Time-Frequency-Domain Copula-Based Granger Causality and Application to Corticomuscular Coupling in Stroke

Qingshan She*,‡, Hang Zheng*, Tongcai Tan†, Botao Zhang*, Yingle Fan* and Zhizeng Luo*

*School of Automation, Hangzhou Dianzi University, Hangzhou, Zhejiang 310018, P. R. China
†Department of Rehabilitation Medicine, Zhejiang Provincial People’s Hospital, People’s Hospital of Hangzhou Medical College, Hangzhou, Zhejiang 310014, P. R. China
‡qsshe@hdu.edu.cn

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The corticomuscular coupling (CMC) characterization between the motor cortex and muscles during motion control is a valid biomarker of motor system function after stroke, which can improve clinical decision-making. However, traditional CMC analysis is mainly based on the coherence method that can’t determine the coupling direction, whereas Granger Causality (GC) is limited in identifying linear cause–effect relationship. In this paper, a time-frequency domain copula-based GC (copula-GC) method is proposed to assess CMC characteristic. The 32-channel electroencephalogram (EEG) signals over brain scalp and electromyography (EMG) signals from upper limb were recorded during controlling and maintaining steady-state force output for five stroke patients and five healthy controls. Then, the time-frequency copula-GC analysis was applied to evaluate the CMC strength in both directions. Experimental results show that the CMC strength of descending direction is greater than that of ascending direction in the time domain for healthy controls. With the increase of grip strength, the bi-directional CMC strength has an increasing trend. Meanwhile, the bi-directional CMC strength of right hand is larger than that of left hand. In addition, the bi-directional CMC strength of stroke patients is lower than that of healthy controls. In the frequency domain, the strongest CMC is observed at the beta frequency band. Additionally, the CMC strength of descending direction is slightly larger than that of ascending direction in healthy controls, while the CMC strength of descending direction is lower than that of ascending direction in stroke patients. We suggest that the proposed time-frequency domain analysis approach based on copula-GC can effectively detect complex functional coupling between cortical oscillations and muscle activities, and provide a potential quantitative analysis measure for motion control and rehabilitation evaluation.

Keywords: Corticomuscular coupling; Copula; Granger causality; Stroke; EEG; EMG.

‡Corresponding author.
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1. Introduction

The oscillation coupling and synchronous discharge of neurons play a crucial role in the neural control process of human motion, and the motor nerve system transfers motion control information through nerve oscillations. The nerve center achieves functional regulation and integration through the interactions with various regions, mainly manifested in the phenomenon of synchronization between electrophysiological signals, including electroencephalogram (EEG) and electromyography (EMG). Nerve injuries prevent the conduction of nerve oscillations and lead to motor dysfunction in the patients with central nervous system lesions.

The corticomuscular coupling (CMC) with rhythm plays key roles in neural communication and interaction between the central nervous system and the periphery. Since Conway et al. first reported the synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in 1995, extensive studies have been carried out using various synchronization analysis methods to explore the pathological mechanism of the diseases related with movement. However, traditional coherence approaches do not reflect the coupling direction characteristics. Specially, it is difficult to distinguish whether the neuromuscular control of power output originates in the descending or ascending direction. To better understand the functional interactions and information transfer characteristics between the motor cortex and corresponding effector muscles, Granger causality (GC) has been applied to analyze the EEG–EMG coupling. Although GC can describe the bidirectional information transmission, it has some inherent limitations: (1) It only considers the noise term correlation of the autoregressive model and has no connection with the coefficients of the model, and thus it may lose some important information, and (2) It can only find the linear coupling causality between time series. However, the coupling model of EEG–EMG signals is not known, and there is nonlinear causal relationship between the functional corticomuscular coupling. Therefore, the GC method cannot effectively describe the nonlinear coupling characteristics of EEG–EMG signals. In order to address these problems, different nonlinear causal algorithms have been extended based on GC, such as Kernel-based GC (KGC), variance GC (VGC), and modified backward-in-time selection GC (mBTS-GC). They have obtained better prediction performance than traditional GC on neural signal analysis. Meanwhile, transfer entropy (TE) which is an alternative measure of effective connectivity based on information theory has been developed and applied to the CMC analysis, yielding impressive results. Although TE does not involve explicit model that is different from GC based on the linear regression model, they both are essentially derived from Wiener’s construction of causality.

Recently, the copula theory developed from the fields of mathematics and statistics has many advantages in analyzing the correlation structure between multiple variables, and it also contributes to resolve the above-mentioned defects. Copula theory studied and applied in finance and neuroscience yields some
important results. Hu et al.\textsuperscript{34} have proposed an effective model-free, copula-based GC (copula-GC) measure that can be used to reveal nonlinear and high-order moment causality, and obtained better performance than GC in the cause–effect assessment of neural time series, such as local field potential (LFP) and neural spike trains (NST).\textsuperscript{16,31,34} Geng et al.\textsuperscript{30} have proposed a conditional GC method based on copula by extending the bivariate copula-GC to multivariate time series analysis. It achieved better performance than linear GC, VGC and KGC in motor imagery EEG data analysis. Dauwels et al.\textsuperscript{29} and Gao et al.\textsuperscript{32} used copula Gaussian graphical models to characterize the interdependence of multi-channel EEG signal oscillation activities and infer the connectivity in various regions of the brain. Ince et al.\textsuperscript{33} proposed the statistical framework of Gaussian copula mutual information (GCMI), which can be applied to various types of neural signals and promote comparative study of neural information in order to better understand the information processing function of brain network. From the above research work, the copula method has a solid theoretical foundation and strong application potential, and provides a new research approach for analyzing nonlinear correlation between neural signal variables.

In this study, a time-frequency domain copula-GC method was proposed to investigate the CMC strength between the cerebral cortex and the contralateral muscles for both stroke patients and healthy controls. The copula-GC was applied to EEG and EMG data collected during controlling and maintaining steady-state force output in both time-domain and frequency-domain. Such studies can provide some new characteristics of the CMC strength and flow after stroke as well as strengthen the understanding of mechanisms underlying motor dysfunction.

2. Materials and Methods

2.1. Subjects

Five stroke patients (PA) who had motor deficits of the upper limb (Table 1; mean age ± SD: 47.8 ± 2.3 years; range, 45–51 years; all male; all right handed) and five healthy controls (HC; mean age ± SD, 25.8 ± 1.3 years; range, 24–27 years; all male; all right handed) without any history of neurological or psychiatric disease were recruited in this study. None of the subjects were involved in regular strength or endurance training. S1–S5 are healthy volunteers, S6–S8 are patients with mild stroke, S9 and S10 are patients with severe stroke. This study was performed with the oversight of the Institutional Review Board of Guangdong Provincial Work Injury Rehabilitation Hospital. All subjects gave informed consent prior to their participation.

2.2. Experimental paradigm and data recording

2.2.1. Experiment paradigm

During the experimental, the subjects sat in an electrically shielded and dimly lit room. In order to control and maintain the steady-state force output, a spring grip
A meter (EH101, Lynx Mall, China) was used in grip tasks at 5 kg, 10 kg and 20 kg force levels. The experimental paradigm is shown in Fig. 1. The task was performed with each hand separately and the hand order was counter-balanced between the subjects. Each steady-state force output trial started with 25 s rest and then the subjects were instructed to perform specific steady-state grip output for 5 s, and subsequently they relaxed for 25 s. Each steady-state grip task included 10 trials with each hand. After each specific steady-state grip task was completed, the subjects rested for 20 min, and then switched to next steady-state grip output task in order to avoid muscle fatigue. As the stroke subjects were weak in exercise performance, the gripping tasks were only performed at 5 kg and 10 kg force levels with each hand. Control subjects successfully accomplished all the steady-state grip tasks.

![Fig. 1. Illustration of the experimental paradigm.](image-url)
2.2.2. EEG and EMG data recording

EEG and EMG data were acquired with BrainAmp (Brain Products, Germany) amplifiers, filtered in the frequency range of 0.5–150 Hz and the sampling frequency was set to 1000 Hz during the acquisition. The EEG signals were referenced to binaural mastoid and recorded using an EEG cap with 32 scalp positions using the international 10–20 standard system. The EMG signals were recorded from the ulnar wrist flexor (UWF), flexor digitorum superficialis (FDS), radial wrist flexor (RWF), brachioradialis muscle (BM), musculus biceps brachii (MBB) and triceps (Fig. 2(b)). Before the electrodes were attached, the hair was needed to clean, and the skin surface was cleaned with alcohol. EEG signals from C3/C4 channels were located in the primary motor zone, and EMG signals from the FDS and UWF channels were selected to calculate the copula-GC values which are further used for analysis in our study.

2.3. Time-frequency domain analysis based on copula-GC

2.3.1. Copula

In probability theory, copula is a function that links a univariate marginal distribution to a multivariate joint distribution. With copula, the edge distribution can be separated from its joint density distribution, and only the statistical dependency between variables is concerned. Sklar’s theorem\textsuperscript{35} is the core of copula’s statistical

Fig. 2. (a) Environment of data measurement; (b) 6-channel EMG electrode positions.
theory, pointing out that any multivariate distribution can be expressed as a copula function evaluated on each marginal distribution.

Formally, let $X = (x_1, \ldots, x_N)$ be a vector random variable with corresponding probability distribution $F$ defined on $R^N$. The copula associated with $F$ is a distribution function $C : [0,1]^N \rightarrow [0,1]$ that satisfies $F(x) = C(F_1(x_1), \ldots, F_N(x_N))$, $X \in R^N$. If $F$ is a continuous distribution on $R^N$ with univariate marginal $F_1, \ldots, F_N$, then $C(u) = F(F_1^{-1}(u_1), \ldots, F_N^{-1}(u_N))$ is unique. Assuming that $F$ has $N$th order partial derivatives, its probability density function can be obtained from the distribution function by differentiation:

$$p(X) = \frac{\partial^N F(X)}{\partial x_1 \cdots \partial x_N} = \frac{\partial^N C(u)}{\partial u_1 \cdots \partial u_N} \prod_{i=1}^N \frac{\partial u_i}{\partial x_i} = c(u) \prod_{i=1}^N p_i(x_i),$$

(1)

where $c(u)$ is the copula density function, and $p_i(x_i)$ is the individual marginal probability density function. The copula function is independent of the marginal distribution and represents the overall dependent structure between the variables.

### 2.3.2. Copula-based Granger causality

GC is a statistical measure of directional influences between two time series. Although increasingly used in various fields to detect causal effects, GC has not been well adopted to time-varying volatility time series and reveals nonlinear causality. Hu et al.\(^{34}\) have developed an effective copula-based Granger causality (copula-GC, cGC) method for detecting nonlinear and high-order causal relationships without explicit models. Let $\{X = x_t, Y = y_t\}$ be a sample of a stationary stochastic process, and the null hypothesis of causality $X \rightarrow Y$ is described as

$$f(y_{t+1} | y_t^n, x_t^m) = f(y_{t+1} | y_t^n),$$

(2)

where $f$ refers to conditional probability density, $x_t^m = (x_t, \ldots, x_{t-m+1})$ and $y_t^n = (y_t, \ldots, y_{t-n+1})$ represent the past information of $X$ and $Y$ with $m$ and $n$ orders, respectively.

According to the concept of copula-based Granger causality,\(^{34}\) the GC measure with a log-likelihood ratio is defined as follows:

$$GC_{X \rightarrow Y} = E \left[ \log \frac{E[f(y_{t+1} | y_t^n, x_t^m)]}{f(y_{t+1} | y_t^n)} \right],$$

(3)

where $E$ is the desired operation of the sample space. Such a definition can be shown as equivalent to TE as a log-likelihood ratio.$^{36}$ The main advantage of this definition is that no explicit model is needed, but the question is how to perform reliable GC estimation in case of finite samples efficiently. Through recursively representing high-dimensional copula as a set of low-dimensional ones by conditional copula,$^{34}$ an efficient model-free GC estimation measure is written as

$$GC_{X \rightarrow Y} = E \left[ \log \frac{h(y_{t+1}, x_t^m | y_t^n)}{f(y_{t+1} | y_t^n) \times g(x_t^m | y_t^n)} \right],$$

(4)
where $h$ refers to the conditional joint density of $(X, Y)$, $f$ and $g$ are the conditional marginal densities of $Y$ and $X$, respectively. According to Sklar’s theorem, the conditional joint density $h$ can be further written in the form of a conditional copula density function $c$:

$$
h(y_{t+1}, x_t^m|y_t^n) = f(y_{t+1}|y_t^n) \times g(x_t^m|y_t^n) \times c(u, v|y_t^n),$$

where $u = F(y_{t+1}|y_t^n)$ and $v = G(x_t^m|y_t^n)$. $F$ and $G$ represent the condition marginal distributions of $Y$ and $X$, respectively. Thus, substituting Eq. (5) in Eq. (4), we obtain GC of $X \rightarrow Y$ given by

$$
c_{GCX \rightarrow Y} = E \left[ \log \frac{f(y_{t+1}|y_t^n, x_t^m)}{f(y_{t+1}|y_t^n)} \right]
= E \left[ \log \frac{h(y_{t+1}, x_t^m|y_t^n)}{f(y_{t+1}|y_t^n) \times g(x_t^m|y_t^n)} \right]
= E \left[ \log \frac{c(F(y_{t+1}|y_t^n), G(x_t^m|y_t^n)|y_t^n) \times f(y_{t+1}|y_t^n) \times g(x_t^m|y_t^n)}{f(y_{t+1}|y_t^n) \times g(x_t^m|y_t^n)} \right]
= E[\log c(F(y_{t+1}|y_t^n), G(x_t^m|y_t^n)|y_t^n)].$$

It is evident from Eq. (6) that the copula-GC is represented in terms of conditional copula, and it does not involve explicit models.

### 2.3.3. Time-frequency analysis of EEG–EMG based on copula-GC

The information on the interaction of EEG–EMG signals in the time-frequency domain can reveal the functional relationship between the brain and muscles. In order to quantitatively analyze the interaction between EEG and EMG, the copula-GC value of EEG–EMG is first calculated in time domain. Next, EEG and EMG data were filtered into 49 sub-band signals, and then the copula-GC value is computed in each sub-band to perform functional coupling analysis in frequency domain. The detailed steps of the identification method are described as follows:

(i) Data Preprocessing

EEG and EMG data were exported to MATLAB 9.3.0 (R2017b, Mathworks Inc, Natick, MA, USA) for subsequent preprocessing and analysis steps. EEG and EMG data are vulnerable bioelectrical signal. They are susceptible to noise in the environment, including power frequency interference and baseline drift. The premise of EEG processing and analytical research is to improve the purity of the signal. The 50 Hz power frequency interference has been filtered out in the acquisition software in the acquisition process and a high-pass filter was used to remove baseline drift. In this paper, independent component analysis (ICA) was employed to remove the electrooculogram (EOG) signals and then clear the artifacts in the data by using the threshold denoising approach on each layer after wavelet decomposition.

(ii) Time-Domain Analysis

The copula-GC value of EEG–EMG data can reflect the number of information exchanges between the cerebral cortex and motoneurons. According to Eq. (6), the
calculations of copula-GC are performed on the preprocessed EEG and EMG data, where the lag orders of the variables are determined by regression analysis using the Bayesian information criterion (BIC). The copula-GC value of EEG–EMG data can indicate the information exchange between the cortical and spinal cord activities during the execution of a movement.

(iii) Frequency-Domain Analysis

Through the preprocessing of Step 1, the EEG and EMG data were denoted as $X$ and $Y$, respectively. In order to describe the CMC characterization in specific frequency-domain, $X$ and $Y$, which ranged from 1 Hz to 50 Hz, are divided into sub-band data with a frequency interval of 1 Hz using a FIR filter. In each specific sub-band, the copula-GC values are then calculated based on the definition of Eq. (6). The bilateral copula-GC values between EEG and EMG data in each sub-band at a given frequency $f$ are marked as $cGC_{X\rightarrow Y}(f)$ and $cGC_{Y\rightarrow X}(f)$. According to the definition of copula-GC, the greater the copula-GC value is, the more information is transferred in this sub-band. And to quantitatively analyze CMC characterization in a specific frequency band, a parameter called coupling strength (CS) which refers to the coherence and TE analysis\textsuperscript{11,18} was employed to quantitatively calculate the CMC strength in both directions. The CS of descending direction is marked as $CS_{X\rightarrow Y}$, which represents the information of the cerebral cortex transit to the motor neuron. Similarly, The CS of ascending direction is defined as $CS_{Y\rightarrow X}$, which shows the feedback of the motor neuron to the control of cerebral cortex.

$$CS_{X\rightarrow Y} = \sum_f \Delta f \cdot cGC_{X\rightarrow Y}(f),$$  \hspace{1cm} (7)$$

$$CS_{Y\rightarrow X} = \sum_f \Delta f \cdot cGC_{Y\rightarrow X}(f),$$  \hspace{1cm} (8)$$

where $cGC_{X\rightarrow Y}(f)$ and $cGC_{Y\rightarrow X}(f)$ are the bilateral copula-GC value at the frequency $f$, respectively, and $\Delta f$ denotes frequency resolution.

3. Results

3.1. Copula-GC values for PA and HC in time-domain

The copula-GC values in descending and ascending directions were calculated in the time-domain for all healthy controls and stroke patients. Figure 3 showed average bi-directional copula-GC values for all motor tasks across all subjects. Healthy controls showed higher copula-GC values in descending direction than those in the opposite direction. Additionally, we analyzed the difference among different gripping tasks at 5 kg, 10 kg and 20 kg force levels and found that the copula-GC values of right-handed (skilled) are higher than those of left hand in both directions. It can also be noticed that the interaction strength of stroke patients had a decreased trend compared to healthy controls for all motor tasks. This may be due to the intracranial hemorrhage leading to the inability of the motor neurons in the motor area to control
movements stably, resulting in the obstruction of information transmission between EEG and EMG. In order to further describe the difference of CMC strength for PA and HC, according to the calculated copula-GC value, the difference between the ascending pathway and descending pathway with respect to each steady-state grip task was assessed by two sample $t$-test using SPSS 24.0 for windows (IBM SPSS Inc., USA). Results indicated that there was a significant difference ($p < 0.05$) among PA and HC in both directions for each task.

For comparative purpose, linear GC was also applied to the same data. Figure 4 illustrates the results by GC using the MVGC toolbox.\textsuperscript{37} The results show that the copula-GC method has achieved better performance than GC in the cause-effect assessment of neural time series. As shown in Fig. 4, it can be observed that the overall value of copula-GC is greater than that of GC. This may be due to the reason that the GC method can only reflect the linear causality between time series, while copula-GC can detect the linear and nonlinear causality. In addition, it revealed no significant difference in either direction between HC and PA subjects using GC. This
These results suggest that the copula-GC method is a sensitive measure which can be used to detect significant causal influence between HC and PA subjects.

3.2. Coupling strength values for PA and HC at each frequency band

Different EEG rhythms may be involved in different ways during motion, the oscillatory responses of different frequency bands may differ for different movements. Therefore, to further demonstrate the differences of CMC between PA and HC subjects at theta, alpha, beta and gamma frequency bands, we calculated the copula-GC values in each specific frequency band for all motor tasks across all subjects according to the detailed description in the Sec. 2.2.3. According to Eqs. (7) and (8), the calculated CS values in both two directions are shown in Figs. 5 and 6, respectively. Figure 5 showed the mean CS values in two directions for HC (S1–S5), and Fig. 6 demonstrated the results for stroke patients (S6–S10). Table 2 showed the mean and standard deviation of the CS for all motor tasks across all subjects.

Fig. 4. The group-averaged GC values in descending and ascending directions with respect to each steady-state grip task for both stroke patients and healthy controls, respectively. (a) 5 kg force level for left hand; (b) 5 kg force level for right hand; (c) 10 kg force level for left hand; (d) 10 kg force level for right hand; (e) 20 kg force level for left hand and (f) 20 kg force level for right hand; PA: Patients; HC: Healthy controls.
Fig. 5. The group-averaged CS of healthy controls (S1–S5) for each steady-state grip task. (a) 5 kg force level for left hand; (b) 5 kg force level for right hand; (c) 10 kg force level for left hand; (d) 10 kg force level for right hand; (e) 20 kg force level for left hand and (f) 20 kg force level for right hand; PA: Patients; HC: Healthy controls.

Fig. 6. The group-averaged CS of patient group (S6–S10) for each steady-state grip task. (a) 5 kg force level for left hand; (b) 5 kg force level for right hand; (c) 10 kg force level for left hand and (d) 10 kg force level for right hand; PA: Patients; HC: Healthy controls.
The results show that the CS is significant in both descending and ascending directions at beta and gamma bands for all grip tasks. Meanwhile, the CS in descending direction was slightly higher than that in ascending direction for HC. In particular, the results also demonstrated that PA had weaker coupling at the beta band in descending direction compared to HC, while the opposite result was observed in ascending direction. Therefore, the CS in descending direction was slightly lower than that in ascending direction for HC. In addition, the CS differences between the ascending pathway and descending pathway at the beta band with respect to each steady-state grip task was also assessed using two sample t-test. Results indicated that there was a significant difference (p < 0.05) in the CS among PA and HC in both directions for each task.

4. Discussion

It is generally believed that post-stroke motor deficits arise essentially from the impairments in neural network that controls movement. CMC is believed to be a direct phenomenon of interactions between physiological oscillatory activities from the brain and the controlled muscles. The cerebral cortex controls the movement of muscle tissue through the spinal cord and peripheral nerves, enabling the limb to perform certain motor functions, and the movement of the limbs affects the activity of the cerebral cortex through the afferent nerves. The CMC strength in descending

| Levels | Fre | Group | Left hand |  | Right hand |  |
|---|---|---|---|---|---|---|
| 5 kg | \(\theta\) | HC | 0.37 ± 0.12 | 0.45 ± 0.15 | 0.40 ± 0.16 | 0.38 ± 0.15 |
| | | PA | 0.39 ± 0.12 | 0.38 ± 0.11 | 0.40 ± 0.10 | 0.38 ± 0.16 |
| | \(\alpha\) | HC | 0.85 ± 0.22 | 0.88 ± 0.35 | 0.85 ± 0.24 | 0.86 ± 0.26 |
| | | PA | 0.81 ± 0.24 | 0.73 ± 0.18 | 0.99 ± 0.21 | 0.87 ± 0.28 |
| | \(\beta\) | HC | 2.43 ± 0.42 | 2.21 ± 0.33 | 2.51 ± 0.54 | 2.31 ± 0.56 |
| | | PA | 2.36 ± 0.41 | 2.67 ± 0.42 | 2.26 ± 0.39 | 2.40 ± 0.47 |
| | \(\gamma\) | HC | 1.87 ± 0.31 | 1.84 ± 0.38 | 1.95 ± 0.43 | 1.97 ± 0.40 |
| | | PA | 2.03 ± 0.54 | 1.91 ± 0.39 | 2.06 ± 0.35 | 1.94 ± 0.37 |
| 10 kg | \(\theta\) | HC | 0.38 ± 0.12 | 0.46 ± 0.23 | 0.40 ± 0.19 | 0.35 ± 0.15 |
| | | PA | 0.43 ± 0.13 | 0.39 ± 0.11 | 0.43 ± 0.16 | 0.37 ± 0.10 |
| | \(\alpha\) | HC | 0.83 ± 0.19 | 0.76 ± 0.28 | 0.86 ± 0.26 | 0.84 ± 0.25 |
| | | PA | 0.76 ± 0.24 | 0.81 ± 0.22 | 0.92 ± 0.31 | 1.00 ± 0.45 |
| | \(\beta\) | HC | 2.34 ± 0.40 | 2.21 ± 0.36 | 2.64 ± 0.52 | 2.43 ± 0.58 |
| | | PA | 2.20 ± 0.43 | 2.38 ± 0.45 | 2.43 ± 0.52 | 2.55 ± 0.42 |
| | \(\gamma\) | HC | 1.72 ± 0.23 | 1.71 ± 0.30 | 2.08 ± 0.39 | 1.99 ± 0.36 |
| | | PA | 1.82 ± 0.33 | 1.91 ± 0.35 | 1.72 ± 0.28 | 1.80 ± 0.32 |
| 20 kg | \(\theta\) | HC | 0.47 ± 0.25 | 0.45 ± 0.16 | 0.38 ± 0.15 | 0.39 ± 0.13 |
| | | PA | 0.78 ± 0.20 | 0.86 ± 0.30 | 0.83 ± 0.22 | 0.81 ± 0.17 |
| | \(\beta\) | HC | 2.33 ± 0.34 | 2.18 ± 0.35 | 2.70 ± 0.56 | 2.46 ± 0.54 |
| | | PA | 2.04 ± 0.35 | 2.12 ± 0.44 | 2.10 ± 0.34 | 2.08 ± 0.42 |
direction indicated the amount of information that the cerebral cortex transmits to the control muscle neurons, and that in ascending direction represented the amount of information that muscle neurons feed back to the cerebral cortex. It can be seen that the CMC is bilateral, and it has a closed-loop structure.

In time-domain, the results (Fig. 3) indicated that the coupling between in both directions is more significant as the grip strength increases. One possible explanation is that the functional coupling of the cortex muscles reflects the relatively steady-state of control of the cerebral motor cortex. The motor cortex consumes less energy to maintain steady-state motion. As the grip strength increases, more neurons need to be synchronized, resulting in the motor cortex requiring more energy to maintain steady-state motion. This is consistent with the existing research results. The CMC of right-handed (skilled) is greater than that of left-handed, and it may be due to the reason that the brain has stronger control over the dominant hand. In addition, the CMC strength in both directions at each steady-state grip task was also decreased for PA compared to HC. This difference may be due to the motor control dysfunction caused by the damage of the cerebral motor function area and thus prevent them activate the motoneuron and motor cortex exactly. The exact underlying mechanism behind the appearance of abnormal coordination patterns during post-stroke recovery has not been conclusively determined, but might be associated with a loss in cortical control and an increased usage of undamaged, indirect descending direct corticospinal pathway to the proximal and distal muscles via the brainstem.

In the frequency domain, the results from Figs. 5 and 6 and Table 2 showed that the CMC in both directions was mainly reflected at the beta frequency band, indicating that the control movement of the upper limb was dominated within the whole beta band, which is consistent with the literatures. It also indicated that the coupling oscillation at the beta band can reflect the maintenance function of the motor cortex for stable motion output. Similarly, the CMC differences between PA and HC mainly occurred at the beta band, and this was consistent with the literatures. However, it was inconsistent with the literature in which the CMC differences between PA and HC mainly occurred in the gamma band. This can be explained by the fact that different experiment paradigm was used. The CMC differences demonstrated that the CS at the beta band in descending direction was slightly higher than that in ascending direction for control groups, while the opposite result was observed for stroke patients. The reason is that the CS for PA in descending direction at the beta band decreased, and that in ascending direction was increased compared to HC. One explanation is that intracranial haemorrhage may cause the neurons in the cerebral motion area unable to control the stable motion, leading to more information feedback to the cerebral motor cortex to activate more neurons.

There were some limitations in this initial study, which was that the conclusion by the proposed time-frequency domain copula-GC was obtained from a limited number of subjects with small size of EEG and EMG data. However, we believed the current discoveries can provide some biomarkers and biological insights that might be useful.
for the rehabilitative evaluation of motor function impairment after stroke. Further studies will recruit more subjects to further validate the proposed method. Meanwhile, although the copula-GC method has the ability to detecting nonlinear and high-order causal relationships, it cannot separate linear and nonlinear causal components. Recently, Schaeck et al.\textsuperscript{46} has proposed a robust time-varying generalized partial directed coherence (rTV-gPDC) method, which can independently obtain the linear and nonlinear causalities, and contrastively analyze the linear and nonlinear relationships in time-frequency domain to study the CMC phenomenon and pathological mechanism of the diseases related with movement.

5. Conclusion

In this study, a time-frequency domain copula-GC method was proposed to assess the CMC strength of both PA and HC during steady-state grip tasks. Results showed that the CMC phenomenon is bi-directional. In time-domain, the CMC in descending direction is stronger than that in ascending direction for healthy controls. Meanwhile, the CMC increases with the increasing grip strength, and the CMC of right-handed (skilled) is larger than that of the left hand in both directions. It can also be noticed that the CMC for PA tends to be lower than that for HC in both directions. As for the frequency domain, the strongest predefined CS was observed at the beta frequency band during the steady-state grip output. In addition, the CS in descending direction for healthy controls was slightly larger than that in ascending direction. Moreover, PA show a lower CS in descending direction compared to healthy controls, but the CS in ascending direction is increased for PA. Therefore, the CS in descending direction is lower than that in ascending direction for PA. From the preliminary results of this study, the proposed time-frequency domain copula-GC method can effectively characterize the coupling characteristics of cortical muscles at different frequency bands and in different directions of delivery, and can provide a theoretical basis for understanding motor control processes and the pathological mechanisms of movement disorders.

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References

1. S. N. Baker, Oscillatory interactions between sensorimotor cortex and the periphery, Curr. Opin. Neurobiol. 17(6) (2007) 649–655.
2. P. Grosse, M. J. Cassidy and P. Brown, EEG-EMG, MEG-EMG and EMG-EMG frequency analysis: Physiological principles and clinical applications, Clin. Neurophysiol. 113(10) (2002) 1523–1531.
3. B. A. Conway, D. M. Halliday, S. F. Farmer, U. Shahani, P. Maas, A. I. Weir and J. R. Rosenberg, Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man, *J. Physiol.* **489**(3) (1995) 917–924.

4. C. G. Von, Z. Bayraktaroglu, F. U. Hohlfeld, F. Losch, G. Curio and V. V. Nikulin, Corticomuscular coherence in acute and chronic stroke, *Clin. Neurophysiol.* **125**(6) (2014) 1182–1191.

5. B. Schelter, J. Timmer and M. Eichler, Assessing the strength of directed influences among neural signals using renormalized partial directed coherence, *J. Neurosci. Meth.* **179**(1) (2009) 121–130.

6. Y. Fang, J. J. Daly, J. Sun, K. Hvorat, E. Fredrickson, S. Pundik, V. Sahgal and G. H. Yue, Functional corticomuscular connection during reaching is weakened following stroke, *Clin. Neurophysiol.* **120**(5) (2009) 994–1002.

7. T. Shibata, Y. Suhara, T. Oga, Y. Ueki, T. Mima and S. Ishii, Application of multivariate autoregressive modeling for analyzing the interaction between EEG and EMG in humans, *Int. Congress* **1270** (2004) 249–253.

8. R. Kristeva, T. Popa, V. Chakarov and S. Hummel, Cortico-muscular coupling in a patient with postural myoclonus, *Neurosci. Lett.* **366**(3) (2004) 259–263.

9. T. Mima, K. Toma, B. Koshy and M. Hallett, Coherence between cortical and muscular activities after subcortical stroke, *Stroke* **32**(11) (2001) 2597.

10. Z. Yang, P. Yu, G. Xu, L. Li and J. Wang, Using corticomuscular coherence to reflect function recovery of paretic upper limb after stroke, *Front. Neurol.* **8** (2017) 728.

11. P. Ma, Y. Chen, Y. Du, Y. Su, X. Wu, Z. Liang and P. Xie, Analysis of corticomuscular coherence during rehabilitation exercises after stroke, *J. Biomed. Eng.* **31**(5) (2014) 971–977.

12. S. N. Baker, M. Chiu and E. E. Fetz, Afferent encoding of central oscillations in the monkey arm, *J. Neurophysiol.* **95**(6) (2006) 3904–3910.

13. C. L. Witham, M. Wang and S. N. Baker, Corticomuscular coherence between motor cortex, somatosensory areas and forearm muscles in the monkey, *Front. Syst. Neurosci.* **4** (2010) 38.

14. Y. Zhang, C. Zou, X. Chen, Y. Yin, S. Cheng, Y. Chen and P. Xie, Synchronous analysis of corticomuscular coherence based on Gabor wavelet-transfer entropy, *J. Biomed. Eng.* **34**(6) (2017) 850–856.

15. S. Hu, G. Dai, G. A. Worrell, Q. Dai and H. Liang, Causality analysis of neural connectivity: Critical examination of existing methods and advances of new methods, *IEEE Trans. Neural Netw.* **22**(6) (2011) 829–844.

16. M. Hu, M. Li, W. Li and H. Liang, Joint analysis of spikes and local field potentials using copula, *Neuroimage* **133** (2016) 457–467.

17. S. Hu, H. Wang, J. Zhang, W. Kong, C. Yu and R. Kozna, Comparison analysis: Granger causality and new causality and their applications to motor imagery, *IEEE Trans. Neural Netw. Learn. Syst.* **27**(7) (2016) 1439–1444.

18. P. Xie, F. Yang, X. Chen, Y. Du and X. Wu, Functional coupling analyses of electroencephalogram and electromyogram based on multiscale transfer entropy, *Acta Phys. Sin.* **64**(24) (2015) 248702.

19. G. V. Karanikolas, G. B. Giannakis, K. Slavakis and R. M. Leahy, Multi-kernel based nonlinear models for connectivity identification of brain networks, in *IEEE International Conf. Acoustics, Speech and Signal Processing (ICASSP)* (IEEE Press, Shanghai, China, 2016), pp. 6315–6319.

20. Q. Luo, T. Ge, F. Grabenhorst, J. Feng and E. T. Rolls, Attention-dependent modulation of cortical taste circuits revealed by Granger causality with signal-dependent noise, *PLoS Comput. Biol.* **9**(10) (2013) e1003265.
21. E. Siggiridou and D. Kugiumtzis, Granger causality in multivariate time series using a time-ordered restricted vector autoregressive model, *IEEE Trans. Signal Process.* **64**(7) (2016) 1759–1773.

22. T. Schreiber, Measuring information transfer, *Phys. Rev. Lett.* **85**(2) (2000) 461–464.

23. X. Chen, P. Xie, Y. Zhang, Y. Chen, F. Yang, L. Zhang and X. Li, Multiscale information transfer in functional corticomuscular coupling estimation following stroke: A pilot study, *Front. Neurol.* **9** (2018) 287.

24. Y. Gao, L. Ren, R. Li and Y. Zhang, Electroencephalogram-electromyography coupling analysis in stroke based on symbolic transfer entropy, *Front. Neurol.* **8** (2017) 716.

25. L. Barnett, A. B. Barrett and A. K. Seth, Granger causality and transfer entropy are equivalent for Gaussian variables, *Phys. Rev. Lett.* **103**(23) (2009) 238701.

26. R. B. Nelsen (eds.), *An Introduction to Copulas* (Springer Science & Business Media, New York, 2006), pp. 7–50.

27. D. H. Oh and A. J. Patton, High-dimensional copula-based distributions with mixed frequency data, *J. Econ.* **193**(2) (2016) 349–366.

28. D. Qian, B. Wang, X. Qing, T. Zhang, Y. Zhang, X. Wang and M. Nakamura, Drowsiness detection by bayesian-copula discriminant classifier based on EEG signals during daytime short nap, *IEEE Trans. Biomed. Eng.* **64**(4) (2016) 743–754.

29. J. Dauwels, H. Yu, X. Wang, F. Vialatte, C. Latchoumane, J. Jeong and A. Cichocki, Inferring brain networks through graphical models with hidden variables, in *Machine Learning and Interpretation in Neuroimaging* (Springer, Berlin, Heidelberg, 2012), pp. 194–201.

30. X. Geng, Q. She, Q. Zhang and Z. Luo, Multivariate causality analysis method of motor imagery EEG signals based on copula, *Space Med. Med. Eng.* **31**(1) (2018) 49–56.

31. M. Hu, W. Li and H. Liang, A copula-based Granger causality measure for the analysis of neural spike train data, *IEEE/ACM Trans. Comput. Biol. Bioinform.* **15**(2) (2018) 562–569.

32. X. Gao, W. Shen, C. Ting, S. C. Cramer, R. Srinivasan and H. Ombao, Modeling brain connectivity with graphical models on frequency domain, arXiv:1810.03279.

33. R. A. Ince, B. L. Giordano, C. Kayser, G. A. Rousselet, J. Gross and P. G. Schyns, A statistical framework for neuroimaging data analysis based on mutual information estimated via a gaussian copula, *Hum. Brain Mapp.* **38**(3) (2017) 1541–1573.

34. M. Hu and H. Liang, A copula approach to assessing Granger causality, *Neuroimage* **100** (2014) 125–134.

35. A. Sklar, Random variables, joint distribution functions, and copulas, *Kybernetika* **9**(6) (1973) 449–460.

36. B. Lionel and B. Terry, Transfer entropy as a log-likelihood ratio, *Phys. Rev. Lett.* **109**(13) (2012) 138105.

37. L. Barnett and A. K. Seth, The MVGC multivariate Granger causality toolbox: A new approach to Granger-causal inference, *J. Neurosci. Meth.* **223** (2014) 50–68.

38. P. Brown, Cortical drives to human muscle: The Piper and related rhythms, *Prog. Neurobiol.* **60**(1) (2000) 97–108.

39. T. Ono, M. Mukaino and J. Ushiba, Functional recovery in upper limb function in stroke survivors by using brain-computer interface A single case A-B-A-B design, in *Annual Int. Conf. IEEE Eng. Med. Biol. Soc. (EMBC)* (IEEE Press, Osaka, Japan, 2013), pp. 265–268.

40. R. Kristeva, L. Patino and W. Omlor, Beta-range cortical motor spectral power and corticomuscular coherence as a mechanism for effective corticospinal interaction during steady-state motor output, *Neuroimage* **36**(3) (2007) 785–792.
41. C. M. Laine, F. Negro and D. Farina, Neural correlates of task-related changes in physiological tremor, *J. Neurophysiol.* **110**(1) (2013) 170–176.
42. T. Gilbertson, E. Lalo, L. Doyle, V. Di Lazzaro, B. Cioni and P. Brown, Existing motor state is favored at the expense of new movement during 13–35 Hz oscillatory synchrony in the human corticospinal system, *J. Neurosci.* **25**(34) (2005) 7771–7779.
43. A. G. Androulidakis, L. M. Doyle, T. P. Gilbertson and P. Brown, Corrective movements in response to displacements in visual feedback are more effective during periods of 13–35 Hz oscillatory synchrony in the human corticospinal system, *Eur. J. Neurosci.* **24**(11) (2006) 3299–3304.
44. P. L. Nunez and R. Srinivasan (eds.), *Electric Fields of The Brain: The Neurophysics of EEG.* (Oxford University Press, New York, 2006), pp. 15–102.
45. V. Siemionow, G. H. Yue, V. K. Ranganathan, J. Z. Liu and V. Sahgal, Relationship between motor activity-related cortical potential and voluntary muscle activation, *Exp. Brain Res.* **133**(3) (2000) 303–311.
46. T. Schäck, M. Muma, M. Feng, C. Guan and A. M. Zoubir, Robust nonlinear causality analysis of nonstationary multivariate physiological time series, *IEEE Trans. Biomed. Eng.* **65**(6) (2018) 1213–1225.

Qingshan She received the B.S. and M.S. degrees in Materials Science and Engineering from Lanzhou University of Technology, Lanzhou, and the Ph.D. degree in Control Science and Engineering from Zhejiang University, Hangzhou, China. He is currently an Associate Professor with the School of Automation, Hangzhou Dianzi University, Hangzhou, China. His research interests include rehabilitation robot, machine learning, brain-computer interface and its applications.

Hang Zheng received the B.S. degree in Electrical Engineering and Automation and the M.S. degree in Pattern Recognition and Intelligent System from Hangzhou Dianzi University, Hangzhou, China. His research interests include biological signal processing, corticomuscular coupling.

Tongcai Tan received the B.S. degree in rehabilitation medical technology from West China Medical University and M.S. degree in acupuncture and massage from Zhejiang Chinese Medical University. He is currently an assistant of director and chief therapist of the Department of Rehabilitation Medicine, Zhejiang Provincial People’s Hospital, affiliated to Hangzhou Medical College. His research interests include nerve rehabilitation, bone and joint rehabilitation, and human-computer interaction.
Botao Zhang received the Ph.D. degree in control from East China University of Science and Technology, Shanghai, China, in 2012. He is presently an Associate Professor at the School of Automation, Hangzhou Dianzi University, Hangzhou, China. His current research interests include robot navigation, path planning and robot vision.

Yingle Fan received the B.S. degree in Industrial Automation and the Ph.D. degree in Biomedical Engineering from Zhejiang University, Hangzhou, China. He is currently a Professor with the School of Automation, Hangzhou Dianzi University, Hangzhou, China. His research interests include neural information coding, biological vision mechanism, and brain-computer interaction.

Zhizeng Luo received the B.S. degree in mechatronic engineering from University of Electronic Science and Technology of China, Chengdu, and the Ph.D. degree in industrial automation from Zhejiang University, Hangzhou, China. He is currently a Professor with the School of Automation, Hangzhou Dianzi University. He is also the director with the Institute of Intelligent Control and Robotics. His research interests include pattern recognition and intelligent systems, rehabilitation robot, and biological information processing.