The Dynamic Measurements of Regional Brain Activity for Resting-State fMRI: d-ALFF, d-fALFF and d-ReHo

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Abstract. The human brain is always in the process of constantly changing. Given that the conventional measurements of regional brain activity are less sensitive to changes over time, three dynamic measurements were proposed to capture the temporal variability of regional brain activity. In this study, dynamic amplitude of low frequency fluctuation (d-ALFF), dynamic fractional amplitude of low frequency fluctuation (d-fALFF) and dynamic regional homogeneity (d-ReHo) were obtained from resting-state functional magnetic resonance imaging (rs-fMRI) of both 238 ADHD and 239 typical developing (TD) subjects. Then, they were applied to detecting the regional activity differences between ADHD and TD group. Compared with the conventional measurements (ALFF, fALFF and ReHo), the dynamic measurements were more sensitive in exploring the differences of regional brain activity between ADHD and TD group. The three new measurements not only enrich the diversity of methods for investigating the dynamic variation of regional brain activity, but also emphasize the significance of detecting the temporal variability of regional brain activity.

Keywords: rs-fMRI · Temporal variability · d-ALFF · d-fALFF and d-ReHo

1 Introduction

The investigation for dynamic brain activity from resting-state fMRI is mainly based on two patterns: the dynamics of spontaneous brain activities and the dynamics of functional interconnections between spontaneous brain activities [1]. Presently, most of studies for dynamic brain activity are concentrated on exploring the dynamic functional connectivity which mainly involve in the flexible and adjustable configuration between brain networks [2–4]. Several approaches have been proposed for probing time-varying patterns in fMRI imaging data such as sliding window analysis [5], time-frequency analysis [6], point process analysis [7] and temporal graph analysis [8]. Especially, the most common method used for describing brain network dynamics is sliding windows analysis with temporal resolution from seconds to minutes.

Traditionally, voxel-wise methods such as ALFF, fALFF and ReHo have been widely applied to exploring the regional brain activities [9–11]. However, these

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measurements don't perfectly capture the dynamic characteristics of regional brain activity over different times.

In view of the limitations of conventional measurements, we proposed three novel dynamic measurements (d-ALFF, d-fALFF and d-ReHo) by combining the sliding window technique with the three conventional measurements (ALFF, fALFF and ReHo) to investigate the temporal variability of voxel-wise brain activity. We hypothesized that our methods were more sensitive than conventional static measurements in detecting the differences of regional brain activity between ADHD and TD group. To verify the effectiveness of our methods, we compared the results obtained by the new measurements with those obtained by the conventional measurements.

2 Materials and Methods

2.1 Subjects

The resting-state fMRI and structural MRI image data of 238 ADHD and 239 TD were obtained from ADHD-200 [12] and Autism Brain Image Date Exchange (ABIDE) [13] across multiple independent imaging sites. Specially, only the data of typically developing control in the ABIDE were used in this study. For both ADHD and TD subjects, the inclusion criteria included: no history of neurological disease and no diagnosis of either schizophrenia or affective disorder, image at least cover 95% of brain, IQ scores >80. More details of demographic information of these participants were listed in the Table 1.

Table 1. Demographic information.

	ADHD (n = 238)			TD (n = 239)		
Sites	N	Age (mean)	Gender (M/F)	N	Age (mean)	Gender (M/F)
KKI	17	9.64	11/6	40	9.88	24/16
NYU	119	10.24	88/31	114	11.86	68/46
Peking	93	11.58	81/12	85	11.08	50/35
NeuroIMAGE	9	14.67	9/0			
Total	238	10.89	189/49	239	11.26	142/97

2.2 Data Pre-processing

T1 and resting-state fMRI data were preprocessed with DPARSF [14]. The first ten volumes of rs-fMRI images were discarded for scanner calibration. All images were corrected for within-scan acquisition time differences between slices and were realigned to the middle volume to cut down on inter-scan head motions. Then, these images were registered onto the Montreal Neurological Institute (MNI) standard template and were subsequently resampled to 3 mm isotropic resolution. Spatial smoothing was applied with a Gaussian kernel of 8 mm full-width at half-maximum

(FWHM) to improve the signal-to-noise ratio (SNR). Furthermore, the mean signal of white matter and cerebrospinal fluid were removed as covariates. Linear trend removal coupled with band-pass filtering (0.01–0.1 Hz) were also performed.

2.3 Dynamic Measurements

As shown in Fig. 1, our method mainly consists of two parts: segmentation of time windows (Fig. 1A) and calculation of three dynamic measurements (Fig. 1B). In the first part, taking one rs-fMRI image as an example, we firstly divided all BOLD time series of k voxels across the whole brain into n overlapping windows (W_1, W_2, W_3… W_{n-1}, W_n) each with specific length l and interval d between time windows. In this study, we chose 50 s and 30 s as the length of time window and interval between time windows respectively. In the second part, in order to explore the temporal variability of regional brain activity, we proposed three new measurements dynamic Amplitude of Low Frequency Fluctuation (d-ALFF), dynamic fractional Amplitude of Low Frequency Fluctuation (d-fALFF) and dynamic Regional Homogeneity (d-ReHo) based on the combination of the time windows technique and the conventional measurements (ALFF, fALFF and ReHo).

d-ALFF Measurement

d-ALFF was calculated based on several different time windows which contained the time series over a specific period of time. Briefly, for a given voxel, the time series was first transformed to the frequency domain using a Fast Fourier Transform (FFT) and the power spectrum was obtained. Subsequently, the square root of the power spectrum was calculated and then averaged over a prespecified frequency band (0.01–0.08 Hz) and the averaged square root was known as ALFF at the given voxel. After calculating ALFF of all voxel in time windows, each participant will get several window-based ALFF maps. Then, we computed the mean and standard deviation of each voxel in all window-based ALFF maps for each subject and further got the corresponding coefficient of variation (CV) which was acquired by dividing the standard deviation by the mean. To better measure the dynamic variation of regional brain activity between different individuals, we used CV as d-ALFF, which represented the temporal variability of absolute energy consumption in low-frequency regional brain activity.

d-fALFF Measurement

d-fALFF represented the degree of changes over a period of time in a ratio of the power of each frequency at the low-frequency range (0.01–0.08 Hz) to that of the entire frequency range (0–0.25 Hz). Firstly, the linear trend of time series was eliminated. Secondly, the time series for each voxel were transformed to a frequency domain without band-pass filtering. Thirdly, the square root was calculated at each frequency of the power spectrum with FFT. Finally, the sum of amplitude in the 0.01–0.08 Hz frequency range was divided by that in the 0–0.25 Hz frequency range. Similar to d-ALFF, for each subject, the CV value calculated from the mean and standard deviation of multiple windows-based fALFF maps was regarded as the indication of temporal variability of relative energy consumption of regional brain at low frequency band.

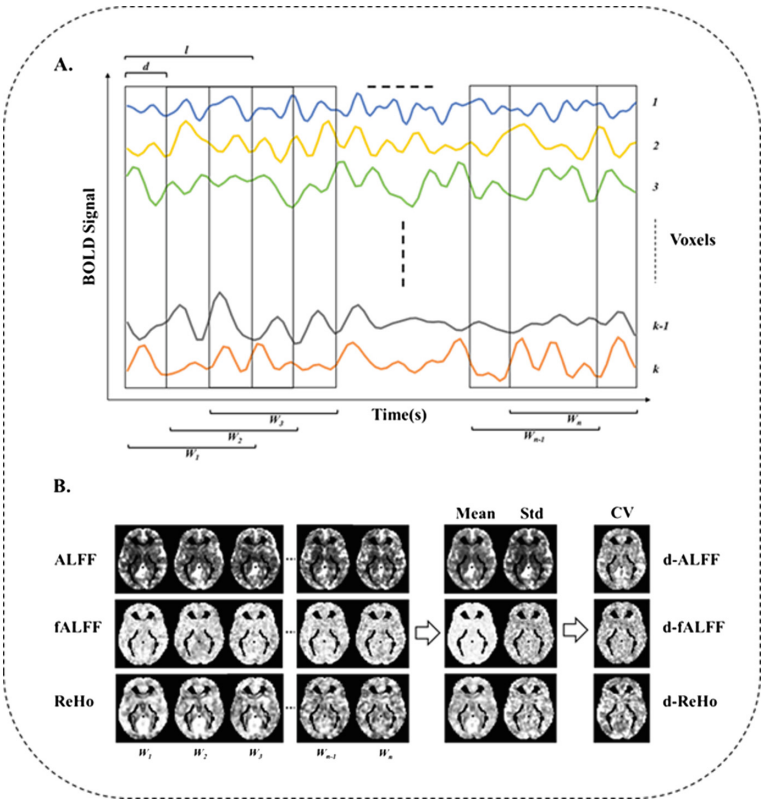

Fig. 1. The flow chart of dynamic analysis of regional brain activity. (A) Segmentation of time windows. The colored curve represented the time series across the whole brain and each time series indicated the BOLD signal of each voxel in a participant. The time series were segmented into different time windows and further analysis was constructed on the segmented windows. (B) Calculation of three dynamic measurements. The dynamic measurements (d-ALFF, d-fALFF and d-ReHo) were represented by the coefficient of variation (CV) of the static measurements (ALFF, fALFF and ReHo) calculated from different time windows. The CV was obtained from the mean of static measurements over different time windows divided by corresponding standard deviation (Std).

d-ReHo Measurement

Similar to ReHo, d-ReHo was also based on the hypothesis that a given voxel's activity was usually correlated to that of its neighbors. Firstly, we got ReHo value of all voxels across different time windows by calculating the Kendall coefficient of concordance (KCC) of time series of a voxel with those of its nearest 26 neighbors. Then, after calculating the mean and standard deviation of each voxel in all time windows, we considered CV value which was equal to the standard deviation divided by the mean as the measurement of temporal variability of regional brain activity, which characterized the dynamic changes of local synchronization of spontaneous fMRI signals within a cluster.

3 Statistics Analysis

In order to reduce the effect of noise, spatial smoothing was again carried out with a Gaussian kernel of 8 mm FWHM before further statistics analysis. The dynamic measurements (d-ALFF, d-fALFF and d-ReHo) of regional brain activity between ADHD and TD group were compared by two-sample t-test on each voxel, taking a significant threshold of $P < 0.001$ (uncorrected), with age and gender as covariates. Voxels with $P < 0.001$ and cluster size > 540 mm^3 were regarded as the significant group differences.

4 Results

4.1 The Comparison of ALFF and d-ALFF

As shown in the Fig. 2, compared to ALFF, there were more significant group differences between ADHD and TD group using d-ALFF. For d-ALFF, compared to TD group, ADHD group showed increased d-ALFF in the right supramarginal gyrus (SMG), right putamen, right precentral gyrus, left inferior temporal gyrus (ITG), bilateral middle temporal gyrus (MTG) as well as cerebellum, and decreased d-ALFF in the right medial superior frontal gyrus (mSFG), right thalamus, right fusiform, right insula, right posterior cingulate gyrus (PCC), left superior temporal pole, left hippocampus and cerebellum. In contrast, when using ALFF, no significant group difference between ADHD and TD group was found.

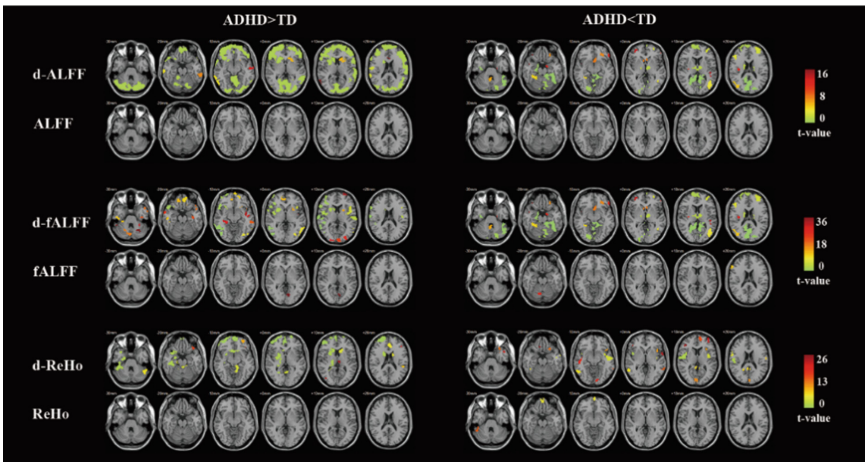

Fig. 2. The comparison of static (ALFF, fALFF, ReHo) and dynamic (d-ALFF, d-fALFF, d-ReHo) measurements for regional brain activity between ADHD and TD group. The first and second rows show the group differences between ADHD and TD group using d-ALFF and ALFF respectively. The third and fourth rows show the group differences between ADHD and TD group using d-fALFF and fALFF respectively. The fifth and sixth rows show the group differences between ADHD and TD group using d-ReHo and ReHo respectively.

4.2 The Comparison of fALFF and d-fALFF

Clearly, d-fALFF was more sensitive than fALFF in discovering group differences between ADHD and TD group. Using d-fALFF, compared to TD group, ADHD group exhibited obvious increase in the right ITG, bilateral MTG, bilateral putamen, bilateral temporal pole and cerebellum as well as decrease in the left precuneus, bilateral middle frontal gyrus (MFG), bilateral middle frontal gyrus (SFG), right fusiform, right middle occipital gyrus (MOG) and cerebellum. However, using fALFF, there were only a small amount of group differences between ADHD and TD group, such as left lingual gyrus, right angular gyrus, right inferior frontal gyrus (IFG) and cerebellum. More details were shown in the Fig. 2.

4.3 The Comparison of ReHo and d-ReHo

As we can see, there were more significant differences between ADHD and TD group using d-ReHo than those of using ReHo (Fig. 2). Compared with TD group, the increased d-ReHo in ADHD group appeared at the left caudate, left orbital frontal gyrus (OFG), left anterior cingulate gyrus (ACC), left angular gyrus, left fusiform, left thalamus, right MOG, left supramarginal gyrus and cerebellum. Besides, the deceased d-ReHo in ADHD group appeared at the left ITG, bilateral MTG, bilateral postcentral gyrus, left insula and right IFG. Nonetheless, no clusters showed increased ReHo in ADHD group and the bilateral IFG, MFG, left superior parietal gyrus (SPG) as well as cerebellum exhibited decreased ReHo in ADHD group compared with TD group.

5 Discussion

In this study, three dynamic measurements (d-ALFF, d-fALFF and d-ReHo) were primarily constructed on the combination of the time windows technique and the conventional measurements (ALFF, fALFF and ReHo) which were widely recognized as effective methods to measure regional brain activity in voxel-wise way. For one thing, d-ALFF and d-fALFF described the temporal changes of energy consumption according to the level of oxygen content in spontaneous brain activity. For another, d-ReHo revealed the dynamic variation of functional consistency in local regions by calculating the correlation between time series. Furthermore, we compared the new measurements with the conventional measurements by examining the sensibility of these measurements to distinguish the different regional brain activity between ADHD patients and health people. As predicted, we easily observed more significant differences between ADHD and TD group using the new measurements than those using the conventional measurements. These results were basically consistent with previous anatomical MRI studies [15–17], indicating that the involved regions of abnormal regional brain activities of ADHD patients were awfully wide such as frontal lobe, ACC, caudate and cerebellum.

In summary, the new measurements were suitable to exploring the dynamic changes of regional brain activity between ADHD and TD group. The results showed that the new approaches were more sensitive and stable than the conventional

approaches. Although there were a wide range of differences between ADHD and TD group in regional brain activity using new measurements, the effectiveness of results still need further study. For example, the length of each time window and interval between time windows may have a critical influence on the temporal variability of regional brain activity. Besides, although the brain activity in low-frequency band (<0.1 Hz) has been extensively studied [18–20], the changeable and various brain activity is not confined to low-frequency band [21, 22]. Therefore, it is worthwhile to explore the temporal variability of distinct types of brain activity in different frequency ranges. In the aspect of practicability, the three dynamic measurements also need to be retested on more disease studies such as autism and schizophrenia. Altogether, these new measurements not only enrich the diversity of research methods for detecting the regional brain activity, but also contribute to understanding of dynamic measurements.

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