Novel analysis of fNIRS acquired dynamic hemoglobin concentrations: application in young children with autism spectrum disorder

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Abstract: A novel analysis of the spatial complexity of functional connectivity (SCFC) was proposed to investigate the spatial complexity of multiple dynamic functional connectivity series in an fNIRS study, using an approach combining principal component analysis and normalized entropy. The analysis was designed to describe the complex spatial features of phase synchrony based dynamic functional connectivity (dFC), which are unexplained in traditional approaches. The feasibility and validity of this method were verified in a sample of young patients with autism spectrum disorders (ASD). Our results showed that there were information exchange deficits in the right prefrontal cortex (PFC) of children with ASD, with markedly higher interregion SCFCs between the right PFC and other brain regions than those of normal controls. Furthermore, the global SCFC was significantly higher in young patients with ASD, along with considerably higher intraregion SCFCs in the prefrontal and temporal lobes which represents more diverse information exchange in these areas. The study suggests a novel method to analyze the fNIRS required dynamic hemoglobin concentrations by using concepts of SCFC. Moreover, the clinical results extend our understanding of ASD pathology, suggesting the crucial role of the right PFC during the information exchange process.

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OCIS codes: (170.2655) Functional monitoring and imaging; (170.5380) Physiology; (170.3880) Medical and biological imaging.

References and links

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1. Introduction

Various kinds of neural signals have been obtained by functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIRS), electroencephalography (EEG), and magnetoencephalography (MEG) in both resting-state or task-related states. The statistical interdependence or synchronization between neural signals of spatially remote brain areas, referred to as functional connectivity (FC), has always been computed to describe the...
functional architecture of brain [1–4]. Moreover, those characteristics are regarded to be closely associated with various psychiatric disorders and cognitive processes [5–8].

The graph theory provides mathematical tools to obtain the features of FC to represent the functional architecture of brain [9, 10]. In the theory, a complex network of the human brain is defined by a collection of nodes and links between pairs of nodes. The nodes (a measurement location with a serial of neural signals) usually represent brain regions determined by certain parcellation schemes in fMRI studies and measurement areas in EEG/fNIRS/MEG studies, whereas links represent the FC between pairs of nodes. In the traditional way, the FC only exists if the absolute value of Pearson’s correlation coefficient computed between two serials of signals was larger than a thresholding value defined by the researcher. Recently, a new algorithm based on phase synchrony (i.e., phase-locking value) was proposed to better understanding the characters of FC [11]. However, there are still two limitations in the traditional FC analyses. First, thresholding using either absolute or proportional values to decide if the FC exits is a necessary step even though there is no consensus on what specific threshold should be used [12]. Second, the traditional complex network approach implicitly assumes that FCs are constant during recording, thus time-averaged FC metrics are commonly evaluated. Nevertheless, this hypothesis has been challenged by many recently studies [13, 14], because the traditional time-averaged or static FC metrics only provided an average of complex spatial-temporal phenomena.

Using either sliding window analysis or time-frequency analysis, recent studies have begun to uncover the temporal features of FC [15, 16]. Emerging evidence suggests that dynamic FC (dFC) metrics may reflect the dynamic changes in macroscopic neural activity patterns underlying critical aspects of cognition and behavior [14]. In addition, examining temporal features of FC could provide a more accurate description of brain disorders, and potential prognostic and diagnostic biomarkers [13, 14].

Spatial complexity is commonly used to assess the number of spatial modes of multi-region neural signals, and varies inversely with global synchronization across spatially distributed brain regions [17, 18]. The omega complexity, proposed by Wackermann (1996), could be considered an index of spatial complexity. It was sensitive to different types of cognitive processes, chronological ages, neuroactive substances, and neuropathological variables [19–23]. Traditionally, spatial complexity analysis was applied to neural signals, especially multi-channel EEG data. Since the dFCs could be considered as physiologically significant time series (i.e., dFC-series), it remains unknown whether testing the spatial complexity of multiple dFC-series would help us uncover the complex spatial-temporal information of FC. Thus, in the current study, we proposed an approach to investigate the spatial complexity of multiple dFC-series, defined as spatial complexity of functional connectivity (SCFC), and hypothesized that the SCFC analysis would provide results that were consistent with and extended previous findings using other techniques (i.e., time-averaged or dynamic FC analysis, complex network analysis).

Autism spectrum disorder (ASD) describes a range of developmental disorders that is characterized by impairments in social and communicative development, along with repetitive stereotyped behaviors and/or restricted interests [24]. It is also a disorder with an aberrant pattern of FC. Many studies have found that children with ASD exhibited lower levels of FC among brain regions, such as the interhemispheric FC [25], the connectivity in networks that are associated with self-referential, autobiographical memory, face recognition, theory of mind [26], sentence apprehension [27], and so on. Moreover, an fNIRS study conducted by our group revealed that, compared with normal controls, young children with ASD exhibited information exchange deficits in the right PFC, appearing as a lower level of linkages with the left PFC and the bilateral temporal cortex [9]. However, in that study, we used the traditional complex network approach to construct functional networks. Considering the evidence for the aberrant pattern of FC and the right PFC impairment, we would apply the novel SCFC analysis to young children with ASD and testify to its feasibility and validity.
fNIRS, a non-invasive brain imaging tool, is a promising technique to investigate the neurodevelopment of young children with ASD. This technique monitors neural activity by measuring the absorption of near-infrared light between 650 nm and 950 nm through the intact skull. fNIRS is safe, portable, cost-effective, and relatively insensitive to head movement [7, 9, 28, 29]. Thus, it was applied to the acquisition of neural signals of young children with ASD in the current study.

In all, the current study has two main goals. First, we aimed to verify the feasibility and validity of spatial complexity analysis for multiple dFC-series in an fNIRS study by exploring the neuropathological mechanism of ASD. Specially, considering a previous study [9], we hypothesized that abnormal information exchange patterns would be found between the right PFC and other brain regions. Second, we aimed to test whether SCFC (i.e., the global and local SCFCs) could be a good index to represent the unique psychopathology of young children with ASD, suggesting additional information of their brain abnormalities beyond the traditional FC analysis.

2. Methods

2.1 Participants

Thirty-five children with ASD (mean age = 5.96 years, SD = 1.22 years; 4 to 9 years of age) and thirty-one age-matched typically developing (TD) children (mean age = 6.56 years, SD = 1.2 years; 4 to 9 years of age) participated in this study. The patients and controls did not differ significantly with respect to age (p > 0.05). All the clinical children were recruited from a local special school (Nanjing Mingxin Intelligence-Promoting School). They all received an ASD diagnosis according to the fourth edition of the Diagnostic and Statistical Manual (DSM-IV) in Nanjing Brain Hospital.

None of the children in the ASD group ever been diagnosed with the comorbidity of attention-deficit/hyperactivity disorder (ADHD), and were identified as having high-functioning autism (within the near normal or normal range of intelligence) according to their teachers’ reports. None of the children in the TD group had a history of psychiatric or neurological disorder. Parents of all participants signed an informed consent form for the present experiment, which was approved by the local Ethics Committee.

2.2 Experimental protocol

During fNIRS signal recording, the child was held by his/her parent or teacher to ensure the child would feel safe during the experiment. Since children with ASD cannot keep their eyes closed or open for a relatively long time and were usually irritable during the fNIRS scanning, all children in both groups were asked to watch the first episode of the popular Chinese cartoon named “BEAR.” Besides, the children’s behaviors during the whole experiment were recorded using a camera. For more information about the experimental protocol, see previous studies conducted by our group [9, 30].

2.3 fNIRS data acquisition

The fNIRS signals were recorded by a 44-channel real-time fNIRS system, LABNIRS (Shimadzu Corporation, Kyoto, Japan) with a scanning rate of 27 ms (i.e., a sampling rate of about 37 Hz). The 16 emitter probes and 16 detector probes were plugged into a customized cap (distance between adjacent probes was 30 mm), resulting in 44 measurement channels. The probes were positioned according to the international 10-20 system, as shown in Fig. 1. Each emitter probe could generate near infrared light at three wavelengths (i.e., 780, 805, and 830 nm), which were received by the adjacent detector probes after traveling through the head. A pair of emitter and neighboring detector probes formed one channel. The location of each channel was defined as the center position of the emitter-detector optodes. The changes in oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) concentration for each time-
point and each channel were determined by the modified Beer-Lambert law [31]. The concentration of total-hemoglobin (total-Hb) was defined as the sum of the concentration of oxy-Hb and deoxy-Hb.

Fig. 1. Schematic of the probe and channel configurations on the head. Orange circles indicate the light sources (emitter probes); Gray circles indicate the light detectors (detector probes). Numbers 1 to 44 represent the 44 measurement channels located between each emitter-detector pair.

2.4 Data preprocessing

Contaminated data fragments caused by large head movements, unexpected behaviors, and sharp changes in fNIRS signals were removed by a visual inspection [9, 30]. Five children in the ASD group and two children in the TD group with too short retention time (i.e., less than 8 min) or with one or more poor signal-to-noise ratio channels were excluded from further data analysis. The infomax ICA algorithm was then performed on oxy-Hb, deoxy-Hb and total-Hb, respectively. Independent components related to low-frequency (< 0.003 Hz) drift, sudden jumps, motion-induced artifacts, cardiac pulsations and respiratory signals were identified and rejected manually [32]. One child with ASD was excluded from further analysis due to extremely low signal-to-noise ratio. Afterwards, a band-pass filtering (0.009-0.08 Hz) was performed on the hemoglobin concentration signals as suggested by previous studies [9, 33, 34]. Such strict noise-control procedures (i.e., adopting ICA denoising and band-pass filtering) could validly reduce the influence of typical noise components in fNIRS signals. The remaining data set of 29 children in the ASD group (mean age = 6.0 ± 1.2 years; 23 boys) and 29 children in the TD group (mean age = 6.5 ± 1.2 years; 20 boys) was used for further SCFC analysis. The final data set did not differ in age and gender (p>0.05) between the two groups. Lastly, to suppress the edge effect in band-pass filtering and eliminate the influence of signal length on group difference, only the time series of the hemoglobin concentration signals between 1 to 8 min were included in the SCFC analysis.

The relationships between different kinds of fNIRS signals and the BOLD signal are still highly debated as discussed in previous studies [34, 35]. Nonetheless, our previous findings supported that the oxy-Hb signals had more vigorous effects than the deoxy-Hb and total-Hb.
signals [9, 30]. Thus, the oxy-Hb concentration was chosen to compute dFCs and estimate the SCFC of participants in the current study. SCFC analyses using the deoxy-Hb and total-Hb concentration were reported as well, which should be helpful to understand the consistency among these three kinds of brain signals.

2.5 Estimating the SCFC

Here, the SCFC is defined as the heterogeneity of multiple dFC-series between certain brain regions. If these dFC-series were completely homogeneous (e.g., the pairwise correlation coefficients between these dFC-series were equal to 1), then a minimum SCFC is found (i.e., these dFC-series have only one spatial mode). If these dFC-series were completely heterogeneous (i.e., the pairwise correlation coefficients between these dFC-series were equal to 0), then a maximum SCFC is revealed (i.e., these dFC-series consist of N spatial modes, where N is the number of dFC-series). Figure 2 shows an example of these two cases. Note that, the above two situations only represent two extreme conditions, since in typical neuroimaging studies the pairwise correlation coefficients between these dFC-series are distributed between 0 and 1. In the current study, an approach based on the temporal principal component analysis (PCA) and the normalized entropy was proposed to compute the SCFC, which was calculated as the “normalized entropy of the Eigenspectrum of the covariance matrix for multiple dFC-series”.

Fig. 2. An illustration of the spatial complexity of dFC-series in two extreme situations. Top panel: The two dFC-series (i.e., dFC-series a and b) shown in this panel are completely heterogeneous (i.e., the Pearson correlation coefficient between these dFC-series was equal to 0). In this case, a maximum SCFC is revealed (i.e., the two dFC-series consist of two spatial modes). Bottom panel: The two dFC-series (i.e., dFC-series a and c) shown in this panel are completely homogeneous (i.e., the Pearson correlation coefficient between these dFC-series was equal to 1). In this case, a minimum SCFC is detected (i.e., the two dFC-series consist of only one spatial mode).

The entire procedure of the SCFC estimation is comprised of the following three steps, as shown in Fig. 3:
(1) Estimating dFC-series

For each participant, the dFC-series of signals were estimated by use of the sliding-window approach [14], as shown in Fig. 3. Note that few studies have examined the time-varying nature of functional connectivity in fNIRS signals [36]. Since it is not clear how frequently the FC changes in fNIRS signals, several window lengths (i.e., 10, 30, 50, 70 and 90 sec) were used to avoid the arbitrary selection of window length. The overlap between adjacent windows is 99%. Much evidence pointed that phase synchrony was a basic mechanism of functional integration in the human brain and has more advantages than the Pearson’s correlation approach in understanding complex collective dynamical behavior, such as brain activities [11, 37]. Thus, FC within each time window was computed for each pair of channels by use of the phase-locking value (PLV).

With the Hilbert transform, the instantaneous phase $\varphi(t)$ of signal $x(t)$ can be calculated as

$$\varphi(t) = \arctan \left( \frac{x_H(t)}{x(t)} \right),$$

(1)

in which $x_H(t)$ is the Hilbert transform of $x(t)$ and is given by

$$x_H(t) = \frac{1}{\pi} PV \int_{-\infty}^{t} \frac{x(\tau)}{t-\tau} d\tau,$$

(2)

and where $PV$ is Cauchy’s principal value.

The $PLV$ between channel $u$ and $v$ in a time window ($PLV_{uv}$) is determined by

$$PLV_{uv} = \left| \frac{1}{n} \sum_{i=1}^{n} e^{i [\varphi_i(u) - \varphi_i(v)]} \right|,$$

(3)
where $\phi_u(t_k)$ and $\phi_v(t_k)$ are the instantaneous phase of hemoglobin concentration of channel $u$ and $v$ at time $t_k$ respectively, and $n$ is the length of the time window (here, $n = 370, 1110, 1850, 2590$ and $3330$ for window lengths $10$ sec, $30$ sec, $50$ sec, $70$ sec, and $90$ sec, respectively). Using this sliding-window approach, we could estimate the PLV of each window between each pair of channels, resulting in dynamic functional connectivity (dFC) series between each pair of channels.

Since the calculation of the Hilbert transform requires integration over infinite time, $10\%$ of the calculated instantaneous values are discarded on each side of signal, which means that the final retention time of instantaneous phase time series for each participant is about $367$ sec. Thus, by the above approach, $10$ sec, $30$ sec, $50$ sec, $70$ sec and $90$ sec time windows yielded $3576, 1126, 636, 426$ and $309$ sliding-windows and thus resulted in $3576, 1126, 636, 426, \text{and } 309$ FC maps.

(2) Extracting dFC-series of interest

After estimating the dFC-series, the dFC-series of interest were extracted: the global SCFC, the intraregion SCFC, and the interregion SCFC.

The global SCFC was defined as the spatial complexity of dFC-series for all pairs of $44$ scalp channels, whereas the intraregion SCFC was defined as the spatial complexity of dFC-series for all pairs of channels within a certain brain region. The dFC-series involving any channel in the other brain regions were excluded during intraregion SCFC computation. Lastly, the interregion SCFC between brain regions $A$ and $B$ was referred to as the spatial complexity of dFC-series between a channel located in region $A$ and another channel located in region $B$.

The scalp areas measured in the current study could be divided into $6$ regions, i.e., left prefrontal cortex (LP, channels 1-10), right prefrontal cortex (RP, channels 23-32), left temporal lobe (LT, channels 11-18), right temporal lobe (RT, channels 33-40), left occipital lobe (LO, channels 19-22), and right occipital lobe (RO, channels 41-44). Thus, $6$ intraregion SCFCs and $15$ (i.e., $C_6^2$) interregion SCFCs were extracted.

(3) Computing SCFC

The global SCFC, intraregion SCFCs, and interregion SCFCs were estimated for each participant, for each kind of fNIRS signals (i.e., oxy-Hb, deoxy-Hb, and total-Hb) at each window length (i.e., $10$, $30$, $50$, $70$ and $90$ sec) by the following process.

First, temporal PCA was conducted for the dFC series of interest, which yielded $m$ principal components ($m$ is the number of dFC-series of interest) and spectrum of eigenvalues.

Second, to assess the relative contribution of each principal component to the total variance, the eigenvalues of principal components were normalized to the unit sum. The normalized eigenvalue of the $i$-th principal component was calculated as

$$\lambda'_i = \lambda_i / \sum_{j=1}^{m} \lambda_j,$$

where $m$ was the number of principal components or dFCs-series of interest, and $\lambda_i$ and $\lambda'_i$ represented the eigenvalue and the normalized eigenvalue of the $i$-th principal component respectively.
Lastly, the SCFC, defined as the normalized entropy of normalized eigenvalues, was computed with the following equation:

\[
SCFC = -\frac{\sum_{i=1}^{m} \lambda_i \log \lambda_i}{\log m}.
\]  

According to Eq. (5), the SCFC would attain values from the interval 0 to 1. The lowest value SCFC = 0 means the dFC-series of interest consisted of exactly one principal component or spatial mode, and a maximum synchronization between dFC-series of interest is detected. The highest value SCFC = 1 indicates the total data variance is uniformly distributed across all \(m\) principal components (i.e., all \(m\) dFC-series), and a maximum spatial complexity is found.

2.6 Statistical tests

An independent samples \(t\)-test was conducted to evaluate the group differences of the global, intraregion, and interregion SCFCs for each kind of fNIRS signals (i.e., oxy-Hb, deoxy-Hb, and total-Hb) at each window length (i.e., 10, 30, 50, 70, and 90 sec), respectively. To control for multiple comparisons, the significance level (\(p\) value) was corrected by the false discovery rate (FDR) procedure [38].

3. Results

3.1 Global SCFC

As shown in Table 1, the global SCFC of oxy-Hb in the ASD group was significantly higher than that in the TD group, when the window length was 10 sec, 30 sec, and 50 sec. However, this significant group effect (ASD > TD) could only be found in the global SCFC of deoxy-Hb at a window length of 10 sec and 30 sec, and in the global SCFC of total-Hb at a window length of 10 sec.

### Table 1. The group differences of global SCFC at different window lengths.

|                | ASD (mean ± SD) | TD (mean ± SD) | \(t(56)\) | \(p\)  |
|----------------|-----------------|----------------|----------|-------|
| oxy-Hb 10 s    | 0.530 ± 0.012   | 0.513 ± 0.022  | 3.784    | 0.001 |
| oxy-Hb 30 s    | 0.451 ± 0.013   | 0.436 ± 0.021  | 3.286    | 0.002 |
| oxy-Hb 50 s    | 0.383 ± 0.014   | 0.372 ± 0.019  | 2.550    | 0.014 |
| oxy-Hb 70 s    | 0.334 ± 0.015   | 0.325 ± 0.016  | 2.157    | 0.035 |
| oxy-Hb 90 s    | 0.295 ± 0.016   | 0.287 ± 0.013  | 2.230    | 0.03  |
| deoxy-Hb 10 s  | 0.530 ± 0.011   | 0.521 ± 0.011  | 3.084    | 0.003 |
| deoxy-Hb 30 s  | 0.449 ± 0.010   | 0.441 ± 0.013  | 2.640    | 0.011 |
| deoxy-Hb 50 s  | 0.384 ± 0.010   | 0.377 ± 0.013  | 2.130    | 0.038 |
| deoxy-Hb 70 s  | 0.334 ± 0.011   | 0.329 ± 0.012  | 1.835    | 0.072 |
| deoxy-Hb 90 s  | 0.295 ± 0.012   | 0.291 ± 0.012  | 1.149    | 0.255 |
| total-Hb 10 s  | 0.528 ± 0.018   | 0.517 ± 0.016  | 2.476    | 0.016 |
| total-Hb 30 s  | 0.451 ± 0.013   | 0.443 ± 0.013  | 2.171    | 0.034 |
| total-Hb 50 s  | 0.386 ± 0.015   | 0.380 ± 0.014  | 1.438    | 0.156 |
| total-Hb 70 s  | 0.336 ± 0.015   | 0.333 ± 0.014  | 0.821    | 0.415 |
| total-Hb 90 s  | 0.298 ± 0.015   | 0.295 ± 0.015  | 0.728    | 0.470 |
3.2 Intraregion SCFC

Figure 4 shows the results of the independent samples t-tests of intraregion SCFC. For oxy-Hb results, we found that (1) the RP-SCFC was significantly higher in the ASD group than in the TD group, no matter which window length was selected; (2) the LT-SCFC was significantly higher in the ASD group than in the TD group at 30 sec and 90 sec window length; (3) the LP-SCFC and RT-SCFC were significantly higher in the ASD group than in the TD group at 30 sec window length. As for the deoxy-Hb results, group differences (ASD > TD) could only be found in LP-SCFC and RP-SCFC at window lengths of 10 sec and 30 sec. However, no other significant differences of intraregion SCFC between the two groups were revealed for the total-Hb results.

Fig. 4. The group differences of intraregion SCFC. Panel A and B show the brain regions with significant group differences (ASD > TD) for oxy-Hb and deoxy-Hb, respectively. For each kind of fNIRS signals at each window length, the brain regions with significant group differences (ASD > TD) are masked in black.

3.3 Interregion SCFC

The results of statistical tests on interregion SCFC are displayed in Fig. 5. The independent samples t-tests on inter-region SCFC of oxy-Hb were as follows: (1) At a window length of 10 sec, most of the interregion SCFCs were significantly higher in the ASD group than in the TD group, except the interregion SCFC between LT and RO and that between LO and RO; (2) at a window length of 30 sec, most of the interregion SCFCs were significantly higher in the ASD group than in the TD group, except the interregion SCFC between LT and LO, between RT and RO, between LO and RO, and between LP and LO; (3) at a window length longer than 30 sec (i.e., 50, 70, or 90 sec), we found that the interregion SCFCs between RP and the other 5 brain regions were significantly higher in the ASD group than in the TD group. No other significant group differences of interregion SCFC between the two groups were detected.

As for the interregion SCFC of deoxy-Hb, the following results were revealed: (1) At a window length of 10 sec, interregion SCFCs (i.e., SCFCs of LP-LO, LP-RP, LP-RT, RP-LO, and RP-RT) were significantly higher in the ASD group than in the TD group; (2) at a window length of 30 sec, interregion SCFCs (i.e., SCFCs of LP-RP, LP-RT, LP-RO, RP-LT, RP-LO and RP-RO) were significantly higher in the ASD group than in the TD group; (3) at a window length of 50 sec, the interregion SCFCs between LP and regions located in the right hemisphere (i.e., RP, RT, and RO) and that between RP and RT were significantly higher in the ASD group than in the TD group; (4) when the window length was assumed to be 70 sec,
the interregion SCFCs between LP and two regions of right hemisphere (i.e., RP and RO) were significantly higher in the ASD group than in the TD group; (5) the interregion SCFC between LP and RP was significantly higher in the ASD group than in the TD group at a window length of 90 sec. No other significant group differences of interregion SCFC between the two groups were detected.

Lastly, for the interregion SCFC of total-Hb, we found that (1) at 10 sec window length, most of the interregion SCFCs were significantly higher in the ASD group than in the TD group, except the SCFC of LT-RO; (2) when the window length was longer than 10 sec (i.e., 30 sec, 50 sec, 70 sec, and 90 sec), no significant group differences of interregion SCFC were found. No other significant group differences of inter-region SCFC between the two groups were detected.

Fig. 5. The results of statistical tests on interregion SCFCs. The lines show the interregion SCFCs with significant group difference (ASD > TD) after the FDR procedure.
4. Discussion

4.1 The introduction of SCFC and its functional significance

Examining the functional integration or neural connection among different brain regions during either resting- or task-related states can help us understand the neural mechanism of mental processes and the neuropathological mechanisms of psychiatric disorders [39, 40]. In recent years, studies in the fields of static or dynamic FC have revealed a rich functional architecture of brain, manifesting as large-scale, coherent neural networks, which are closely associated with various psychiatric disorders and cognitive processes [13, 41]. With BOLD signal fluctuations at resting-state, several “resting-state networks,” also referred to as “intrinsic connectivity networks,” including sensory, motor, sensory association, and default mode networks, have been identified and reproduced in many studies [6, 7, 42]. As has been mentioned above, the dFC between two brain regions could be considered as a time series, i.e., dFC-series, when evaluated by the sliding-window approach. Inspired by the spatial complexity analysis of multichannel EEG signals, we proposed that the spatial complexity of multiple dFC-series, defined as SCFC, should be evaluated to provide more information about brain function beyond the traditional time-averaged FC analysis and dFC analysis.

To estimate the SCFCs, the dFC-series were computed in the first step, by use of the time-varying PLV. The PLV, or phase synchrony, is originally defined as the locking of phases in coupled signals, independent of their amplitudes, which has more advantages than the Pearson's correlation approach in understanding complex collective dynamical behavior, such as the brain activities [37]. In addition, many studies supported the idea that phase synchrony was a basic mechanism of functional integration in the human brain, and seemed to be a promising tool for discovering the mechanisms of brain activities [11, 43]. After all the dFC-series were computed, an approach combining temporal PCA and normalized entropy was used to compute the spatial complexity of dFC-series of interest. A similar complexity analysis approach called PCA entropy was previously applied when quantifying the temporal complexity of ECG signals [44]. However, instead of focusing on the temporal complexity of some given time series, the current study aimed to describe the spatial complexity of time-varying functional connectivity series. Moreover, the SCFC values attained in the current study ranged from 0 to 1, regardless of the intrinsic characters of the signals to be analyzed (e.g., the number and length of signals), while values of PCA entropy ranged from 0 to log2(D) and were subjected to D (the dimension of the delay vectors).

In the present study, three kinds of SCFCs were evaluated: the global SCFC, the intraregion SCFC, and the interregion SCFC, which reflected the heterogeneity of information exchange patterns of all brain regions, that within certain brain region and that between two brain regions, respectively. A lower SCFC value suggests lower heterogeneity (or higher homogeneity) of information patterns, whereas a higher SCFC value indicates that the information exchange patterns are much more diverse. Future investigations are needed to determine whether higher or lower SCFCs reflect more optimal information-processing efficiency, and whether the abnormality of SCFC is closely associated with neurological and psychiatric disorders. One possible hypothesis is that a lower SCFC is related to better cognitive performance, since higher homogeneity of information exchange patterns among subregions of a certain brain region or between subregions of two certain regions should enhance the functional connections of different regions.

4.2 Higher SCFCs in young children with ASDs

The fMRI studies targeted to detect the biological abnormalities of autism suggested an abnormal pattern of connectivity among distant brain networks, such as the default mode network, the theory-of-mind network, and the mirror neuron system [45–48]. Based on these findings, a popular hypothesis called disrupted cerebral connectivity was proposed, which postulates that deficiencies in the coordinating and synchronizing activity among distant brain
regions could lead to the social, cognitive and behavioral phenotype in ASD [26, 47, 49, 50]. Previous studies found that the right PFC acted as a hub for information integration [51]. Moreover, the PFC abnormality was found to be central in autism and its abnormality could contribute to the social and nonsocial dysfunction in individuals’ behavioral development [9, 52]. For example, using fNIRS, a study conducted by our group revealed a lower level of interregion connectivity between the right PFC and other brain regions [9]. The researchers highlighted that the impairment of the right PFC contributes majorly to the psychopathology of young children with ASD, which is consistent with the findings in the current study. We found that the information exchange patterns between different cortical areas were significantly more heterogeneous in autistic children, especially for the oxy-Hb-based SCFC between the right PFC and other brain regions. Such results again confirmed the importance of the PFC and extended our understanding of the crucial role of the right PFC in autism, which may be the starting point of observed dysfunction in verbal and nonverbal communication, social interaction, face and emotion perception, and joint attention. In addition, consistent findings of higher interregion SCFCs in young children with ASD, representing an aberrant information exchanging pattern in the right PFC, could be regarded as proof in supporting the feasibility and validity of the SCFC analysis in an fNIRS study.

We examined whether ASD was associated with abnormal SCFC and found that the global and intraregion SCFCs of the prefrontal and temporal lobes were higher in young children with ASD. The results suggest that the information exchange patterns within the prefrontal and temporal lobes were much more diverse in young children with ASD, supporting the notion that the frontal and temporal lobes play a crucial role in the social dysfunctions of ASD [53–55]. Unfortunately, our previous study using the traditional FC analysis did not find any aberrant lobe-level intraregion connection [9]. Here, using the index of SCFC, we pointed out additional information of brain abnormalities in children with ASD, indicating the SCFC analysis might be more sensitive when discriminating the difference between children with and without ASD. Moreover, the SCFC might be a good index for representing the abnormalities of clinical sample.

In this study, more significant group effects were found in the SCFCs of oxy-Hb signals than of deoxy-Hb or total-Hb signals. It was difficult to explain because many researchers found inconsistency among the results based on the oxy-, deoxy-, and total-Hb signals [56–58]. Perhaps it was related to the difference of machines, experimental setups, and so on. However, it is still worthwhile discussing and presenting the results derived from different kinds of hemoglobin for future investigation. In addition, the group differences were most robust when the window length was 10 sec and 30 sec. This may be related to the power spectrum analysis results, which showed that the grand-average power spectra of the three kinds of hemoglobin changes peaked at about 0.036 Hz (corresponding to about 28 sec) for both groups, as shown in Fig. 6. These results were consistent with those of previous research, which showed that the topological descriptions of brain networks stabilized at window lengths of roughly 30 sec [59], and suggest that using a time window no longer than 30 sec in the dFC and SCFC analyses may produce the most robust results. However, using too short a window length (e.g., shorter than 10 sec) may hamper the robust estimation of dFC-series (hence the SCFC), since (1) the overall variability in sliding-window FC tends to increase as window length shrinks; and (2) there are too few time points available to evaluate the FC [14].
Fig. 6. The grand-average power spectra of the three types of hemoglobin changes for both ASD and TD groups. In each panel, each colored line represents the power spectrum of a certain channel (i.e., there are 44 colored lines in each panel). The power spectrum analysis showed that the grand-average power spectra for the three kinds of hemoglobin changes peaked at about 0.036 Hz (corresponding to 28 s) for both groups.

4.3 Limitations and future directions

Moreover, the results presented here must be considered in the context of several experimental and methodological limitations. First, unlike previous work on ASD [60, 61], the children who participated in the current study lack an ASD diagnostic confirmation owing to limited access to the golden diagnostic tools of ADI-R or ADOS in China [62]. Second, although the fNIRS is a non-invasive, child-appropriate neuroimaging tool for the autism research, this technique is unlikely to supplant fMRI for basic research, due to the high spatial resolution (< 3 mm) and whole-brain coverage of fMRI. The fNIRS channels used here only cover the bilateral prefrontal, temporal, and occipital regions, thus other cortex areas that may be important to autism research (such as the parietal cortex) were not studied. The regions-of-interest in the current study was divided based on the relative positions of scalp channels to the classical 10-20 landmarks. Such a rough segmentation should be improved in the future. Lastly, although the SCFC was initially developed to assess the spatial complexity of dFC-series of fNIRS signals, it could be easily applied to other brain imaging modalities. Even so, it should be mentioned that in contrast to fNIRS, which measured the local brain activity directly below the probes, the EEG/MEG technique could not successfully distinguish the signal from nearby measured brain regions due to the volume conduction effect which may...
cause spurious results [2]. However, the current study is the first to use SCFC to analyze the fNIRS acquired hemoglobin concentrations and provides remarkable findings that extend our understanding of the pathology in young children with ASD.

5. Conclusion

Inspired by the spatial complexity analysis of multiregion neural signals, we proposed that the SCFC should be evaluated in an fNIRS study, since the dFCs could be considered as a physiologically significant time series. Here, the SCFC was estimated by use of an approach combining temporal PCA and normalized entropy. Consistent with previous findings, we found that, for oxy-Hb results, the SCFCs between the right PFC and the other brain regions were much higher in young children with ASD, no matter which window length was used. Such results verified the feasibility and validity of the SCFC analysis. In addition, we found higher levels of the global SCFC, and the intraregion SCFCs of the prefrontal and temporal lobes in young children with ASD, indicating that the information exchange patterns within the prefrontal and temporal lobes were much more diverse in young children with ASD. Moreover, the results extended our understanding of the crucial role of the right PFC in autism, which may be the starting point of the observed dysfunction in verbal and nonverbal communication, social interaction, face and emotion perception, and joint attention. The heterogeneity of the information exchange patterns revealed by the SCFC analysis might efficiently discriminate children with and without ASD.

Non-Standard Abbreviations

fMRI, functional magnetic resonance imaging
fNIRS, functional near-infrared spectroscopy
EEG, electroencephalography
MEG, magnetoencephalography
FC, functional connectivity
dFC, dynamic FC
SCFC, spatial complexity of functional connectivity
ASD, autism spectrum disorder
TD, typically developing
DSM-IV, Diagnostic and Statistical Manual, 4th Edition
ADHD, attention-deficit/hyperactivity disorder
PLV, phase-locking value
FDR, false discovery rate
oxy-Hb, oxy-hemoglobin
deoxy-Hb, deoxy-hemoglobin
total-Hb, total-hemoglobin

Acknowledgments

We are grateful for the children and families who volunteered to participate in this study.
Funding

National Natural Science Foundation of China (61673113, 61273224, and 61074126); High-level Cultivation Project of Nanjing Xiaozhuang University (2017NXY13); Open Research Fund of the State Key Laboratory of Cognitive Neuroscience and Learning (CNLYB1308).

Disclosures

The authors declare that there are no conflicts of interest related to this article.