NeuroImage: Clinical 20 (2018) 424–432

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Attenuation of long-range temporal correlations of neuronal oscillations in young children with autism spectrum disorder

Huibin Jia[a,1], Yanwei Li[b,1], Dongchuan Yu[a,*]

[a] Key Laboratory of Child Development and Learning Science of Ministry of Education, School of Biological Sciences & Medical Engineering, Southeast University, Nanjing, Jiangsu, China

[b] College of Preschool Education, Nanjing Xiaozhuang University, Nanjing, Jiangsu, China

ARTICLE INFO

Keywords:
Long-range temporal correlations
Autism spectrum disorder
fNIRS
Left temporal region

ABSTRACT

Although autism spectrum disorder (ASD) was previously found to be associated with aberrant brain structure, neuronal amplitudes and spatial neuronal interactions, surprisingly little is known about the temporal dynamics of neuronal oscillations in this disease. Here, the hemoglobin concentration signals (i.e., oxy-Hb and deoxy-Hb) of young children with ASD and typically developing (TD) children were recorded via functional near infrared spectroscopy (fNIRS) when they were watching a cartoon. The long-range temporal correlations (LRTCs) of hemoglobin concentration signals were quantified using detrended fluctuation analysis (DFA). Compared with TD group, the DFA exponents of young children with ASD were significantly smaller over left temporal region for oxy-Hb signal, and over bilateral temporo-occipital regions for deoxy-Hb signals, indicating a shift-to-randomness of brain oscillations in the children with ASD. Testing the relationship between age and DFA exponents revealed that this association could be modulated by autism. The correlation coefficients between age and DFA exponents were significantly more positive in TD group, compared to those in ASD group over several brain regions. Furthermore, the DFA exponents of oxy-Hb in left temporal region were negatively correlated with autistic symptom severity. These results suggest that the decreased DFA exponent of hemoglobin concentration signals may be one of the pathologic changes in ASD, and studying the temporal structure of brain activity via fNIRS technique may provide physiological indicators for autism.

1. Introduction

Autism spectrum disorder (ASD) describes a range of developmental disorders that are characterized by impairments in social communicative development, along with repetitive stereotyped behaviors and/or restricted interests (Woolfenden et al., 2012; Yirmiya et al., 1994). Despite its importance in early diagnosis and efficient treatment, the exact pathophysiological mechanism of ASD is still controversial. In this field, a series of theories have been proposed, e.g., brain enlargement, dysfunction in mirror neuron system, aberrant neural connectivity and abnormality in temporal lobe (Bachevalier, 1994; Cheng et al., 2015; Hazlett et al., 2017; Just et al., 2012; Kana et al., 2015).

The major focuses in these prior researches are placed on the brain structure, neuronal amplitudes and spatial neuronal interactions of patients with ASD. Few reports were involved in the autocorrelations or temporal structure of the brain activity in ASD, which may be caused by the fact that researchers in the field did not familiar with this technique. Studies in recent years point out the amplitude of brain signals recorded by functional magnetic resonance imaging (fMRI), electroencephalography (EEG) and magnetoencephalography (MEG) possesses power-law-form long-range temporal correlations (LRTCs) in the temporal scale from seconds to hundreds of seconds, which indicates that physiological events in the past affect the development of the brain process in the future and has been deeply investigated via several techniques (e.g., detrended fluctuation analysis [DFA] or Hurst exponent analysis) (Hahn et al., 2012; He, 2011; Lee et al., 2007; Maxim et al., 2005; Montez et al., 2009). The existence of LRTCs is believed to be advantageous for a reliable transfer of information in neuronal networks, and alterations of LRTCs have been associated with age, gender, cognitive operations and neurological conditions (Berthouze et al., 2010; He, 2011; Montez et al., 2009; Nikulin and Brismar, 2005). In the field of ASD researches, only one study has probed into the LRTCs of physiological signals in patients with ASD to the best of our knowledge (Lai et al., 2010). Using Hurst exponent, a significant shift to

* Corresponding author at: Room 323, Liwenzheng Building, Southeast University, No. 2, Sipailou, Xuanwu District, Nanjing 210096, China.
E-mail address: dcyu@seu.edu.cn (D. Yu).

[1] Huibin Jia and Yanwei Li contributed equally to this work.

https://doi.org/10.1016/j.nicl.2018.08.012
Received 22 December 2017; Received in revised form 12 July 2018; Accepted 8 August 2018
Available online 09 August 2018

randomness (i.e, reduced Hurst exponent) in the resting-state fMRI signals of the ASD group was revealed in Lai et al. (2010), compared with neurotypical volunteers. Between-group differences in Hurst exponent, which was always reduced in the ASD group, were seen in most regions previously reported to be involved in autism, including cortical midline structures, medial temporal structures, lateral temporal and parietal structures, insula, amygdala, basal ganglia, thalamus and inferior frontal gyrus (Lai et al., 2010). Moreover, severity of autistic symptoms was negatively correlated with the Hurst exponent in retrosplenial and right anterior insular cortex in Lai et al. (2010). These results suggest that the measures in LRTCs analysis (e.g., DFA exponent and Hurst exponent) may provide physiological indicators for autism as they have done for other medical conditions.

Although the study from Lai et al. (2010) provided preliminary evidence that ASD is associated with a small but significant shift to randomness of endogenous brain oscillations (i.e., significantly lower LRTCs) and has important implications for the neurobiology of autism, it also has limitations in our opinion. This study was limited to high-functioning adults, thus it is unknown how the results may generalize to individuals of other ages. Since early diagnosis and then timely treatment are very crucial in preventing disease's progression, investigating the temporal structure of neuronal activity in young children with ASD and high-risk infants may provide more useful pathophysiological information regarding to ASD. Thus, in the current study we investigated the LRTCs of neural signals in young children with ASD. For these children, the resting-state fMRI technique used in Lai et al. (2010) is not appropriate, since they are usually unwilling to lay down into such a claustrophobic space. This may result in unacceptable head movements, which could significantly affect the metrics estimated via fMRI signals. Here, the functional near-infrared spectroscopy (fNIRS) technique was used to investigate the LRTCs in young children (younger than 8 years old) with ASD. Among all the neuroimaging techniques, fNIRS, which monitors neural activity by measuring the absorption of near infrared light between 650 nm and 950 nm through the intact skull, is a promising non-invasive brain imaging technique to investigate the neurodevelopment of young children with ASD, since it's safe, portable, low cost, and relatively insensitive to head movement (Lu et al., 2010). The value of fNIRS in ASD researches has been confirmed by quite a few studies (Iwanaga et al., 2013; Keehn et al., 2013; Kita et al., 2011; Li and Yu, 2016). For example, an fNIRS study conducted by our group revealed significantly weaker lobe-level inter-region connections in the right prefrontal cortex in young children with ASD when compared with healthy age- and gender-matched children, including its linkages with the left prefrontal cortex and the bilateral temporal cortex (Li and Yu, 2016).

In the current study, the DFA exponent derived from detrended fluctuation analysis on fNIRS signals (i.e., the hemoglobin concentration signals), which could quantify the strength of LRTCs, was used to investigate the neuropathological mechanisms of ASD. We hypothesized that the DFA exponent of hemoglobin concentration signals should be attenuated in young children with ASD, especially in brain regions known to be involved in autism. Moreover, we hypothesized that the relationship between age and DFA exponent may be distinct between young children with ASD and typically developing (TD) children. Lastly, we hypothesized that severity of autistic symptoms was negatively correlated with the DFA exponent in certain regions (e.g., the frontal region, the left temporal lobe and temporo-occipital region) known to be involved in autism.

2. Methods

2.1. Participants

Thirty-five children with ASD (mean age = 5.96 years, SD = 1.22 years; aged from 4 to 9 years; 23 boys) and thirty-one age- and gender-matched TD children (mean age = 6.56 years, SD = 1.2 years; aged from 4 to 9 years; 20 boys) participated in this study. The two groups did not significantly differ with respect to age ($p > 0.05$).

All the children in ASD group were diagnosed with ASD in Nanjing Brain Hospital. Before fNIRS data acquisition, their parents were asked to fill out a questionnaire, i.e., the Autism Behavior Checklist (Yirmiya et al., 1994), which could provide some information about autistic symptom severity. All these children had never been diagnosed with other diseases, such as the attention-deficit/hyperactivity disorder (ADHD), and were high-functioning autism (within the near normal or normal range of intelligence). None of the children in the TD group had a history of psychiatric or neurological disorder. Parents of all participants signed an informed consent for the present experiment, which was approved by the institutional review board.

2.2. Experimental protocol

In order to make the children feel comfortable, their caregivers or teachers held them during the whole experiment. Resting-state fNIRS signals were not collected, since these children could not keep their eyes closed or open for a relatively long time. The children watched a very popular cartoon in China during the experiment. Exactly the same scenes of the cartoon were displayed for all the children. They watched the cartoon for 14 min. Besides, the behaviors of children during the whole experiment were recorded using a camera so that the corrupted data caused by large head or body movements or other unexpected behaviors could be removed according to the camera recording (Li and Yu, 2016).

2.3. fNIRS data acquisition

A real-time fNIRS system, LABNIRS (Shimadzu Corporation, Kyoto, Japan), was used to collect the changes of the hemoglobin concentration signals. A customized cap with 16 emitter probes and 16 detector probes was designed by our group (Fig. 1). The spatial distance between adjacent probes was 30 mm. A pair of emitter probe and neighboring detector probe formed one channel. The spatial location of each channel defined as the center position of the emitter-detector pair was determined according to the international 10–20 system. The foremost channels were located at Fp1 and Fp2, the backmost channels were placed around PO7 and PO8. Moreover, the leftmost and rightmost channel was placed around T3 and T4 respectively (Li and Yu, 2016). The montage of these probes resulted in 44 channels and a scanning rate of 27 ms (about 37 Hz). The near infrared light at three wavelengths (i.e., 780, 805, and 830 nm) were emitted by the emitter probes and received by their adjacent detector probes after travelling through the head. The concentration changes in oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) were estimated through the modified Beer-Lambert law (Cope and Delpy, 1988).

2.4. Data preprocessing

The data preprocessing in the current study has the following steps:

Firstly, contaminated data fragments caused by large head movements, unexpected behaviors and sharp changes in fNIRS signals were removed according to the camera recording. Five children in the ASD group and two children in the TD group with too short retention time (i.e., < 8 min) or with one or more poor signal-to-noise ratio channels were excluded from further data analysis.

Secondly, the infomax ICA algorithm was performed on oxy-Hb and deoxy-Hb respectively. Independent components related to the low-frequency (< 0.003 Hz) drift, sudden jumps, motion-induced artifacts, cardiac pulsations, respiratory signals and high-frequency (> 0.1 Hz) noise were identified and rejected manually (Zhang et al., 2010). One child with ASD was excluded from further analysis, due to extremely low signal-to-noise ratio.

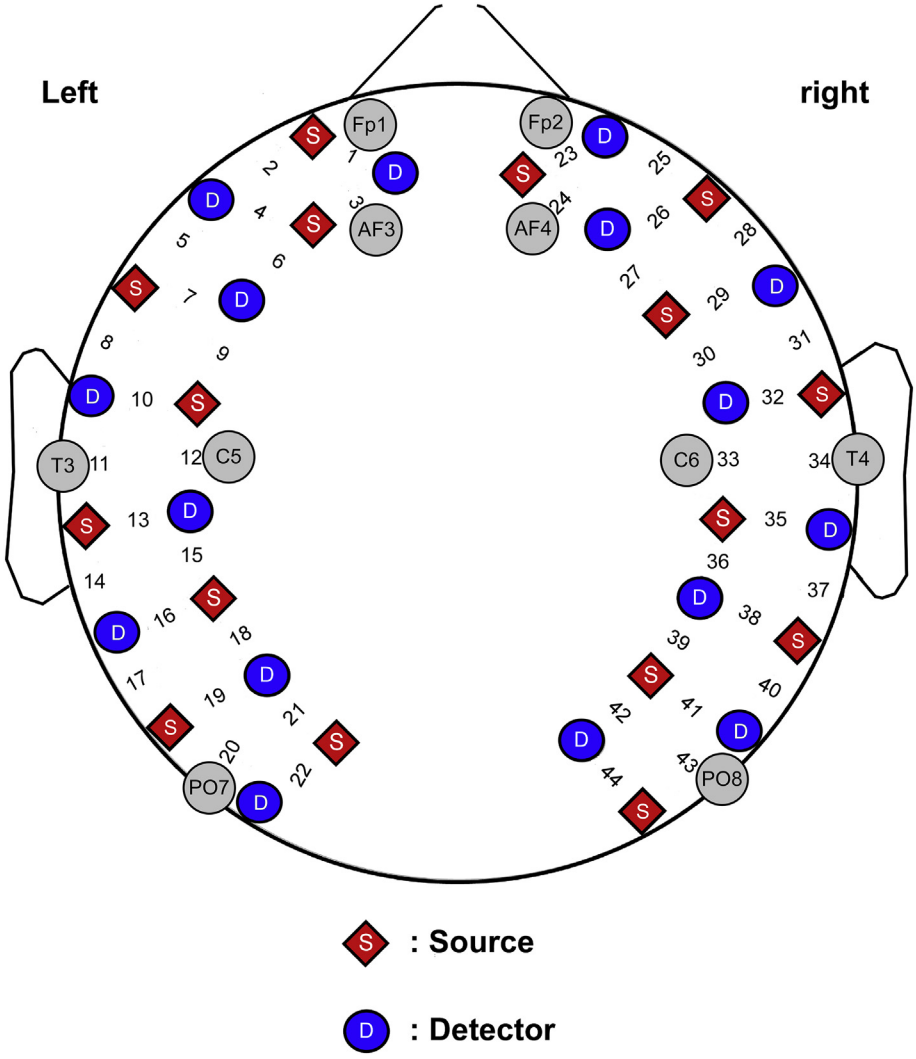

Fig. 1. Schematic of the probe/channel configurations on the head.
Red and blue circles indicate the source emitters and the photon detectors, respectively. The 44 measurement channels are located between emitter/detector pairs.

Thirdly, a low-pass filtering (0.1 Hz) was performed on the hemoglobin concentration signals as suggested by previous studies (Cui et al., 2011; Zhang et al., 2009).

Such strict noise control procedures could validly reduce the influence of typical noise components in fNIRS signals. The data of the remaining 29 children in the ASD group and 29 children in the TD group were used for further DFA.

Lastly, only the time series of the hemoglobin concentration signals between 1 and 8 min were included in DFA, so as to suppress the edge effect in filtering and eliminate the influence of signal length on group difference.

2.5. Detrended fluctuation analysis (DFA)

The LRTCs analysis provides a quantitative measure of statistical dependencies in neural oscillations of different time scales. Historically, the LRTCs were estimated by the Hurst exponent through the rescaled range (R/S) analysis (Wei et al., 2013). The Hurst exponent is evaluated based on the rescaled range on the time span n of observation. The time series with length N is divided into a number of shorter time series of length $n = N, N/2, N/4, \ldots$ The rescaled range is computed via dividing the range of the values exhibited in a shorter time series by the standard deviation of the values over the same time series. However, the Hurst exponent could produce biased estimates for non-stationary series. On the other hand, the DFA has proven to be a particularly robust method for studying the LRTCs in human physiological signals (e.g., EEG, MEG, fMRI), since it is insensitive to the non-stationarity of neurophysiological processes (Gao et al., 2017). In the current study, the DFA was used to detect LRTCs in hemoglobin concentration signals (Peng et al., 1995). As has been illustrated in previous studies (Hardstone et al., 2012; He, 2011; Nikulin and Brismar, 2005), the procedures of DFA for each kind of hemoglobin concentration signals (i.e., oxy-Hb and deoxy-Hb), each channel and each participant can be summarized as follows:

1. Let A(t) be one kind of the hemoglobin concentration signals at time t. Then the signal profile X(t), which was defined as the cumulative sum of A(t), was calculated:
   $X(t) = \sum_{k=1}^{t} A(k) - \langle A \rangle$, where $\langle A \rangle$ is the time-averaged value of A(t).

2. The signal profile X(t) was divided into 50% overlapping windows of size τ with a length varying from 20 to 100 s equidistantly on a logarithmic scale. The main rationale of using 50% overlapping windows is that it could increase the number of windows, resulting into more accurate estimate of the fluctuation function especially for the long-time-scale windows (Hardstone et al., 2012). For each window with size τ, the signal profile was detrended through a least-squares fit, then standard deviation of detrended signal profile was

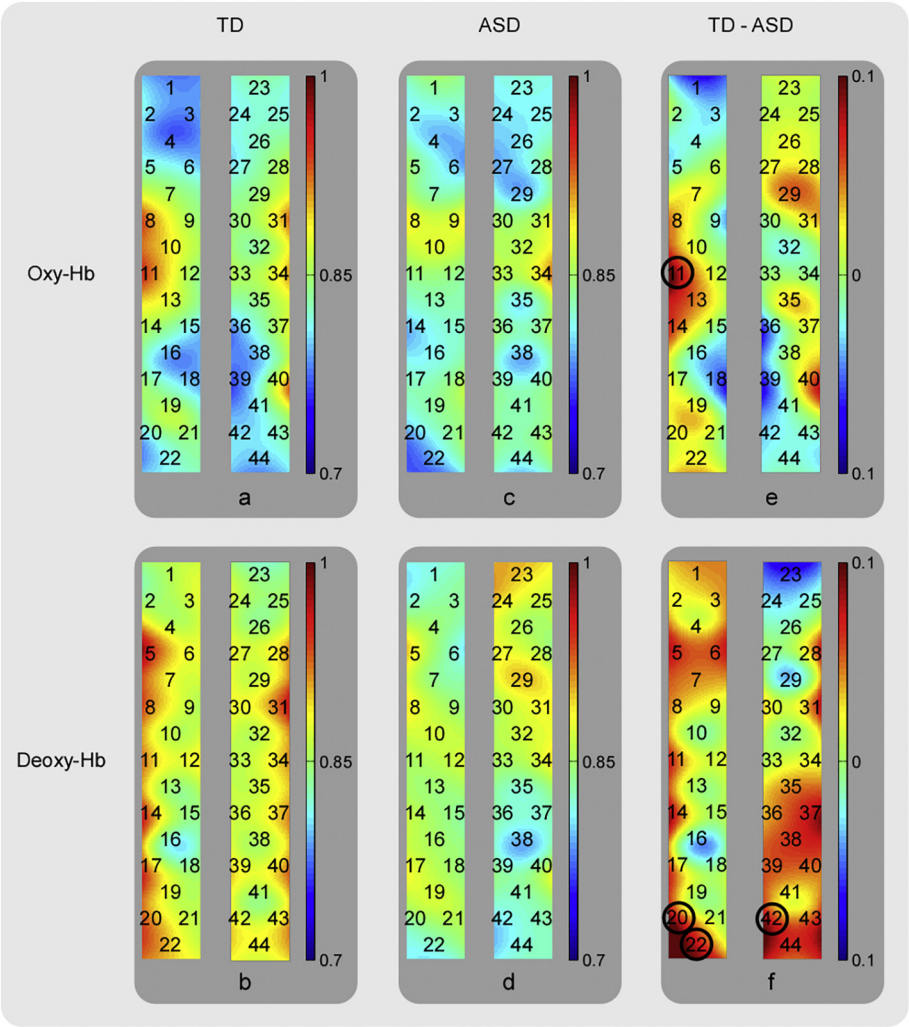

Fig. 2. The group-level maps of DFA exponent for both groups.
The group-level maps of DFA exponent for TD group and ASD group, and the group-level difference maps between the two groups (TD group minus ASD group) are shown in the left panels (a and b), middle panels (c and d) and right panels (e and f) respectively. Black circles denote channels with significant group difference after FDR correction.

computed. Through these operations, we could obtain the fluctuation function of window length τ, $\langle F(\tau)\rangle$ $\langle F(\tau)\rangle$, which was defined as the mean standard deviation of detrended signal profile across all windows with length τ.

3. The fluctuation functions for all window lengths were plotted on logarithmic axes. Usually the relationship between $\langle F(\tau)\rangle$ and τ has a linear form in a double logarithmic coordinate system across many sizes of τ. The slope of the least-squares line in this graph is termed as the DFA exponent. DFA exponent in the 0.5–1.0 range indicates a presence of persistent temporal correlations. Uncorrelated signals (e.g. white noise) have a scaling exponent 0.5. The DFA exponent of non-stationary signals is larger than 1.0.

2.6. Statistical tests

Firstly, for each hemoglobin concentration signal and each channel, independent-samples *t*-test was conducted to test group effect. Since age may modulate the DFA exponent estimation, the age of each participant was included as a covariate. In order to control multiple comparisons, the significance level (*p* value) was corrected using false discovery rate (FDR) procedure (Benjamini and Yekutieli, 2001), which was conducted across all the 44 channels for oxy-Hb and deoxy-Hb separately. The threshold for significance was $p < .05$ for the statistical tests and the alpha value for FDR procedures was 0.05.

Secondly, the relationship between DFA exponent and age, group and their interaction (i.e., age × group) was assessed using a generalized linear model (GLM) for each channel and each hemoglobin concentration signal separately. After the channels with significant interaction effect between age and group were identified, further analyses were performed, which statistically tested whether there were significant differences between two groups for Pearson correlation coefficients (between age and DFA exponent) on these channels using the procedure developed by Fisher (1921). Subgroup analyses were also performed. For each channel, each group and each hemoglobin concentration signal, the Pearson correlation coefficient between age and DFA exponent was computed and its significance was assessed with *t*-statistic. The threshold for significance was $p < 0.05$ for these statistical tests.

Thirdly, for the purpose of systematically assessing the links between DFA exponent and measures of autistic symptom severity in the ASD group, the Pearson correlation coefficients between DFA exponent and measures of autistic symptoms (including language, relating, and social- & self-help in the Autism Behavior Checklist) were calculated for each channel and each hemoglobin concentration signal respectively, after controlling the variable *age*. The significance of the correlation

coefficients was assessed with *t*-statistic. The threshold for significance was $p < 0.05$. Note that, the Autism Behavior Checklist also has two other scores (i.e., body & object use and sensory). Since these two scores do not reflect the core autistic symptoms in our ASD group, we did not assess their relationship with the DFA exponent.

Fourthly, in order to test the role of DFA exponent on disease progression with the increase of age, two kinds of data analysis were performed. Firstly, we assessed the relationship between age of patients and measures of autistic symptom severity (i.e., language score, relating score and social- & self-help score) using the Pearson correlation coefficients. Secondly, we constructed moderation models for each channel and each kind of fNIRS signals respectively. In these models, the age, the DFA exponent and symptom severity were used as independent variable, moderator variable and dependent variable.

3. Results

3.1. Between-group comparisons

The group-level maps of DFA exponent for TD group and ASD group are shown in the left panels (a and b) and middle panels (c and d) of Fig. 2, respectively.

Independent-samples *t*-tests with FDR control were conducted for the purpose of testing group effect on DFA exponent. The group-level difference maps between the two groups (TD group minus ASD group) and the channels with significant group difference after FDR correction are shown in the right panels (e and f) of Fig. 2. The statistical tests on DFA exponent of oxy-Hb revealed that the DFA exponent of TD group was significantly larger than that of ASD group on channel 11 (ASD: 0.8381 ± 0.1646, TD: 0.9443 ± 0.1694), which was located in left temporal region. For deoxy-Hb signal, we found that the DFA exponents of TD group were significantly larger over channels 20 (ASD: 0.8194 ± 0.1965, TD: 0.9421 ± 0.1489) & 22 (ASD: 0.8057 ± 0.1578, TD: 0.8984 ± 0.1497) and channel 42 (ASD: 0.7956 ± 0.1448, TD: 0.8983 ± 0.1251), which were situated in left and right temporo-occipital regions respectively.

3.2. Correlations between age and DFA exponent

The GLMs were used to detect whether the relationship between age and DFA exponents could be modulated by autism. After the GLM was constructed for each channel and each kind of signal, the channels with significant interaction effect between age and group ($p < 0.05$) were identified, which were shown in the right panels (e and f) of Fig. 3. Further analyses found that for oxy-Hb, the Pearson correlation coefficients between age and DFA exponent of TD group were significantly larger than those of ASD group over channel 5 (left fronto-temporal region, $r_{asd} = -0.1869$, $r_{td} = 0.3622$, $p < 0.05$), 11 (left temporal region, $r_{asd} = -0.2300$, $r_{td} = 0.4402$, $p < 0.05$), 19 (left temporo-occipital region, $r_{asd} = -0.4920$, $r_{td} = 0.1623$, $p < 0.05$), 22 (left temporo-occipital region, $r_{asd} = -0.4372$, $r_{td} = 0.1469$, $p < 0.05$), 37 (right temporal region, $r_{asd} = -0.3402$, $r_{td} = 0.1945$, $p < 0.05$) and 40 (right temporo-occipital region, $r_{asd} = -0.2340$, $r_{td} = 0.3881$, $p < 0.05$). However, only two channels, i.e., 5 (left fronto-temporal region, $r_{asd} = -0.3113$, $r_{td} = 0.3248$) and 8 (left temporal region, $r_{asd} = -0.0357$, $r_{td} = 0.5378$), reached significant level at $p < 0.05$ for deoxy-Hb.

Note that, GLMs were used detect which channels with significant interaction effect between age and group. Subgroup analyses (i.e., testing the significance of the Pearson correlation coefficient between age and DFA exponent for each kind of signal, each channel and each group separately) were also needed, which could provide some additional information about the effect of age on DFA exponent for both groups. The results are displayed in the left panels (a and b) and middle panels (c and d) of Fig. 3. For TD group, (1) the Pearson correlation coefficients between DFA exponent of oxy-Hb and age were significant over channel 11 (left temporal region, $r = 0.4402$, $p < 0.05$) and 40 (right temporo-occipital region, $r = 0.3881$, $p < 0.05$); (2) the Pearson correlation coefficients between DFA exponent of deoxy-Hb and age were significant over channel 8 (left temporal region, $r = 0.5378$, $p < 0.05$), 31 (right temporal region, $r = 0.3904$, $p < 0.05$) and 43 (right temporo-occipital region, $r = 0.4034$, $p < 0.05$). For ASD group, (1) the Pearson correlation coefficients between DFA exponent of oxy-Hb and age were significant over channel 2 (left frontal region, $r = -0.4375$, $p < 0.05$), 10 (left temporal region, $r = -0.4305$, $p < 0.05$), 18 (left temporo-occipital region, $r = -0.3806$, $p < 0.05$), 19 (left temporo-occipital region, $r = -0.4920$, $p < 0.05$) and 22 (left temporo-occipital region, $r = -0.4372$, $p < 0.05$); (2) the Pearson correlation coefficients between DFA exponent of deoxy-Hb and age were not significant for all channels ($ps > 0.05$).

3.3. Correlations with measures of autistic symptom severity

The Pearson correlation coefficients between DFA exponents and the scores from Autism Behavior Checklist were computed in order to test whether the aberrant DFA exponent in ASD group is associated with measures of autistic symptom severity. These Pearson correlation coefficients are presented in Fig. 4. For oxy-Hb, we found that (1) the DFA exponent was negatively correlated with the language score in channel 7 (left fronto-temporal region, $r = -0.4834$, $p < 0.05$), 8 (left temporal region, $r = -0.6199$, $p < 0.05$), 10 (left temporal region, $r = -0.5410$, $p < 0.05$), 12 (left temporal region, $r = -0.5386$, $p < 0.05$) and 32 (right temporal region, $r = -0.4186$, $p < 0.05$); (2) the DFA exponent was negatively correlated with the relating score in channel 8 (left temporal region, $r = -0.4056$, $p < 0.05$) and 10 (left temporal region, $r = -0.4914$, $p < 0.05$); (3) the DFA exponent was negatively correlated with the social- & self-help score in channel 12 (left temporal region, $r = -0.6276$, $p < 0.05$) and 16 (left temporal region, $r = -0.4528$, $p < 0.05$). No significant correlation coefficient was revealed for DFA exponent of deoxy-Hb ($ps > 0.05$).

3.4. Relationships between age of patients and autistic symptom severity

Firstly, assessing the relationship between age of patients and measures of autistic symptom severity, we found that the age of children with ASD was positively correlated with the measures of symptom severity (the language score: $r = 0.2349$; the relating score: $r = 0.2574$; the social & self-help score: $r = 0.1971$). These correlation coefficients were moderate but non-significant. Secondly, in moderation analysis, the following results were detected. For oxy-Hb signals, we found that (1) the moderation effects of DFA exponent were significant for channel 2, 4 and 26 if dependent variable was the language score ($ps < 0.05$); (2) the moderation effects of DFA exponent were significant for channel 6 and 32 if dependent variable was the relating score ($ps < 0.05$); (3) the moderation effect of DFA exponent was significant for channel 9 if dependent variable was the social & self-help score ($p < 0.05$). For deoxy-Hb signals, the moderation effects were not significant ($ps > 0.05$). Further analyses revealed that a positive relationship between age of children with ASD and the three aspects of symptom severity when DFA exponent was high ($ps < 0.05$), but not when DFA exponent was low ($ps > 0.05$).

4. Discussion

In the current study, DFA exponent which could quantify the LRTCs in fNIRS signals was used to investigate the pathophysiological mechanism of ASD. Several interesting results have been revealed. Firstly, the LRTCs of hemoglobin concentration signals were attenuated in young children with ASD over left temporal region (for oxy-Hb signal) and bilateral temporo-occipital regions (for deoxy-Hb signal), indicating a shift-to-randomness of brain oscillations in young children with ASD. Secondly, the relationship between age and LRTCs of

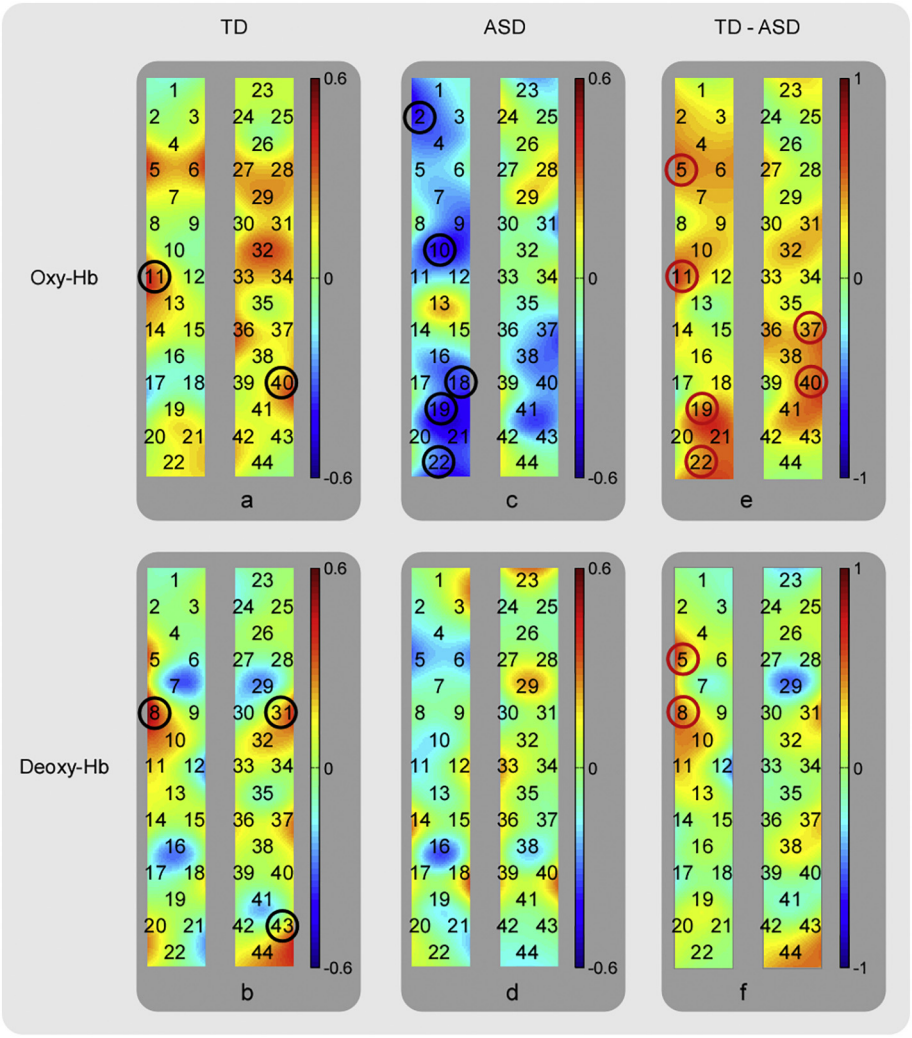

Fig. 3. The Pearson correlation coefficients between DFA exponent and age of TD group and ASD group. The correlation coefficients for TD group and ASD group, along with channels with significant correlation coefficients (denoted by black circles), are displayed in the left panels (a and b) and middle panels (c and d) respectively. The differences between correlation coefficients of two groups (TD − ASD) and the channels (denoted by red circles) with significant interaction effect between age and group revealed by GLMs are presented in the right panels (e and f). For these channels, the Pearson correlation coefficients between age and DFA exponent of TD group were significantly more positive than those of ASD group.

hemoglobin concentration signals tends to be opposite between two groups. Thirdly, the DFA exponents of oxy-Hb in left temporal region were negatively correlated with autistic symptom severity. Fourthly, the moderation effects of DFA exponent on the relationship between age and autistic symptom severity were significant, i.e., the decreased brain functions with age may be more profound in patients with relatively high DFA exponent. These results suggested that the decreased DFA exponent of hemoglobin concentration signals may be one of the pathologic changes in ASD, and studying the temporal structures of brain activity via fNIRS may provide physiological indicators for autism.

Using DFA, the present study revealed markedly weakened LRTCs for both oxy-Hb signal and deoxy-Hb signal in young children with ASD, which can be hypothesized to underlie an excessive switching between the neuronal states in these patients. Note that, the group-averaged DFA exponents of all the two kinds of hemoglobin concentration signals and all the channels were > 0.5 and < 1.0, which indicated that although the DFA exponents of hemoglobin concentration signals were attenuated in these patients, hemoglobin concentration signals in both the young children with ASD and healthy controls exhibited LRTCs with power-law behavior.

The presence of power-law-form LRTCs indicates that events in the past affect the development of the process in the future, which has been detected in various biological time series and natural phenomena (Nikulin and Brismar, 2005; Peng et al., 1995; Varotsos and Kirkdavidoff, 2006). It has been argued that LRTCs of neurophysiological signals could facilitate essential brain functions such as memory formation, rapid information transfer, and the efficient neural network reorganization that promotes learning (Botcharova et al., 2013). Moreover, the presence of LRTCs suggests that the human brain operates with self-organized criticality (SOC), i.e., the neuronal oscillations display a spatial and temporal scale-invariance characteristic of the critical point of a phase transition, but without the need to tune control parameters to a precise value, which might represent an optimal compromise for the competing demands of stability and information transmission in the neuronal networks (Beggs and Plenz, 2003; Linkenkaer-Hansen et al., 2004). Although the distinct levels of decay in LRTCs indicated by the DFA exponents may all reflect SOC, it remains to be determined what the functional significance is of the magnitude of the DFA exponent. Smit et al. (2011) speculated that stronger LRTCs indicated the stronger ability to maintain transiently stable oscillations in support of active neuronal representations during sustained cognitive operations, which was indirectly supported by studies conducted on patients with various cognitive impairments (e.g., major depressive disorder, Alzheimer's disease, schizophrenia, and ASD)(Smit et al., 2011). After all, the decreased DFA exponents for fNIRS signals suggested that ASD should be associated with highly volatile, random and irregular states of neuronal oscillations, which may impair cognitive operations with long-range dependence of neural states (e.g., language, social communication and attention). The amplitude modulation of brain oscillatory activity may hold information about pathophysiological changes in young children with ASD.

The patterns of the association between age and DFA exponent were found to be opposite between two groups through whole-group GLMs.

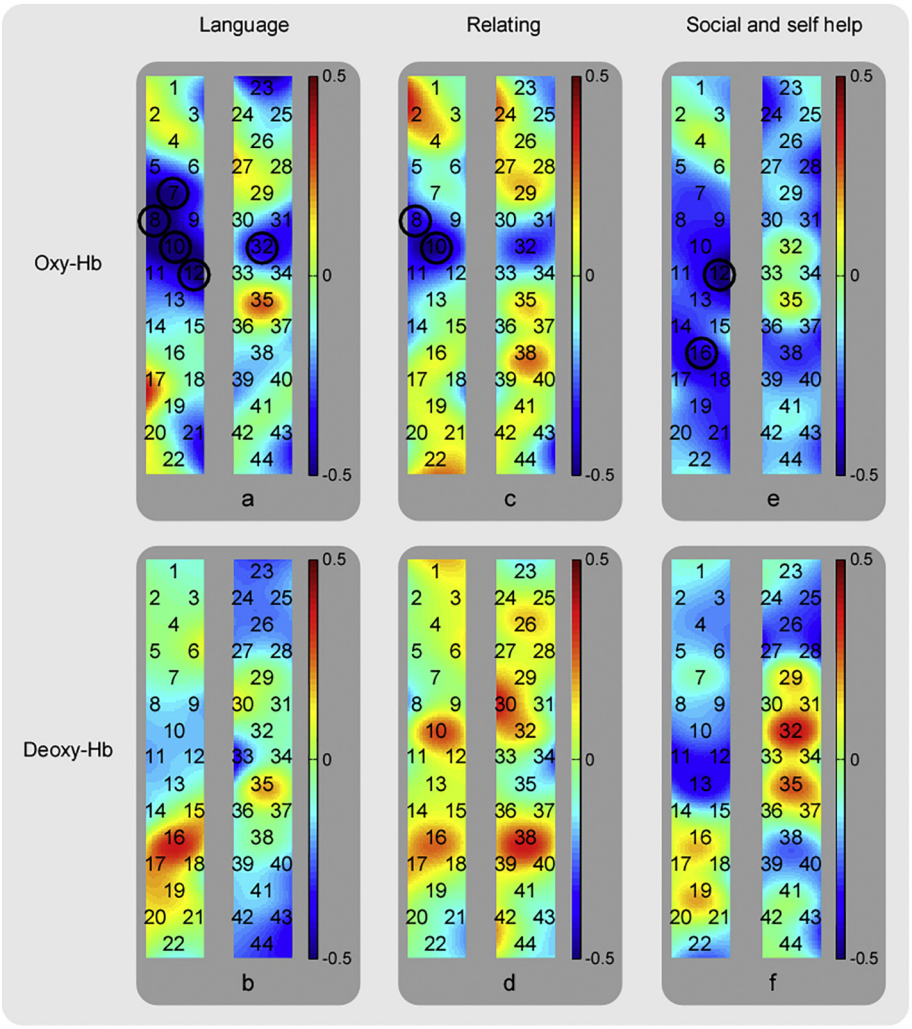

Fig. 4. The Pearson correlation coefficients between DFA exponents and measures of autistic symptom severity in ASD group.
The correlation coefficients for the language score, relating score and social- & self-help score are presented in the left panels (a and b), middle panels (c and d), and right panels (e and f) respectively. Black circles denote channels with significant correlation coefficients.

The Pearson correlation coefficients between age and DFA exponent of TD group were significantly more positive than those of ASD group over several brain regions. We also investigated the Pearson correlation coefficients between DFA exponent and age for TD group and ASD group respectively. For TD group, the DFA exponents of oxy-Hb and deoxy-Hb in left temporal region and right temporo-occipital region increased with age; however, the DFA exponents of oxy-Hb in left frontal lobe, left temporal region and left temporo-occipital region decreased with age for ASD group. Through investigating resting-state EEG oscillations in 1433 subjects from 5 to 71 years, Smit et al. (2011) observed pronounced increases in LRTCs from childhood to adolescence, during adolescence, and even into early adulthood (25 years of age) after which the temporal structure stabilized. Wink et al. (2006) found that healthy elderly volunteers (with mean age approximately 65 years) had significantly increased Hurst exponent (i.e., increase LRTCs) of resting state fMRI time series in bilateral hippocampus compared to a group of younger volunteers (with mean age approximately 22 years) (Wink et al., 2006). These findings indicate that the scale-free modulation of neural oscillations reflects brain maturation, and suggest that LRTCs may prove useful as a biomarker of pathophysiology in neurodevelopmental disorders such as ADHD and ASD. Here, we revealed that the DFA exponents of fNIRS signals in temporal region and right temporo-occipital region increased with age in healthy young children. This result is consistent with these previous studies, and shows that not only LRTCs estimated by EEG and fMRI, but also LRTCs computed from fNIRS signals, could reflect brain maturation. However, the DFA exponents of oxy-Hb in left frontal lobe, left temporal region and left temporo-occipital region decreased with age for ASD group. As far as we know, no previous study has revealed that the LRTCs estimated in neural signals decreased with age in children with ASD.

It should be very interesting to test the role of DFA exponent on disease progression with the increase of age. Firstly, we found that the age of children with ASD was positively correlated with the measures of symptom severity. These correlation coefficients were moderate but non-significant. Barneveld et al. (2014) addressed the impact of age on cognitive functioning of 6- to 15-year-old children and adolescents with ASD, and revealed that the impairments in certain kinds of cognitive functions (e.g., verbal comprehension and social reasoning abilities) were more profound in older children when compared with 6- and 7-year-old children with ASD, which was consistent with our findings (Barneveld et al., 2014). Secondly, we revealed that the moderation effects of DFA exponent on the relationship between age and autistic symptom severity were significant, i.e., the decreased brain functions with age may be more profound in patients with relatively high DFA exponent.

In this study, the regions with weakened LRTCs were mainly focused on left temporal region and temporo-occipital region. It has been

recognized that dysfunction in left temporal region, which is crucial in language production and language comprehension, may result in defect in verbal communication (Eyler et al., 2012). Moreover, significant negative correlation was observed between cerebral blood flow (rCBF) of the left superior temporal gyrus and Autism Diagnostic Interview-Revised (ADI-R) score in Meresse et al. (2005), suggesting that left superior temporal gyrus hypoperfusion is related to autistic behavior severity (Meresse et al., 2005). This is in line with our results, which showed that the DFA exponent of oxy-Hb in left temporal region was negatively correlated with autistic symptom severity assessed by the Autism Behavior Checklist. The weakened LRTCs not only observed in the left temporal region, but also in temporo-occipital region. The fusiform face area (FFA), one of the brain structures in temporo-occipital region, is affected by autism, which might result in defects in social interaction in children with ASD (Schultz, 2005). However, the negative correlations between DFA exponent and autistic symptom severity were only observed in the left temporal region in our study, which suggests the attenuated LRTCs in left temporal region may be more closely related with autistic symptom in our sample.

Observing the Pearson correlation coefficients between DFA exponents and measures of autistic symptom severity in ASD group (Fig. 4), we could find that although the DFA exponents in left temporal region were closely linked to all three aspects of autistic symptoms (i.e., language, relating and social- & self-help) in Autism Behavior Checklist, more significant channels were detected for the language score. These results suggested that the attenuated LRTCs in left temporal region were more closely related to the impairment of language ability, compared to the other two abilities. On the other hand, although only two channels with significant correlation coefficients (i.e., channel 12 and 16 for oxy-Hb) were identified for the social- & self-help score, we could observe that most channels in left hemisphere showed a trend of negative correlation (panels e and f of Fig. 4). This may due to the behaviors in this aspect may not confine to any particular brain region, but may occur in distributed brain networks.

An intriguing and puzzling result was also detected in the current study, i.e., the influences of autism on DFA exponent of oxy-Hb and deoxy-Hb signals were very distinct. Firstly, the channels showing significant group differences (ASD $<$ TD) on DFA exponent located over left temporal region for oxy-Hb signal, whereas significant channels were over bilateral temporo-occipital regions for deoxy-Hb signals. Secondly, the age of both groups and the autistic symptom severity of ASD group were mainly correlated with DFA exponents of oxy-Hb signals, not those of deoxy-Hb signals. Actually, these results were hard to interpret, since the differences between the physiological significance of LRTCs of oxy-Hb and deoxy-Hb were still unknown. One of the possible reasons may be the experimental setups used here (i.e., watching a Chinese cartoon). Observing the waveforms of fNIRS signals of 44 channels, we found that the oxy-Hb signals of TD group were larger than those of ASD group on frontal and temporal channels, whereas for deoxy-Hb signals, the differences between two groups were more distinct over occipital channels. The other possible reason may be the relatively higher signal-to-noise ratio for oxy-Hb compared to deoxy-Hb, thus the group effects of oxy-Hb were more profound than those of deoxy-Hb (Li and Yu, 2016).

5. Conclusion

In the current study, smaller DFA exponents (i.e., weaken LRTCs) were observed in young children with ASD over left temporal region and bilateral temporo-occipital regions. The Pearson correlation coefficients between age and DFA exponent of TD group were significantly more positive than those of ASD group over several brain regions. Moreover, the DFA exponents in left temporal region were negatively correlated with autistic symptom severity. These results indicate that ASD is associated with highly volatile, random and irregular states of neuronal oscillations, which results into impairment of certain brain functions (e.g., language and social ability). The temporal structure of brain oscillatory activity may provide physiological indicators for autism.

Acknowledgement

The work was supported by the Natural Science Foundation of China under Grants 61673113, 61273224, and 61074126, by the Open Research Fund of the State Key Laboratory of Cognitive Neuroscience and Learning under Grant CNLYB1308, by Jiangsu's 13th Five Year Plan for Education Science (C-a/2018/01/01) and by the High-level Cultivation Project of Nanjing Xiaozhuang University (2017NXY13). No conflicts of interest, financial or otherwise, are declared by the authors.

References

Bachevalier, J., 1994. Medial temporal lobe structures and autism: a review of clinical and experimental findings. Neuropsychologia 32, 627–648.
Barneveld, P.S., Swaab, H., Van Engeland, H., De Sonneville, L., 2014. Cross-sectional evidence for a decrease in cognitive function with age in children with autism Spectrum disorders? Autism Res. 7, 527–534.
Beggs, J.M., Plenz, D., 2003. Neuronal avalanches in neocortical circuits. J. Neurosci. 23, 11167–11177.
Benjamini, Y., Yekutieli, D., 2001. The control of the false discovery rate in multiple testing under dependency. Ann. Stat. 29, 1165–1188.
Berthouze, L., James, L.M., Farmer, S.F., 2010. Human EEG shows long-range temporal correlations of oscillation amplitude in Theta, alpha and Beta bands across a wide age range. Clin. Neurophysiol. 121, 1187–1197.
Botcharova, M., Farmer, S.F., Berthouze, L., 2013. A Maximum Likelihood Based Technique for Validating Detrended Fluctuation Analysis (ML-DFA). (arXiv:1306.5075).
Cheng, W., Rolls, E.T., Gu, H., Zhang, J., Feng, J., 2015. Autism: reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self. Brain 138, 1382–1393.
Cope, M., Delpy, D.T., 1988. System for long-term measurement of cerebral blood and tissue oxygenation on newborn infants by near infra-red transillumination. Med. Biol. Eng. Comput. 26, 289–294.
Cui, X., Bray, S., Bryant, D.M., Glover, G.H., Reiss, A.L., 2011. A quantitative comparison of NIRS and fMRI across multiple cognitive tasks. NeuroImage 54, 2808–2821.
Eyler, L.T., Pierce, K., Courchesne, E., 2012. A failure of left temporal cortex to specialize for language is an early emerging and fundamental property of autism. Brain 135, 949.
Fisher, R., 1921. On the “probable error” of a coefficient of correlation deduced from a small sample. Metro 1, 3–32.
Gao, F., Wu, X., Feng, Y., Jia, H., 2017. Attenuation of temporal correlations of neuronal oscillations in patients with mild spastic diplegia. Sci. Rep. 7, 14966.
Hahn, T., Dresler, T., Ehlis, A.C., Pyka, M., Dieler, A.C., Saathoff, C., Jakob, P.M., Lesch, K.P., Fallgatter, A.J., 2012. Randomness of resting-state brain oscillations encodes Gray's personality trait. NeuroImage 59, 1842–1845.
Hardstone, R., Poil, S.S., Schiavone, G., Jansen, R., Nikulin, V.V., Mansvelder, H.D., Linkenkaer-Hansen, K., 2012. Detrended fuctuation analysis: a scale-free view on neuronal oscillations. Front. Physiol. 3, 450.
Hazlett, H.C., Gu, H., Munsell, B.C., Kim, S.H., Styner, M., Wolff, J.J., Elison, J.T., Swanson, M.R., Zhu, H., Botteron, K.N., 2017. Early brain development in infants at high risk for autism spectrum disorder. Nature 542, 348–351.
He, B.J., 2011. Scale-free properties of the functional magnetic resonance imaging signal during rest and task. J. Neurosci. 31, 13786–13795.
Iwanaga, R., Tanaka, G., Nakane, H., Honda, S., Imamura, A., Ozawa, H., 2013. Usefulness of near-infrared spectroscopy to detect brain dysfunction in children with autism spectrum disorder when inferring the mental state of others. Psychiatry Clin. Neurosci. 67, 203–209.
Just, M.A., Keller, T.A., Malave, V.L., Kana, R.K., Varma, S., 2012. Autism as a neural systems disorder: a theory of frontal-posterior underconnectivity. Neurosci. Biobehav. Rev. 36, 1292–1313.
Kana, R.K., Maximo, J.O., Williams, D.L., Keller, T.A., Schipul, S.E., Cherkassky, V.L., Minshew, N.J., Just, M.A., 2015. Aberrant functioning of the theory-of-mind network in children and adolescents with autism. Mol. Autism 6, 59.
Keehn, B., Wagner, J.B., Tagerflusberg, H., Nelson, C.A., 2013. Functional connectivity in the first year of life in infants at-risk for autism: a preliminary near-infrared spectroscopy study. Front. Hum. Neurosci. 7, 444.
Kita, Y., Gunji, A., Inoue, Y., Goto, T., Sakihara, K., Kaga, M., Inagaki, M., Hosokawa, T., 2011. Self-face recognition in children with autism spectrum disorders: a near-infrared spectroscopy study. Brain Dev. 33, 494–503.
Lai, M.C., Lombardo, M.V., Chakrabarti, B., Sadek, S.A., Pasco, G., Wheelwright, S.J., Bullmore, E.T., Baroncohen, S., Suckling, J., 2010. A shift to randomness of brain oscillations in people with autism. Biol. Psychiatry 68, 1092–1099.
Lee, J.S., Yang, B.H., Lee, J.H., Choi, J.H., Choi, I.G., Kim, S.B., 2007. Detrended fluctuation analysis of resting EEG in depressed outpatients and healthy controls. Clin. Neurophysiol. 118, 2489–2496.
Li, Y., Yu, D., 2016. Weak network efficiency in young children with autism Spectrum disorder: evidence from a functional near-infrared spectroscopy study. Brain Cogn.

108, 47–55.
Linkenkaer-Hansen, K., Nikulin, V.V., Palva, J.M., Kaila, K., Ilmoniemi, R.J., 2004. Stimulus-induced change in long-range temporal correlations and scaling behaviour of sensorimotor oscillations. Eur. J. Neurosci. 19, 203–211.
Lu, C.M., Zhang, Y.J., Biswal, B.B., Zang, Y.F., Peng, D.L., Zhu, C.Z., 2010. Use of fNIRS to assess resting state functional connectivity. J. Neurosci. Methods 186, 242–249.
Maxim, V., Şendur, L., Fadili, J., Suckling, J., Gould, R., Howard, R., Bullmore, E., 2005. Fractional Gaussian noise, functional MRI and Alzheimer's disease. NeuroImage 25, 141–158.
Meresse, I.G., Zilbovicius, M., Boddaert, N., Robel, L., Philippe, A., Sfaello, I., Laurier, L., Brunelle, F., Samson, Y., Mouren, M.C., Chabane, N., 2005. Autism severity and temporal lobe functional abnormalities. Ann. Neurol. 58, 466–469.
Montez, T., Poil, S.S., Jones, B.F., Manshanden, I., Verbunt, J.P., van Dijk, B.W., Brussaard, A.B., Van, O.A., Stam, C.J., Scheltens, P., 2009. Altered temporal correlations in parietal alpha and prefrontal theta oscillations in early-stage Alzheimer disease. Proc. Natl. Acad. Sci. U. S. A. 106, 1614–1619.
Nikulin, V.V., Brismar, T., 2005. Long-range temporal correlations in electroencephalographic oscillations: relation to topography, frequency band, age and gender. Neuroscience 130, 549–558.
Peng, C.K., Havlin, S., Stanley, H.E., Goldberger, A.L., 1995. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos 5, 82–87.
Schultz, R.T., 2005. Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. Int. J. Dev. Neurosci. 23, 125–141.
Smit, D.J.A., De Geus, E.J.C., Van De Nieuwenhuijzen, M.E., Van Beijsterveldt, C.E.M., Van Baal, G.C.M., Mansvelder, H.D., Boomsma, D.I., Linkenkaer-Hansen, K., 2011. Scale-free modulation of resting-state neuronal oscillations reflects prolonged brain maturation in humans. J. Neurosci. 31, 13128–13136.
Varotsos, C., Kirkdavidoff, D., 2006. Long-memory processes in ozone and temperature variations at the region 60° S–60° N. Atmos. Chem. Phys. 6, 4093–4100.
Wei, M., Qin, J., Yan, R., Li, H., Yao, Z., Lu, Q., 2013. Identifying major depressive disorder using Hurst exponent of resting-state brain networks. Psychiatry Res. 214, 306–312.
Wink, A.M., Bernard, F., Salvador, R., Bullmore, E., Suckling, J., 2006. Age and cholinergic effects on hemodynamics and functional coherence of human hippocampus. Neurobiol. Aging 27, 1395–1404.
Woolfenden, S., Sarkozy, V., Ridley, G., Williams, K., 2012. A systematic review of the diagnostic stability of autism Spectrum disorder. Res. Autism Spectr. Disord. 6, 345–354.
Yirmiya, N., Sigman, M., Freeman, B.J., 1994. Comparison between diagnostic instruments for identifying high-functioning children with autism. J. Autism Dev. Disord. 24, 281–291.
Zhang, Q., Strangman, G.E., Ganis, G., 2009. Adaptive filtering to reduce global interference in non-invasive NIRS measures of brain activation: how well and when does it work? NeuroImage 45, 788–794.
Zhang, H., Zhang, Y.J., Lu, C.M., Ma, S.Y., Zang, Y.F., Zhu, C.Z., 2010. Functional connectivity as revealed by independent component analysis of resting-state fNIRS measurements. NeuroImage 51, 1150–1161.