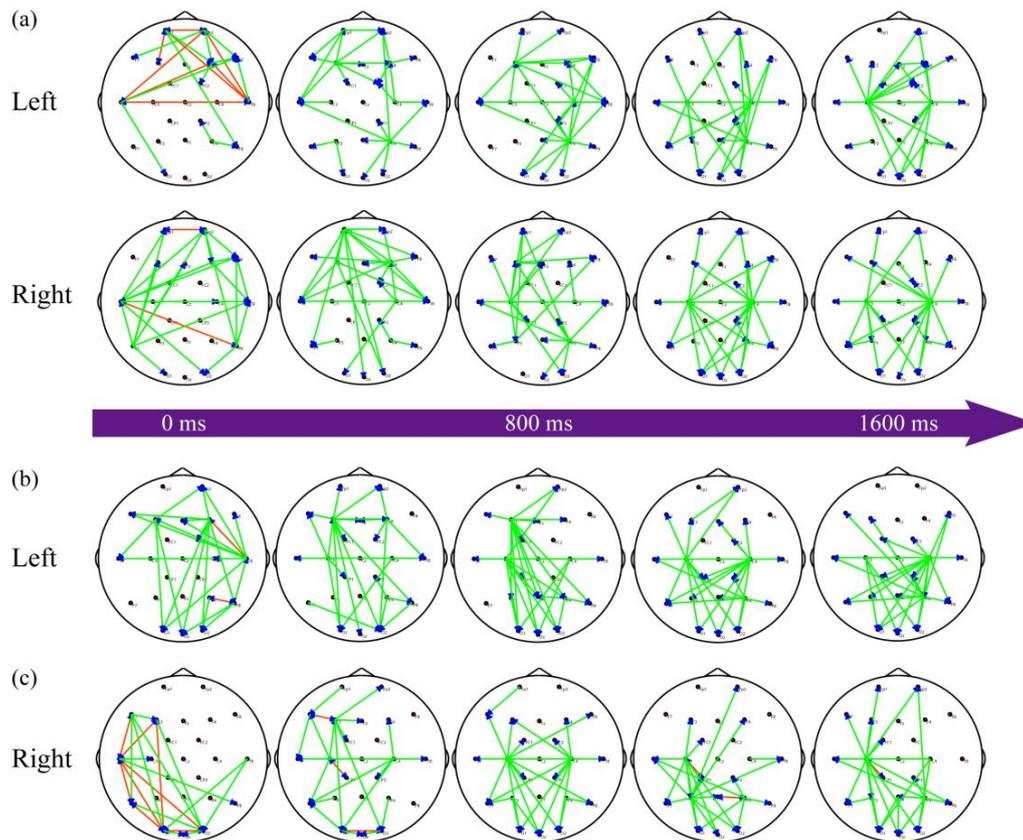
254 transferred to the joint control from bilateral C3 and C4 electrodes. However, for the

255 PL subjects (Fig. 3b), the motor area of the stroked hemisphere (i.e., right hemisphere)

256 showed seldom connectivity when starting to perform the left-hand wrist extension,

257 but the contralateral F3 and C3 electrodes (i.e., at the left hemisphere) extended to the

258 occipital lobe showed the stronger connectivity architectures; while for the PR  
 259 subjects (Fig. 3c), the crucial hubs were found to be located at the contralateral C4  
 260 and P4 and ipsilateral P3, when performing the right-hand wrist extension.

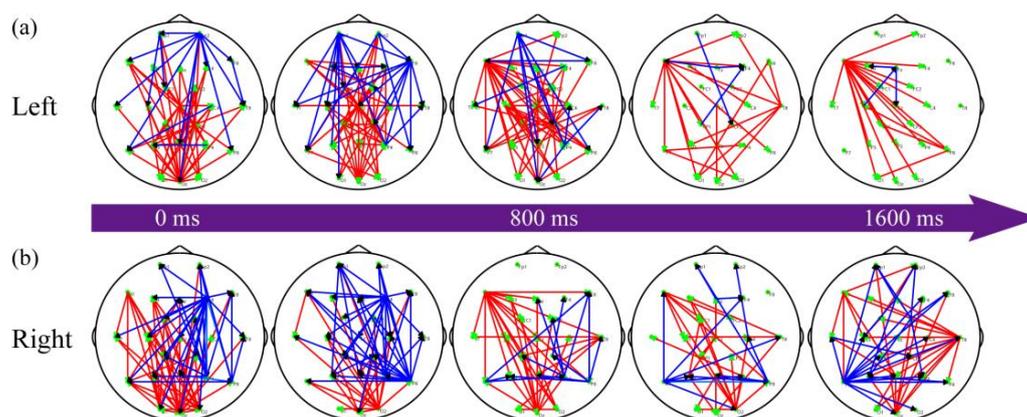


261  
 262 **Fig. 3.** Time-varying information flow when achieving the wrist extension. (a) HC  
 263 subjects, (b) PL subjects, and (c) PR subjects. In each subfigure, the solid green lines  
 264 indicate the directed information flows, the arrows indicate the directions of  
 265 information flows, and the solid red lines denote bidirectional information flows.

266

267 To further explore the differential dynamic network patterns between post-stroke  
 268 hemiplegic patients and healthy people during motor execution, Fig. 4 further displays  
 269 the corresponding statistical network topologies. When comparing the PL and HC

270 subjects (Fig. 4a), the electrodes having stronger information flow in the PL group  
 271 transferred from the occipital lobe (e.g., Oz) to the left frontal lobe (e.g., F7); however,  
 272 for the PS subjects (Fig. 4b), this transmission occurred from occipital lobe (e.g., Oz)  
 273 and left frontal lobe (e.g., F7) to the right temporal lobe (e.g., T6).



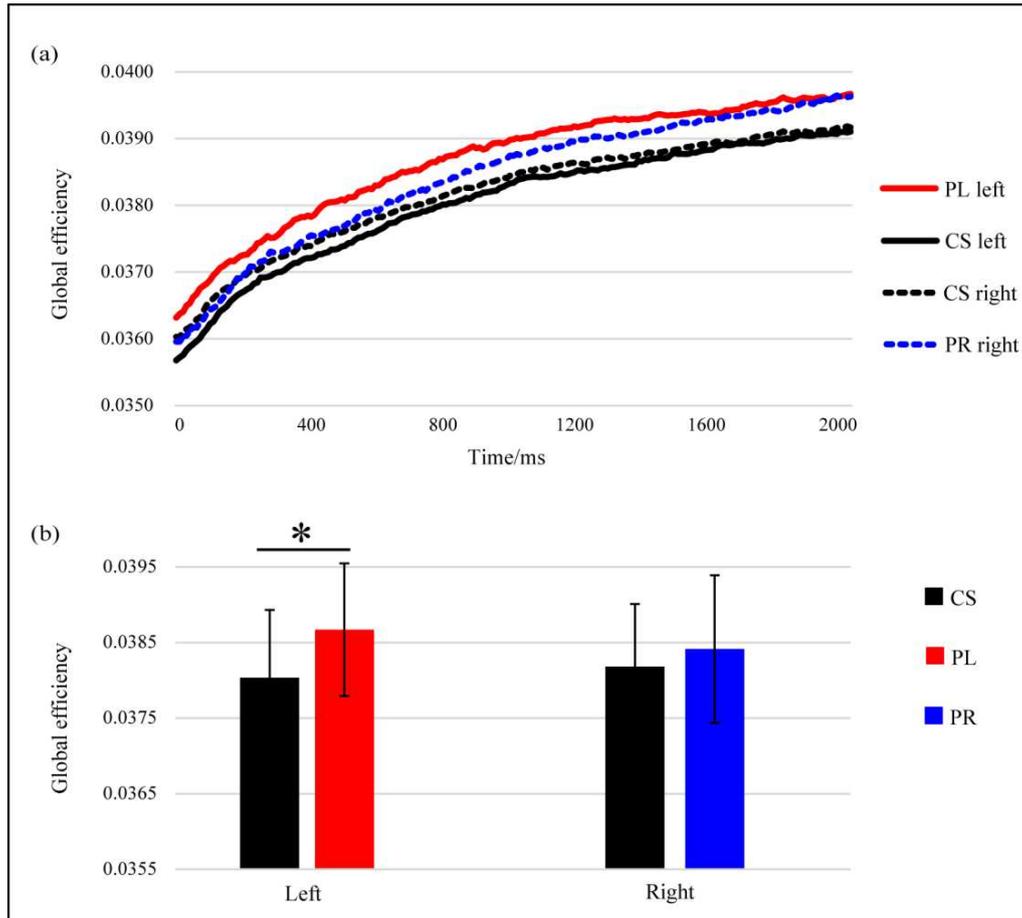
274

275 **Fig. 4.** Differential time-varying network topologies between the pairwise groups. (a)  
 276 PL versus HC groups and (b) PR versus HC groups. In each subfigure, the red and  
 277 blue solid lines indicate significantly stronger and weaker directed information flows  
 278 of the PL/PR group than the HC group, respectively.

279

280 Dynamics of the time-varying *GE*

281 The time-varying *GE* of all subjects in PL, PR, and HC groups at different time points  
 282 were averaged, as illustrated in Fig. 5(a), during the wrist extension, the *GE* increased  
 283 along with the motion. And when quantitatively measuring the potential differences,  
 284 Fig. 5(b) further illustrated that only when performing left-hand wrist extension, the  
 285 *GE* of the PL group was greater than that of the HC group ( $p < 0.05$ ).



286

287 **Fig. 5.** The time-varying *GE* of the three groups. (a) Dynamics of the *GE* and (b)

288 Statistics of the average *GE*.

289

## 290 Discussion

291 Stroke is one of the most important diseases that threaten our lives and further leads to

292 motor impairments in stroke survivors. Compared with healthy people, the interaction

293 among different brain regions is more complicated in post-stroke patients when

294 accomplishing the movements. Hence, in the current study, we proposed to adopt the

295 ADTF to investigate the dynamic network architectures of movement-related activity

296 during the wrist extension in post-stroke hemiplegic patients and healthy people.

297 Before applying the ADTF, the different PSD topographies were first investigated,  
298 as displayed in Fig. 2, although the stronger activities at the left primary motor areas  
299 (e.g., C3) and right parietal and occipital lobes (e.g., P4 and O2) were found for the  
300 PL group compared to the HC group, no differences were found for the PR group.  
301 This result suggested that the contralateral brain areas corresponding to the stroked  
302 hemisphere of PL patients were strongly activated than that of healthy people to  
303 compensate for the damaged lateral brain areas. Unfortunately, the PSD failed to  
304 uncover the detailed interactions among different brain areas that were related to the  
305 wrist extension, which seemed to be more helpful for our understanding of the  
306 post-stroke motion.

307 To explore the dynamic interaction in post-stroke hemiplegic patients (i.e., PL  
308 and PR groups) and healthy people (i.e., HC group) across different brain regions,  
309 time-varying network topologies of the left- and right-hand wrist extension were  
310 calculated and then illustrated in Fig. 3. As displayed in Fig. 3(a), when the "GO"  
311 signal appeared, the networks of earlier motor execution stage (i.e., networks of 0 ms  
312 to 800 ms) for the HC subjects showed strong contralateral connectivity coupling  
313 among right motor area concerning the left-hand wrist extension, while left motor  
314 area showed significant stronger connectivity during right-hand movement, which  
315 then switched to a bilateral connectivity architecture (i.e., networks of 800 ms to 1,  
316 600 ms) with C3 or C4 as hub node. Previous studies have demonstrated that medial  
317 frontal gyrus, parietal lobe, primary motor cortex, and SMA are highly involved

318 during motor execution and exhibit contralateral hemispherical responses  
319 corresponding to the moving hand [22, 23], and similar to the motor imagery, during  
320 the posterior of the required motion, this contralateral hub would be transferred to the  
321 bilateral hubs to accomplish this motion [15], which was consistent with our current  
322 findings.

323 However, since the stroke occurred in PL and PR subjects, as a result, the  
324 network patterns of PL and PR patients would be different from that of healthy people,  
325 and the site and severity of stroke will further affect the degree of neural plasticity  
326 related to the motor-related network architecture [11]. Specifically, investigating Fig.  
327 3(b), when performing the left-hand movement (i.e., networks of 0 ms to 800 ms),  
328 stronger functional coupling existed between F3/C3 and parietal-occipital lobe, while  
329 seldom connectivity of the stroked right hemisphere was observed, which might  
330 account for the deficits in the left-hand wrist extension of the PL subjects. The frontal  
331 lobe is activated to be responsible for the control of body movements, and to  
332 compensate for the deficits brought by the stroked right hemisphere, the ipsilateral  
333 hemisphere then provides the functional compensation for the body movements [24,  
334 25]. Thereafter, hub nodes transferred from F3 and C3 to bilateral motor areas (i.e.,  
335 C3 and C4, networks of 800 ms to 1600 ms), which was similar to that of the HC  
336 subjects. While concerning the right-hand movement of the PR subjects, as displayed  
337 in Fig. 3(c), stronger flows (i.e., networks of 0 ms to 800 ms) directed from F3 were  
338 observed, as well as the bilateral parietal lobe at 1, 600 ms whose hubs were P3 and

339 P4, which might further clarify that besides the participation of the contralateral motor  
340 area of the stroked hemisphere, the other non-motor areas in the injured hemisphere  
341 that were responsible for the high-level cognition, such as motor planning and  
342 attention, may also be involved.

343 To further explore the impaired effective connectivity in PL and PR patients, Fig.  
344 4 then illustrated the different patterns of time-varying networks between PL/PR and  
345 HC group during hand movement. The PL patients exhibited enhanced connectivity to  
346 frontal-parietal and motor areas starting from Oz compared with the HC group, which  
347 is bottom-up architecture (i.e., networks of 0 ms and 400 ms). The occipital lobe is  
348 responsible for visual information processing. After receiving the "GO" signal (i.e., 0  
349 ms), the upper limb dyspraxia in stroke patients led to the delayed movement, the  
350 enhanced bottom-up connectivity might then intensify the motion intention of the  
351 required wrist extension [26], and during the later motion stage (i.e., from 800 ms to 1,  
352 600 ms), the hub gradually transferred from Oz to F7 (Fig. 4a), and the top-down  
353 modulation starting from F7 to bilateral parietal-occipital lobe is significantly  
354 enhanced. As illustrated above, frontal and parietal regions play an irreplaceable role  
355 in motion planning and decision-making associated with motor regulation [27]. When  
356 planning the motion, the parietal lobe is regulated by the prefrontal lobe. That is, their  
357 cooperation helps complete the assigned tasks [28]. However, the stroke in PL  
358 patients destroyed the high-level regulatory involved in exercise execution, to  
359 compensate for the completion of the wrist execution, in our present study, the

360 enhanced connectivity in the contralateral frontal-occipital lobe of the stroked  
361 hemisphere was, therefore, observed for the PL subjects. Concerning the PR patients  
362 (Fig. 4b), the hubs transferred from the occipital lobe (e.g., Oz) and left frontal lobe  
363 (e.g., F7) to the right temporal lobe (e.g., T6), and although the stroke resulted in the  
364 dysfunction of the patients' motor network, more contralateral hemispheric and  
365 ipsilateral non-motor regions were included to compensate for the wrist extension [24,  
366 25], and accordingly, the enhanced time-varying network architectures connecting  
367 related areas facilitated the stroked patients with their motion.

368       Moreover,  $GE$  is the average efficiency of the related brain network and is usually  
369 applied to estimate the potential for functional integration among brain areas. Besides  
370 the above network architecture, just as illustrated in Fig. 5, during the wrist extension,  
371 the time-varying  $GE$  of the HC, PL, and PR groups increased along with the execution.  
372 We speculated that it might be due to the plasticity changes between different brain  
373 regions after stroke, patients with post-stroke hemiplegic activated more other brain  
374 regions as compensation, and the increased interaction could dynamically compensate  
375 for the injured hemisphere to complete our required movement. And indeed, in our  
376 present study, when performing the left-hand wrist extension, the average  $GE$  of the  
377 PL group was significantly larger than that of the HC group (Fig. 5b).

378

## 379 **Conclusions**

380 In conclusion, by using the ADTF, we investigated the time-varying network patterns

381 of the PL, PR, HC groups when they were performing the required wrist extension.  
382 We found the obvious transition of the control hub from the contralateral to the  
383 bilateral hemisphere for the HC subjects. However, concerning the PL and PR patients,  
384 when performing the wrist extension, the effective connectivity between stroked  
385 motor area and others was weaker while that between non-stroked motor area and  
386 others was enhanced for the motor planning and regulation, especially the frontal and  
387 parietal-occipital lobes, to compensate for the dysfunction of the motor behaviors for  
388 the stroked patients. These findings help us better understand the network mechanism  
389 underlying the motor dysfunction of the patients with post-stroke hemiplegic and  
390 might also serve as a reliable biomarker applied to the future rehabilitation of stroke  
391 patients.

392

### 393 **Abbreviations**

394 HC: Healthy Controls; ADTF: Adaptive Directed Transfer Function; PL: Post-stroke  
395 hemiplegic of the Left arm; PR: Post-stroke hemiplegic of the Right arm; IRM:  
396 Instruction Response Movement; REST: Reference Electrode Standardization  
397 Technique; tv-MVAAR: time-varying Multivariate Adaptive Autoregressive; GE:  
398 Global Efficiency; SMA: supplementary motor area; EEG: electroencephalogram;  
399 EOG: Electrooculogram; ICA: independent component analysis; PSD: power spectral  
400 density; FDR: false discovery rate.

401

402 **Authors' contributions**

403 HL and DFH designed the experiment protocol. HL collected the data. FLL, LJ, YQL,  
404 and YLJ analyzed the data. Results were interpreted by FLL, LJ, YLJ, and YHP. The  
405 draft was written by FLL and LJ under supervision of YDZ and PX. HL and XBZ  
406 provided constructive suggestion for writing this draft. All authors read and approved  
407 the final manuscript.

408

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416

417 **Availability of data and materials**

418 The datasets used and/or analysed during the current study are available from the  
419 corresponding author on reasonable request.

420

421 **Ethics approval and consent to participate**

422 The study protocol was approved by the ethics committee of the First Affiliated

423 Hospital of Sun Yat-sen University. All participants were informed of the study  
424 protocol, along with the signed informed consent forms.

425

#### 426 **Consent for publication**

427 All participating subjects signed informed consent for this study and subsequent  
428 publications, and all identifying features were removed.

429

#### 430 **Competing interests**

431 The authors declare that they have no competing interests.

432

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# Figures

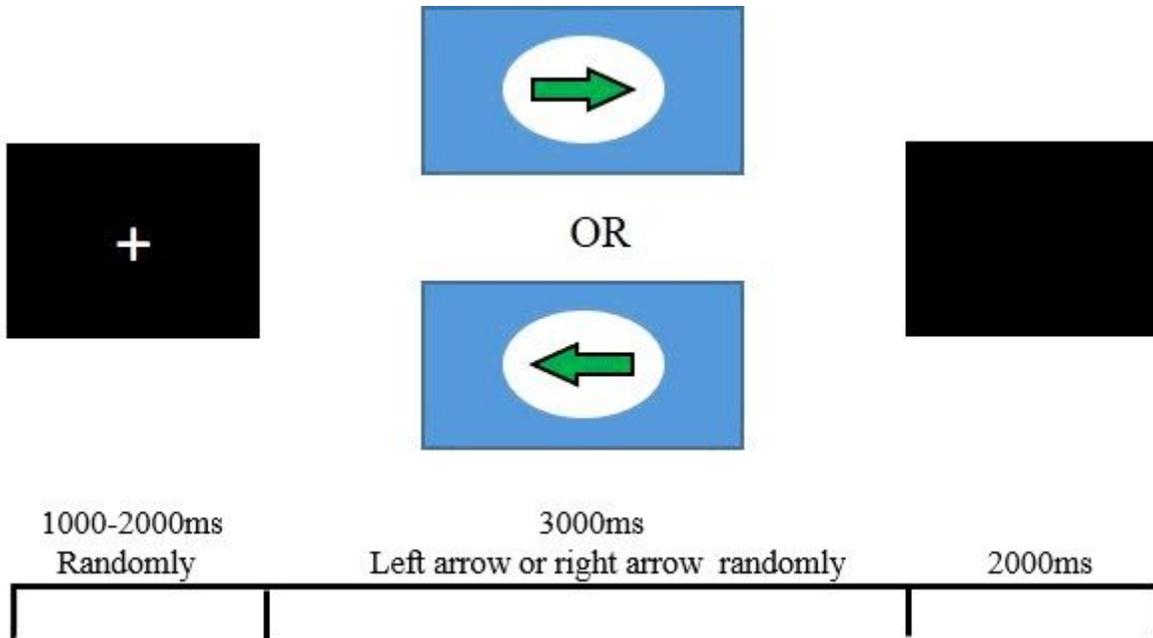


Figure 1

The experimental procedures and the timeline of a task trial.

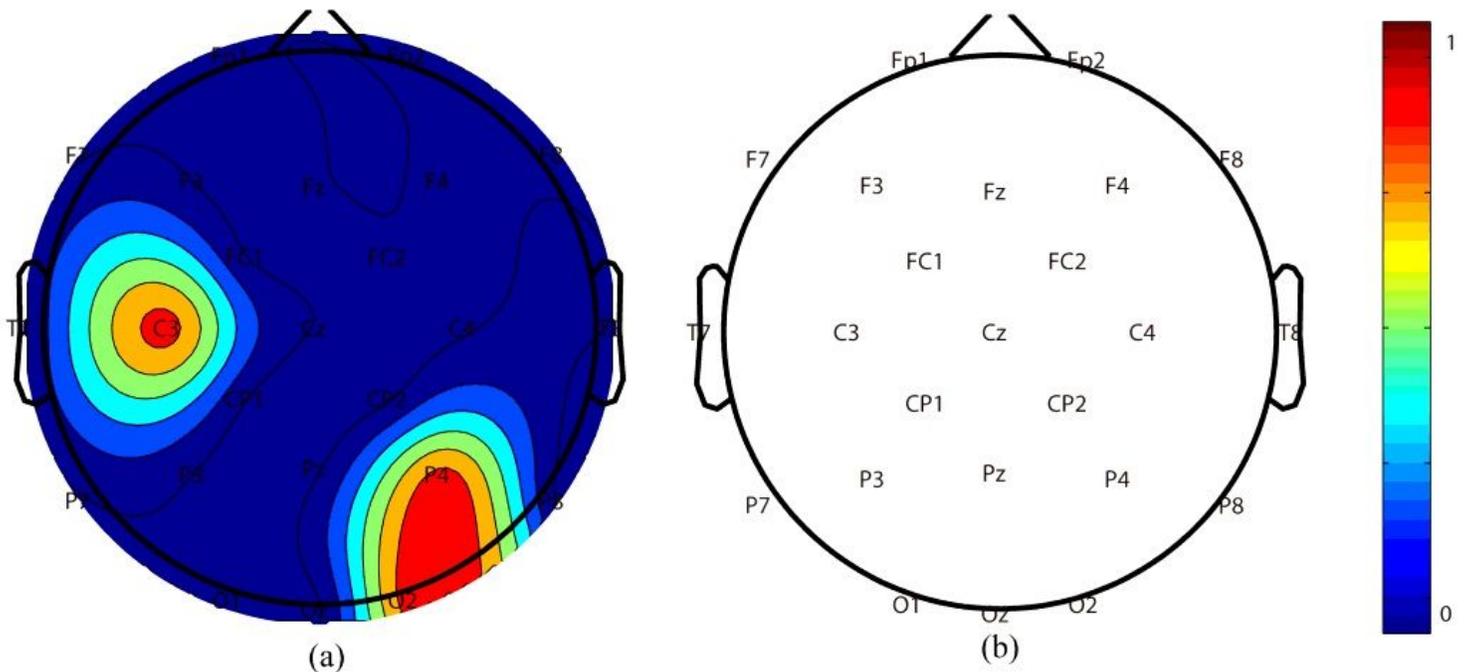
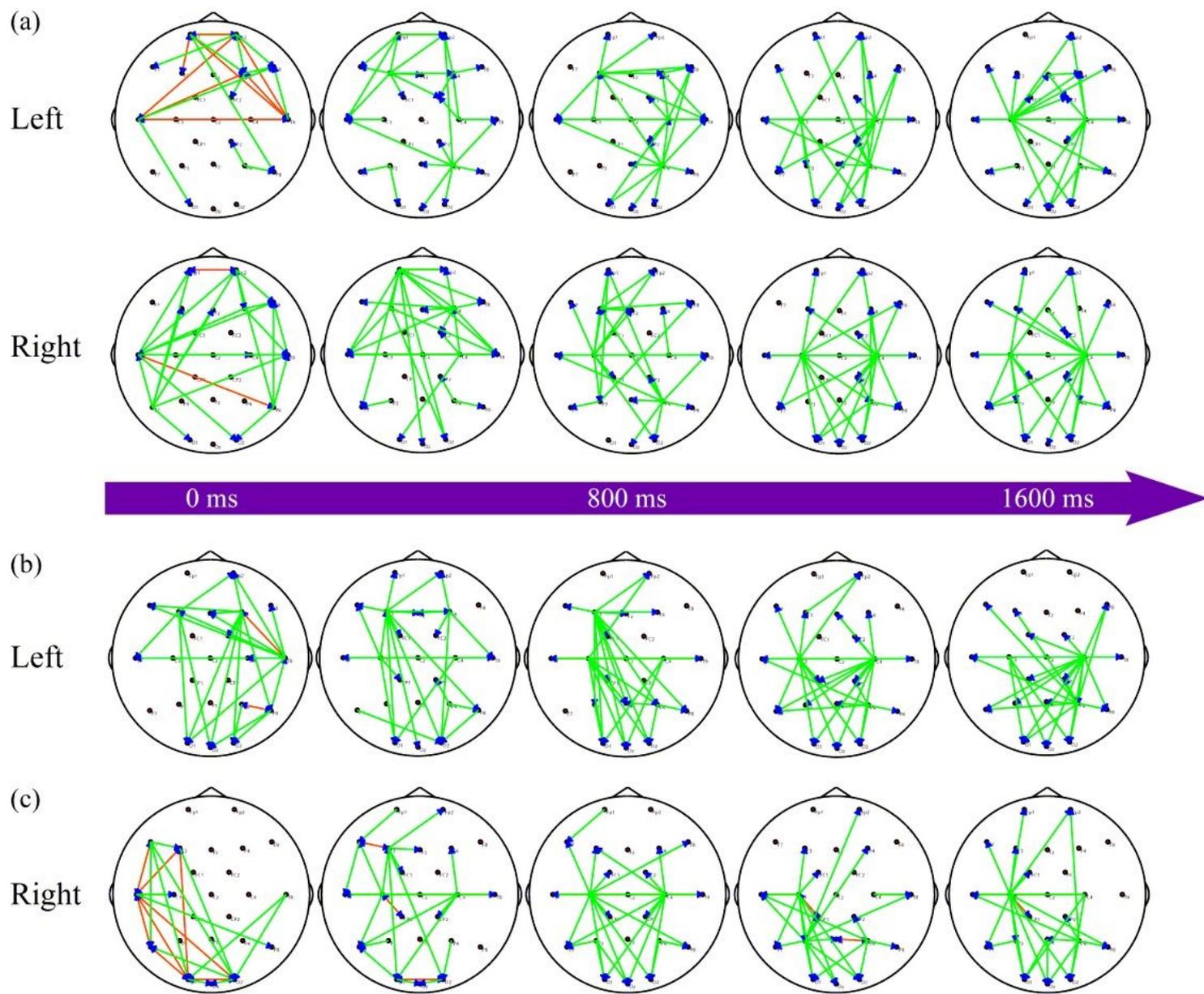


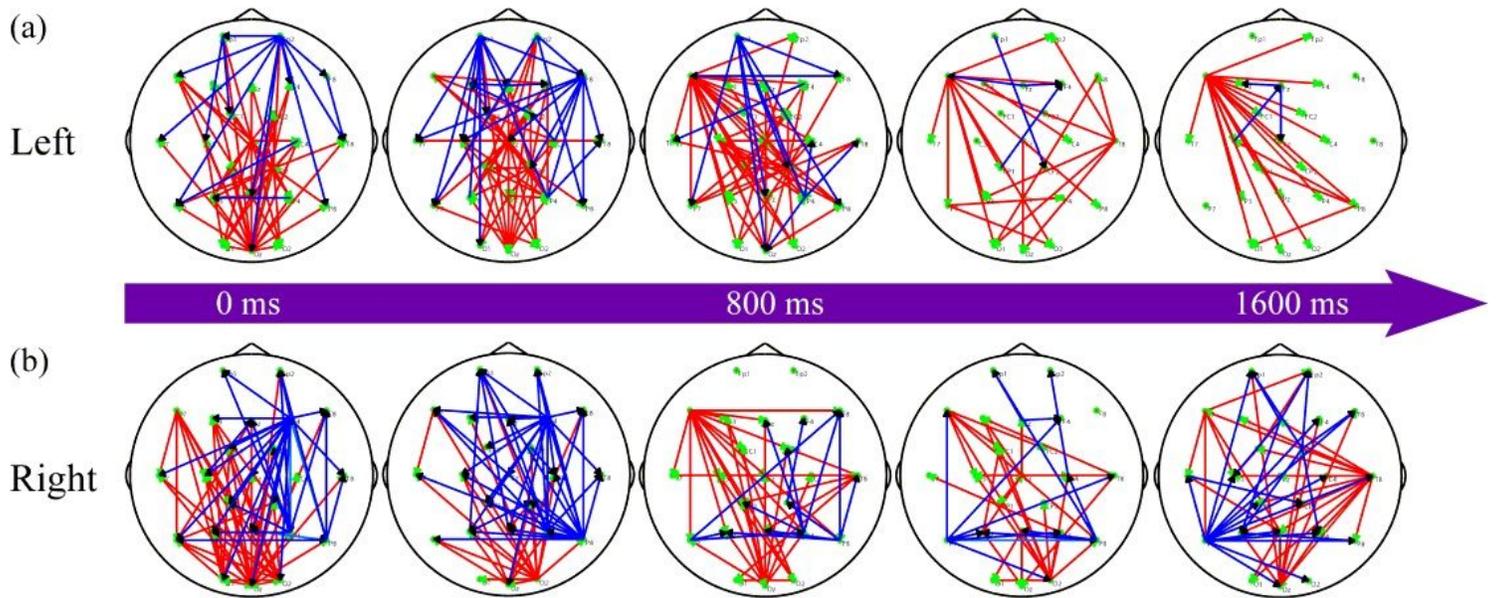
Figure 2

Scalp PSD topographies in 8 - 30 Hz. (a) Between PL and HC groups and (b) Between PR and HC groups. The regions printed with deep red color denote the PSD of the PL/PR group is significantly greater than the HC group, and the blue denotes the opposite.



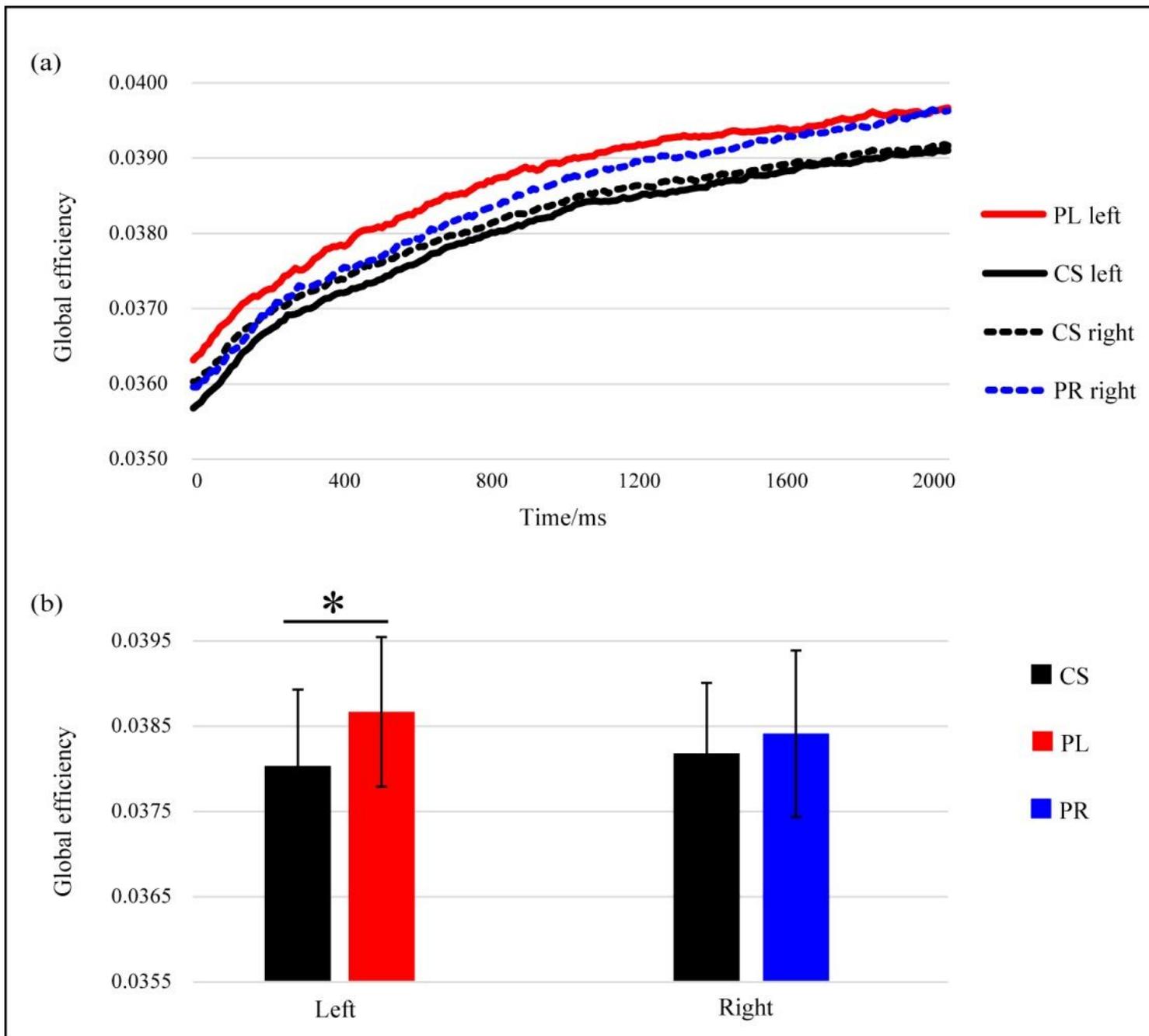
**Figure 3**

Time-varying information flow when achieving the wrist extension. (a) HC subjects, (b) PL subjects, and (c) PR subjects. In each subfigure, the solid green lines indicate the directed information flows, the arrows indicate the directions of information flows, and the solid red lines denote bidirectional information flows.



**Figure 4**

Differential time-varying network topologies between the pairwise groups. (a) PL versus HC groups and (b) PR versus HC groups. In each subfigure, the red and blue solid lines indicate significantly stronger and weaker directed information flows of the PL/PR group than the HC group, respectively.



**Figure 5**

The time-varying GE of the three groups. (a) Dynamics of the GE and (b) Statistics of the average GE.