Power spectrum of spontaneous cerebral homodynamic oscillation shows a distinct pattern in autism spectrum disorder

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Abstract: Spontaneous hemodynamic fluctuations recorded by functional near-infrared spectroscopy (fNIRS) from bilateral temporal lobes were analyzed on 25 children with autism spectrum disorder (ASD) and 22 typically developing (TD) children. By frequency domain analysis, a new characteristic was uncovered that the power spectrum of low frequency cerebral hemodynamic oscillation showed a distinct pattern in ASD. More specifically, at the frequency of 0.0200 Hz, the power of oxygenated hemoglobin was larger for TD than ASD, whereas in the band of 0.0267-0.0333 Hz, the power of deoxygenated hemoglobin was larger for ASD than TD. Using these new features and those identified previously together as feature variables for the support vector machine (SVM) classifier, accurate classification between ASD and TD was achieved with a sensitivity of 90.2%, specificity of 95.1% and accuracy of 92.7%.

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1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with deficits in social interactions, communication impairments and repetitive or stereotypic behaviors [1]. Since diagnosis of ASD currently relies solely on the behavioral observations, e.g., via the Autism Diagnostic Observation Schedule (ADOS) [2], in recent years various brain imaging studies have been performed to explore characteristics inherent to ASD in brain structure and function. For examples, studies with magnetic resonance imaging (MRI) [3] and diffuse tensor imaging (DTI) [4] have demonstrated the difference between ASD patients and normal controls in the cranial capacity and fold degree of the cortex [3]. Brain functional studies with positron emission tomography (PET) [5], functional magnetic resonance imaging (fMRI) [3,6,7], single photon emission computed tomography (SPECT) [8], electroencephalography(EEG) [9,10] and magnetoencephalography (MEG) [11,12] have demonstrated that ASD shows abnormalities in functional connection of the brain. For instance, there is convergent evidence demonstrating that ASD exists weaker remote connection, e.g. between the left and right hemispheres [3]. Besides this, a few studies have also shown a stronger short-range connection in ASD, though this observation is not consistent across different studies [13,14].

Among various brain imaging modalities, functional near-infrared spectroscopy (fNIRS) is a suitable tool for investigating ASD due to its many advantages, including low cost, simplicity of operation, lack of special requirements for the imaging environment, and in particular, weak sensitivity to head motion [15]. In addition, fNIRS has excellent temporal
and acceptable spatial (~centimeter) resolution. These advantages may render fNIRS a promising imaging technique for investigating ASD and screening individuals with risk of ASD.

Several fNIRS studies on ASD have shown that children with ASD experience atypical cortical activity in cognitive tasks [16–19] as well as in resting-state [20,21]. For examples, when watching a cartoon, weak network efficiency and deficits in information exchange were observed in children with ASD [16,17]. In joint-attention task, children with ASD showed distinct activation pattern in the prefrontal cortex [18]. Comparing prefrontal activities induced by working and non-working memory task, typically developing (TD) children showed different activation, whereas children with ASD did not show the difference [19]. In self-face recognition, children with ASD had lower activation in the prefrontal cortex than TD children, and more serious ASD characteristics corresponded to lower activity levels [20]. In resting-state, weaker functional connectivity between the left and right language areas (e.g., the temporal lobes) [21,22], but stronger fluctuation magnitude were observed in children with ASD [21]. All these observations might associate with different aspects of dysfunction in the brain of ASD, and might have the potential to serve as imaging-based biomarkers for predicting the disorder.

Individuals with ASD show diverse patterns of behavior, implying that single imaging-based biomarker may not enough for fully characterizing the disorder. The more characteristics associated with ASD are revealed, the better understanding of ASD may be achieved. Resting-state fMRI studies have shown in patients of ischemic stroke and normal aging adults there is a reduction in the so-called Slow-5 oscillation (i.e., 0.010-0.027 Hz oscillation in brain spontaneous activity [23]). The Slow-5 reduction was explained as being associated with disruption on the brain network [24,25]. Since in the brain of ASD the disruption on the brain network has been well demonstrated [3,5–12,21,22], our hypothesis is that there might exist difference between ASD and TD in the power spectrum of spontaneous cerebral hemodynamic oscillation (e.g., around the Slow-5 band), and the difference could serve as characteristic features for predicting ASD. To test this hypothesis, in this study we reanalyzed fNIRS data we collected in a prior study [21] with the aim of exploring new characteristics inherent to ASD. Instead of using time-domain data processing approach previously used for the data analysis, we performed frequency domain analysis on the fNIRS data, and attempted to find difference between children with ASD and TD children in the spectral structure of oxygenated hemoglobin (HbO₂) and deoxygenated hemoglobin (Hb) signals. Since previous studies [21,22] have demonstrated in the low frequency band (e.g., 0.009-0.080 Hz) of spontaneous hemodynamic fluctuations, ASD showed weaker resting-state functional connectivity (RSFC) and stronger fluctuation magnitude, in the present study this low frequency band was also focused. As result, a distinct pattern was observed in ASD on both hemispheres for HbO₂ and Hb. The alterations located mostly in the frequency band of 0.0200-0.0333 Hz, partly overlapping with the Slow-5 oscillation band. To demonstrate the significance of the alterations in the power spectrum, the statistical hypothesis test was performed. Combining the characteristics uncovered in this study and those already identified [21] as feature variables for the SVM classifier [26,27], a rather accurate classification can be achieved between ASD and TD group.

2. Method
2.1 Experiment summary

Since this work is a reanalysis of fNIRS data collected previously, we give a short description of the experiment including subjects, measurement protocol and setup. For details, the readers can refer to ref [21]. In short, 25 children with ASD (18 boys and 7 girls, 9.3 ± 1.4 years old) and 22 age-matched TD children (18 boys and 4 girls, 9.5 ± 1.6 years old) were included in the study. The difference in IQ was significant between the two groups (p<<0.05). The fNIRS used in the study was a continuous-wave system (FOIRE-3000, Shimadzu Corporation,
Kyoto, Japan). For each subject, approximate 8-min spontaneous fluctuation of HbO₂ and Hb were recorded from the bilateral temporal lobes with 70-ms temporal resolution (i.e., 14.3 Hz sampling frequency). 24 optical channels were used, with 12 channels on each side (see Fig. 1). The source-detector (SD) distance was 3.0 cm for all optical channels. By using the modified Beer-Lambert law, the changes in optical intensity were converted into changes in HbO₂ and Hb. To identify locations of the bilateral temporal lobes, the international 10-10 system for electroencephalography (EEG) was referenced with an EEG cap, in which T3 and T4 correspond to the left and right temporal lobes.

2.2 Data analysis

The data preprocessing was similar to that used in our prior study [21], including a detrending process with a second-order polynomial fit to remove slow drift, and a data filtering using a zero-phase 2nd order Butterworth filter with a pass-band of 0.009 to 0.080 Hz to suppress most of the systemic interferences such as those originated from cardiac cycles (~1 Hz), respirations (~0.2 Hz) and the Mayer waves (~0.1 Hz). After the data preprocessing, each time series of the hemodynamic signal S (HbO₂ or Hb) was centered and normalized via Z = (S-mean(S))/std(S), therefore the average power (or energy) for each signal was equal. This normalization was necessary for evaluating the structural difference in power spectrum of the signal between ASD and TD. In the frequency domain analysis, on each subject the power spectrum was calculated for each channel. To obtain the averaged power spectrum on each hemisphere for each individual, the power spectra of all 12 channels on each hemisphere were averaged. To show the difference between ASD and TD, the averaged power spectrum on each hemisphere was averaged over the two groups (ASD and TD) separately. To improve signal-to-noise ratio of the power spectrum, a moving average with a time window of 150 s was employed when performing the fast Fourier transform (FFT), which resulted in the frequency resolution of 0.0067 Hz. The selection of 150 s for the time window was due to a previous study in which the minimum duration for an accurate and stable fNIRS mapping of brain resting-state connectivity was determined to be 2.5 minutes in children [28]. For statistical hypothesis test, the two-sample t-test was performed with the false discovery rate (FDR) correction for multiple comparisons. The significant level was set at p<0.05. For the data analysis, custom-written MATLAB (MathWorks, Inc.) scripts were used.

For the classification between ASD and TD, a support vector machine (SVM) classifier with a linear kernel function was used. MATLAB built-in functions (svmtrain.m and svmclassify.m) in the bioinformatics toolbox were utilized for the SVM training and predicting. To evaluate the performance of the classification in terms of sensitivity, specificity and accuracy, 50 percent of each group (i.e., 12 ASD and 11 TD children) was randomly
selected for the training and the rest 50 percent for the testing. In total 1000 runs were conducted for this cross-validation.

3. Result

The average power spectrum of the low-frequency hemodynamic oscillation is presented in Fig. 2. For HbO₂, on both hemispheres, the power reaches the maximum at 0.0133 Hz for both TD and ASD, and then it drops differently between TD and ASD. The power for TD drops faster than ASD in particular in the band of 0.0200-0.0333 Hz, thus in the band of 0.0133-0.0200 Hz, the power for TD is larger than ASD, whereas in the band of 0.0267-0.0400 Hz, the power for ASD is larger than TD. The similar differences between ASD and TD are also shown in the power spectrum of Hb.

Two-sample t-test was performed to evaluate the significance level in these differences on the power spectrum between ASD and TD group. Table 1 shows p values for the differences in the frequency band of 0.0133-0.0467 Hz for HbO₂ and Hb. For HbO₂, at frequency of 0.0200 Hz, the difference was significant (marginally significant on the left hemisphere); while for Hb, at frequency of 0.0267 and 0.0333 Hz, the differences were significant, in particular on the right hemisphere.

![Fig. 2. Power spectrum of HbO₂ and Hb on the left and right temporal lobe, for TD (blue line) and ASD (red line), respectively. The error bars are standard error of mean calculated from each group.](image)

Table 1. p values of the differences between ASD and TD in frequency band of 0.0133-0.0467 Hz

|                  | 0.0133 Hz | 0.0200 Hz | 0.0267 Hz | 0.0333 Hz | 0.0400 Hz | 0.0467 Hz |
|------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| HbO₂ (Left)      | 0.3270    | 0.0778    | 0.2544    | 0.4137    | 0.1273    | 0.2251    |
| HbO₂ (Right)     | 0.5724    | 0.0023    | 0.1669    | 0.0346    | 0.4003    | 0.1247    |
| Hb (Left)        | 0.1217    | 0.5449    | 0.0495    | 0.0264    | 0.0230    | 0.3212    |
| Hb (Right)       | 0.5556    | 0.2740    | 0.0049    | 0.0125    | 0.1922    | 0.3976    |

Table 1 shows that the top 3 smallest p values are 0.0023 for HbO₂ at 0.0200 Hz, 0.0049 for Hb at 0.0267 Hz and 0.0125 for Hb at 0.0333 Hz, all locating on the right hemisphere. Therefore, the changes on the right hemisphere were thereafter focused for the selection of discriminative features on the prediction of ASD. Figure 3 shows the average power for ASD and TD groups on the right hemisphere for HbO₂ at 0.0200 Hz and Hb at 0.0267 and 0.0333 Hz. The differences were significant (i.e., p<0.05) between the two groups. On the other hand, statistical power analysis demonstrated with the current sample size (25 children with ASD and 22 TD children) the power was 87.3%, indicating the sample size was appropriate for showing these differences. Since the two groups (ASD and TD) showed significant
difference in IQ, to exclude the possibility that IQ might be a reason for the differences in the power spectrum, we calculated the Pearson correlation coefficient between IQ values and the powers at these three frequencies for ASD group (since ASD showed larger variation in IQ, from 75 to 125). The correlation coefficient was −0.04, 0.19 and 0.06 at 0.0200, 0.0267 and 0.0333 Hz, respectively, indicating there was nearly no relationship between IQ and the powers at these three frequencies.

![Graph](image)

**Fig. 3.** The average (a) and the distribution (b) of power of HbO₂ at 0.0200 Hz, Hb at 0.0267 and 0.0333 Hz, for TD and ASD group, all on the right hemisphere. The differences are significant with p = 0.0023, 0.0049 and 0.0125, respectively. The effect size for the differences in power is 0.9361, 0.8540 and 0.7573, respectively.

To perform classification between ASD and TD, one can consider the three variables, i.e., power of HbO₂ at 0.0200 Hz, power of Hb at 0.0267 and 0.0333 Hz, as three features and include them into the SVM classifier. Since correlated features do not provide more discriminative information on the classification than uncorrelated features, before taking these three features into the SVM classifier, Pearson correlation coefficient r was computed between each pair of these three variables, which gave r(HbO₂ at 0.0200 Hz, Hb at 0.0267 Hz) = −0.19, r(HbO₂ at 0.0200 Hz, Hb at 0.0333 Hz) = −0.22, and r(Hb at 0.0267 Hz, Hb at 0.0333 Hz) = 0.71. Among the three correlation coefficients, the correlation coefficient between the two Hb-related variables was relatively high (r = 0.71), thus we used the average of the two correlated variables as one feature, and HbO₂ at 0.0200 Hz as the other feature. The difference in the first feature (i.e., the average of the two correlated Hb-related variables) was still very significant (p = 0.0039). The Pearson correlation coefficient between these two features was −0.22, indicating they were less correlated. Though the differences between ASD and TD were very significant in these two uncorrelated features, including them into the SVM classifier led to an unsatisfying classification with 77.8% sensitivity, 61.5% specificity and 70.3% accuracy. This indicates again a single type of imaging biomarker may not enough
for accurately differentiating between ASD and TD, which is similar to the classification by using only RSFC as feature variable [6,21].

Since children with ASD show diverse or a broad spectrum of symptoms, implying there exist various deficits in function of the brain, multiple image markers may be necessary to accurately characterize the brain of ASD. Therefore, combining the newly revealed power spectrum-related features and those already identified previously, and taking them into a classifier may lead to a better classification between ASD and TD. In our previous study [21], we used 3 feature variables (i.e., HbO2-based RSFC between Channel 3 and 17, HbO2 and Hb signal magnitudes of Channel 6) and the SVM classifier to achieve the classification with sensitivity of 81.6%, specificity of 94.6%. Including the 2 ‘new’ (i.e., power of HbO2 at 0.0200 Hz, and average power of Hb at 0.0267 and 0.0333 Hz, both on the right hemisphere) and the 3 ‘old’ feature variables into the SVM classifier resulted in a classification with 89.1% sensitivity, 94.8% specificity and 91.7% accuracy. Compared to the classification by using the 3 ‘old’ feature variables, this classification is much better in sensitivity, and similar in specificity.

Since not every channel on the right hemisphere showed significant alteration in the HbO2 power at 0.0200 Hz, and Hb power at 0.0267-0.0333 Hz, the average over the all 12 channels could reduce the significance in the alteration. In fact, among the 12 channels, there were 2 channels (Channel 19 and 22) showing significant alteration in both HbO2 power at 0.0200 Hz (p = 0.0015) and Hb power at 0.0267-0.0333 Hz (p = 0.0135). Therefore using the average power of HbO2 and Hb over the 2 channels (Channel 19 and 22) instead of the average over the whole right hemisphere, we obtained 2 feature variables: Feature1 and Feature2, namely, Feature1 was the average of HbO2 power at 0.0200 Hz over Channel 19 and 22; while Feature2 was the average of Hb power in the band of 0.0267-0.0333 Hz over Channel 19 and 22. Including these 2 feature variables and those 3 used in the previous study [21] into the SVM classifier, the classification was achieved with 90.5% sensitivity, 95.2% specificity and 92.7% accuracy, better than using the average powers of the whole right hemisphere as feature variables. Though the gain in the classification accuracy was small, only 2 channels (Channel 19 and 22) were used for obtaining the power-related features, which greatly simplified the fNIRS measurement and reduced the requirement (e.g., the number of optical channels) for fNIRS setup.

4. Discussion and conclusion

When using the modified Beer-Lambert law to convert the changes in optical intensity into the concentration changes in HbO2 and Hb, the differential pathlength factor (DPF) is usually used in most of fNIRS setups. The average photon pathlength L for a SD pair can be expressed as the SD distance d multiplied by DPF. Since DPF depends on a variety of factors such as wavelength, type of tissue and age of subject [29], to accurately obtain the value for HbO2 and Hb, DPFs have to be chosen carefully. In contrast to most of fNIRS setups, the fNIRS (i.e., FOIRE-3000) used in this study does not take DPF in calculation, thus it provides only the relative changes in HbO2 and Hb, i.e. L·HbO2 and L·Hb containing an unknown average pathlength L. In our data analysis, the time series of the hemodynamic signal S (HbO2 or Hb) was centered and normalized via $Z = (S - \text{mean}(S))/\text{std}(S)$. By this way, the unknown parameter L was cancelled out, and on the other hand, the average power for each signal was equalized, which was helpful in revealing the structural differences in the power spectrum.

In resting-state there is neither overt perceptual input nor behavioral output, therefore recording spontaneous brain activity with fNIRS is a rather easy measurement for both experimenters and subjects, in particular for individuals with ASD who may have difficulty (e.g., low functioning autism) in performing tasks involving cognitive processes. Therefore exploring characteristics associated with ASD in resting-state brain is of particular interest for
understanding the intrinsic nature of autistic brain as well as future clinic application on screening individuals with risk of ASD.

In the present study, we performed frequency domain analysis on the spontaneous cerebral hemodynamic fluctuations in the bilateral temporal lobes. We investigated the spectral structure of the fluctuations in the low frequency band, i.e., 0.009-0.080 Hz, because several previous studies regarding RSFC were focused in this band [21,22,30], and the derived RSFC (i.e., Pearson correlation coefficient between the two low frequency hemodynamic fluctuations arising from two functionally related cortical regions) was demonstrated to be significantly weaker for children with ASD than TD children [6,21,22]. In addition to weaker RSFC, our prior fNIRS study has also demonstrated in this low-frequency band, children with ASD have a higher magnitude in the fluctuations in the bilateral temporal lobes [21]. Therefore the low frequency hemodynamic fluctuations may contain rich information on the intrinsic nature of brain showing differences between ASD and TD. By performing frequency domain analysis on the normalized time series of HbO and Hb, we were able to investigate and reveal the spectral difference between the two groups. We observed the power spectrum for ASD showed a different pattern from TD. Though the spectra for both ASD and TD reached their peaks around 0.0133 Hz, they dropped differently. The power for TD decayed faster than ASD in particular in the frequency band of 0.0200-0.0333 Hz. Moreover, at frequency of 0.0200 Hz, TD children had significantly larger HbO2 power than ASD; whereas at 0.0267 and 0.0333 Hz, children ASD had significantly larger Hb power than TD.

The major alterations of the power spectrum in ASD occur in the frequency band of 0.0200-0.0333 Hz (see Fig. 2 and Table 1), partly overlapping with the so-called Slow-5 oscillation band (0.010-0.027 Hz) [23]. fMRI studies have shown the reduction in Slow-5 oscillation in the brain of ischemic stroke patients or older healthy adults [24,25]. To date there has been no report of alteration in Slow-5 oscillation in ASD. In the present study the frequency resolution was 0.0067 Hz, thus the data points of the power spectrum did not match well with the Slow-5 band. But nevertheless, by linear interpolation we could still obtain the power in the exact Slow-5 band (i.e., 0.010-0.027 Hz), and found in HbO2, children with ASD showed reduced power than TD (27.20 ± 3.27 vs. 28.82 ± 2.98, p = 0.084, on the left hemisphere; 27.29 ± 2.94 vs. 29.30 ± 3.75, p = 0.046, on the right hemisphere). The more significant alteration in Slow-5 oscillation located on the right hemisphere; while on the left hemisphere, the alteration was marginally significant. In Hb, children with ASD also showed smaller Slow-5 oscillation on both hemispheres, but not statistically significant. Thus children with ASD experienced the similar spectral structure as observed in healthy aging individuals or patients with ischemic stroke [24,25].

Since the alteration in Slow-5 oscillation is considered to be associated with the reduction of network co-activation [24], or functional connectivity, Children with the reduction in Slow-5 oscillation in the brain of ASD may also link to the reduced RSFC which has been well demonstrated [3,6,21,22]. On the other hand, it may have been noticed that the power spectrum curve is more symmetric between the left and right for TD than ASD (see Fig. 2), the alteration on the right hemisphere in ASD deteriorates the symmetry, thus leading to the reduced RSFC between the two hemispheres. In addition to observing the reduction of Slow-5 oscillation of HbO2 in ASD, we also observed ASD showed increased Hb power in the band of 0.0267-0.0333 Hz, just crossing the upper bound of the Slow-5 band. Though the underlying physiological mechanism associated with this alteration in Hb component is not clear, this characteristic is useful for the classification, because it is uncorrelated to the feature of HbO2 power at 0.0200 Hz, providing complementary discriminative information on predicting ASD.

The most pronounced differences in the spectral structure between ASD and TD located on the right middle and inferior temporal gyri, e.g., channel 19 and 22. In our previous study [21], the significant alterations in RSFC between ASD and TD were the connectivity between
Channel 3 and 17, Channel 8 and 22, Channel 9 and 21, Channel 10 and 20, Channel 11 and 24. Most of them located on the middle and inferior temporal lobes, implying on the other hand the alteration in the spectral structure might have some relationship with the change in RSFC.

Several imaging studies have demonstrated the right temporal abnormalities in ASD. For examples, in a SPECT study, Ohnishi, et al confirmed that the reduced cerebral blood flow in the right temporal lobe in ASD was correlated with the obsessive desire for sameness [31]. A PET study in ASD showed that both temporal lobes had reduced cerebral blood flow, but region with significant hypoperfusion was larger in the right lobe [32]. A fMRI study demonstrated children with ASD had greater response to language in the right than the left temporal lobe (abnormally right-lateralized temporal lobe response to language), opposite to the response of the TD children [33]. A structural MRI study revealed the gray matter volume in the right inferior gyrus was larger for ASD patients than the normal controls, which could be served as a characteristic feature for distinguishing between ASD and TD groups [34]. Whether these right temporal abnormalities have some underlying relationship with the atypical pattern of the power spectrum observed in ASD is not clear.

A limitation of this study on the classification is the limited size of the sample (25 children with ASD and 22 TD children). Though a rather accurate classification was achieved on the current sample, the high accuracy may not hold if more subjects (i.e., ASD patients and TD controls) are included. Uncovering more characteristics associated with ASD in the future and thus using more discriminative features for the classification may overcome this problem. Another limitation could arise from the fNIRS setup (FOIRE-3000) in which the SD distance was fixed to be 3.0 cm. Therefore the measured signal (HbO₂ and Hb) inevitably contained the systemic interference from the scalp. The low frequency components, in particular those overlapping with the brain neurovascular signal in frequency band, may induce false positives or false negatives in fNIRS measurement [35]. An effective way to get rid of the systemic interference is to use multiple SD distance probes. In this way, the interference from the scalp can be measured separately by the short-SD distance (e.g., ~1.0 cm) probes, and then regressed out from the signal measured with the long-SD (e.g., 3.0 cm) probes. In this study we performed frequency-domain analysis on the spontaneous hemodynamic signal and observed at a few frequencies (e.g., 0.0200, 0.0267, 0.0333 Hz) the powers were different between ASD and TD. In addition, we also observed these differences were not always same across all measurement channels. For example, in some channels (e.g., Channel 19 and 22) the differences were significant, while in other channels there were no significant changes. This implies the systemic interference may not make considerable contribution to the differences between ASD and TD, since the systemic interference tends to make global contribution to all measurement channels, at least several neighboring channels (e.g., Channel 17, Channel 24, in which we did not see the significant differences between the two groups). However, to effectively eliminate the systemic interference and accurately retrieve the neurovascular signal from the brain, optical probes with multiple SD distances (with short- and long-SD) should be used for fNIRS measurement, which can definitely improve the robustness of our result.

In conclusion, with the fNIRS distinct pattern in the power spectrum of hemodynamic fluctuation was observed in ASD in the temporal lobes with more significant alteration on the right side. The major difference in the power spectrum between children with ASD and TD children located in the frequency band of 0.0200-0.0333 Hz. This observation may be helpful for a better understanding of ASD in terms of cerebral hemodynamics. With the observed features and those previously indentified, a rather accurate classification between ASD and TD can be achieved by using SVM classifier, which may render fNIRS a useful image tool for the future use of screening individuals with high risk of ASD.
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