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Reliability of the amplitude of low-frequency fluctuations in resting state in chronic schizophrenia

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Abstract

The resting state amplitude of low frequency fluctuations (ALFF) has been shown to be reliable in healthy subjects, and to correlate with antipsychotic treatment response in antipsychotic–naïve schizophrenia patients. We found moderate to high test-retest stability of ALFF in chronically-treated schizophrenia patients assessed twice over a median interval of 2.5 months.

Keywords

ALFF; schizophrenia; stability

1. Introduction

Resting state functional magnetic resonance imaging (fMRI) studies of schizophrenia have typically focused on functional connectivity, i.e., the degree of temporal correlation of the BOLD signal among anatomically distributed brain regions. Different connectivity patterns within and between several functionally distinct networks have been reported in healthy and schizophrenia groups (Liang et al., 2006; Liu et al., 2006; Jafri et al., 2008; Lui et al., 2009a).

The amplitude of low frequency fluctuations (ALFF) can also be measured from resting fMRI data. These low frequency fluctuations, slower than cardiac or respiratory fluctuations, are considered to be related to spontaneous neural activity within a region, and contribute strongly to the correlations seen in BOLD signal time courses across regions (Cordes et al., 2001; Yang et al., 2007; Lui et al., 2009b). ALFF has recently been shown to be reduced in

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schizophrenia in cross-sectional studies, albeit with some regional inconsistencies (Hoptman et al., 2010; Huang et al., 2010). A promising longitudinal study, however, reported an increase (normalization) of frontal and parietal ALFF in antipsychotic–naïve schizophrenia patients after 6 weeks of antipsychotic drug treatment (Lui et al., 2010). Hence, ALFF may provide a relatively easy and safe method to track antipsychotic response in clinical populations and may shed light on the mechanism of action of these agents. However, the test-retest reliability of ALFF has only been examined in healthy volunteers to date (Zuo et al., 2010), and it is unclear whether ALFF is reliable and stable over the short-term illness course in chronically treated persons with schizophrenia. A related measure, fractional ALFF or fALFF, measures the amount of power in the lower frequency spectrum relative to the total power in the detectable range; however, it is slightly less reliable than ALFF in healthy controls(Zuo et al., 2010). Thus, in the present study we examined the stability of ALFF, with a median test-retest interval of 2.5 months in subjects with chronic schizophrenia.

2. Materials and Methods

2.1. Subjects

The study was approved by the UNM Institutional Review Board (IRB). Data represent a convenience sample, aggregated across studies that collected the same resting state scan on the same scanner. Twenty-one outpatients with DSM-IV-TR schizophrenia (diagnosed based on the Structured Clinical Interview for DSM-IV (First et al., 2002) provided informed consent and participated in the multiple studies. Subjects were outpatients ranging in age from 23 to 62 years (mean 42 years). Positive, negative, and general symptom severity as measured by the Positive and Negative Symptoms Scales (PANSS; (Kay et al., 1987)) were assessed for each subject within one week of each scan. All were treated with antipsychotic medication with clinically equivalent-olanzapine dosages ranging from 2.5 to 70 milligrams/day (Gardner et al., 2010).

2.2. Scanning methods

Patients were scanned twice in a Siemens 3T Tim Trio. Each scanning session included an echo-planar BOLD-weighted resting state scan (33 slices, 165 measurements, 3.8×3.8×3.5 mm voxels, 64 × 64 resolution, FOV 240 mm, axial, TR = 2000 ms, TE = 29 ms, flip angle 75 degrees, 5 min 34 second duration, eyes open). Interscan interval ranged from 5 to 326 days, with a median interval of 2.5 months (mean interval = 112 days, stdev = 97 days).

2.3. ALFF Analysis

Resting state data were pre-processed using SPM5 (Wellcome Department of Imaging Neuroscience, London, England, http://www.fil.ion.ucl.ac.uk). The first two images of each scan were discarded at the scanner to remove T1 equilibration effects; the images were realigned using INRIalign, included in SPM5 (Freire et al., 2002); and slice-timing correction was applied using the middle slice as the reference frame. Data were then spatially normalized to the Montreal Neurological Institute (MNI) echo-planar template, and resliced to 3×3×3mm voxels. Maximal head movement within a scan was less than 5 mm.

Voxelwise ALFF maps were calculated for each patient and scan using the Lui et al (2010) methods implemented in the REST software (http://www.restfmri.net/forum/rest). The ALFF calculation consists of linearly detrending each voxel's time-series, bandpass filtering (0.01–0.08 Hz), then extracting the power spectra via the fast Fourier transform. The ALFF is the averaged square root of the power in the 0.01 to 0.08 Hz window. ALFF maps are normalized by the mean within-brain ALFF value for each subject to account for differences

in scan intensity units, then smoothed with an 8 mm FWHM Gaussian kernel, as done in Lui et al., 2010.

To assess the test-retest stability of the ALFF measures, voxelwise intraclass correlation coefficients (ICC) were calculated as in Zuo et al. (2010). In order to assess the effect of the interscan interval and medication changes on ALFF stability, the relative mean difference in ALFF across scans (the absolute difference of the first and second images scaled by their average) was regressed on the interscan interval and on medication changes in separate analyses.

3. Results

3.1 Clinical stability

On average, the positive, negative, and general symptoms from the PANSS did not differ significantly between scanning sessions ($p < .05$ in each case by a paired t-test). The median scores at the first scans were 15, 15, and 30, respectively; at the 2nd scan, they were 15, 12, and 28. The median absolute differences at the second scan were 3, 2, and 4 points, respectively, with an interquartile range of 3, 3, and 4 points, respectively. Antipsychotic dosages expressed in olanzapine equivalents also did not change significantly; 13 subjects had no change, and the average non-zero change was 1.6 milligrams/day of olanzapine equivalents.

3.2 ALFF stability

A view of the ICC results are shown in Figure 1, overlaid on a structural template. Similar to Zuo et al. (2010), who examined healthy controls, most of the brain voxels showed an ICC of 0.5 or greater; the exceptions included the orbital frontal cortex, and the lateral, frontal parts of the temporal lobe, which showed only localized regions of high stability.

Clusters of at least 50 contiguous voxels with an ICC ≥ 0.80 were found throughout the cortex. The largest cluster, 165 voxels with a maximum ICC of 0.94, was in the left hemisphere, in the inferior parietal cortex into the posterior superior and middle temporal gyrus. The remaining clusters were medial and in the right hemisphere, as follows:

- 154 voxels spanning midline BA6 and 4A, left and right precuneus and mid cingulate cortex, (max ICC = 0.88);
- 154 voxels in right BA 45, middle and inferior frontal gyrus (ICC = 0.9);
- 63 voxels also in the right middle and inferior frontal gyrus but in BA 44/45 (ICC = 0.88);
- 76 voxels in the right inferior parietal cortex and supramarginal gyrus (ICC = 0.95);
- 94 voxels in the right inferior parietal cortex into the middle and superior occipital gyrus, angular gyrus, and precuneus (ICC = 0.87);
- and a 64 voxel cluster from right BA 18 into the midline cuneus and superior parietal lobule (ICC=0.86).

Clusters of less than 50 voxels' extent with ICC ≥ 0.80 were seen in matching areas in the contralateral hemisphere, specifically in left BA 45/44/middle and inferior frontal gyrus, inferior parietal cortex and supramarginal gyrus, and the right posterior superior and middle temporal gyrus.

The effect of interscan interval on ALFF variation was not significant when FWE-corrected for whole-brain analysis. Using a gray matter mask (created using WFUPickatlas (Maldjian

et al., 2003) by dilating the gray matter mask by 2 mm in 2D), and correcting for the restricted number of voxels, a single cluster of 13 voxels in the head and body of the left caudate was significant at the cluster level ($p < 0.03$, FWE corrected), though not at the voxel level ($p < 0.057$, FWE corrected). The average value within these 13 voxels for each subject was extracted using Marsbar (Brett et al., 2002), and regression analysis showed that larger changes in ALFF in this cluster were associated with increasing interscan intervals ($R^2 = 0.76$). The effect of medication changes showed no signification relationship to ALFF variation when corrected for whole-brain analysis (FWE or FDR < 0.05).

4. Discussion

In clinically stable persons with schizophrenia, the measurements of the amplitude of low frequency fluctuations during the resting state are quite reliable over time, similar to what has been found in healthy subjects (Zuo et al., 2010), even though our patients were scanned over longer and more variable interscan intervals. These relatively high stability coefficients over such long durations provide conservative estimates of the likely test-retest reliability of ALFF in patients assessed over a shorter interscan interval.

The stability of the ALFF measures showed some regional variation. Parietal and posterior temporal cortex and the middle and inferior frontal areas may be slightly stable than other regions. In all the regions identified by Lui et al. (2010) as showing changes with treatment, there were areas of moderate to high reliability (ICCs ranging from 0.65 to almost 0.9). The exception was the superior temporal gyrus/BA38 in the temporal pole (max ICC of 0.60 in left BA 38). There may be regional increase in the variation in ALFF with increasing interscan interval, but this relationship was not significant at the voxel level in our sample.

Only one study has investigated whether changes in ALFF track antipsychotic treatment response, and the results were encouraging (Lui et al., 2010). The focus of the Lui et al. 2010 study was only first-episode, drug naïve patients; it is unclear if ALFF can similarly track treatment response in medicated chronic patients undergoing changes in their treatment regimens. However, the present findings of moderate to high test-retest reliability in a sample of chronic, clinically stable, schizophrenia patients lays a foundation for examining the use of ALFF measures to track treatment response in this population.

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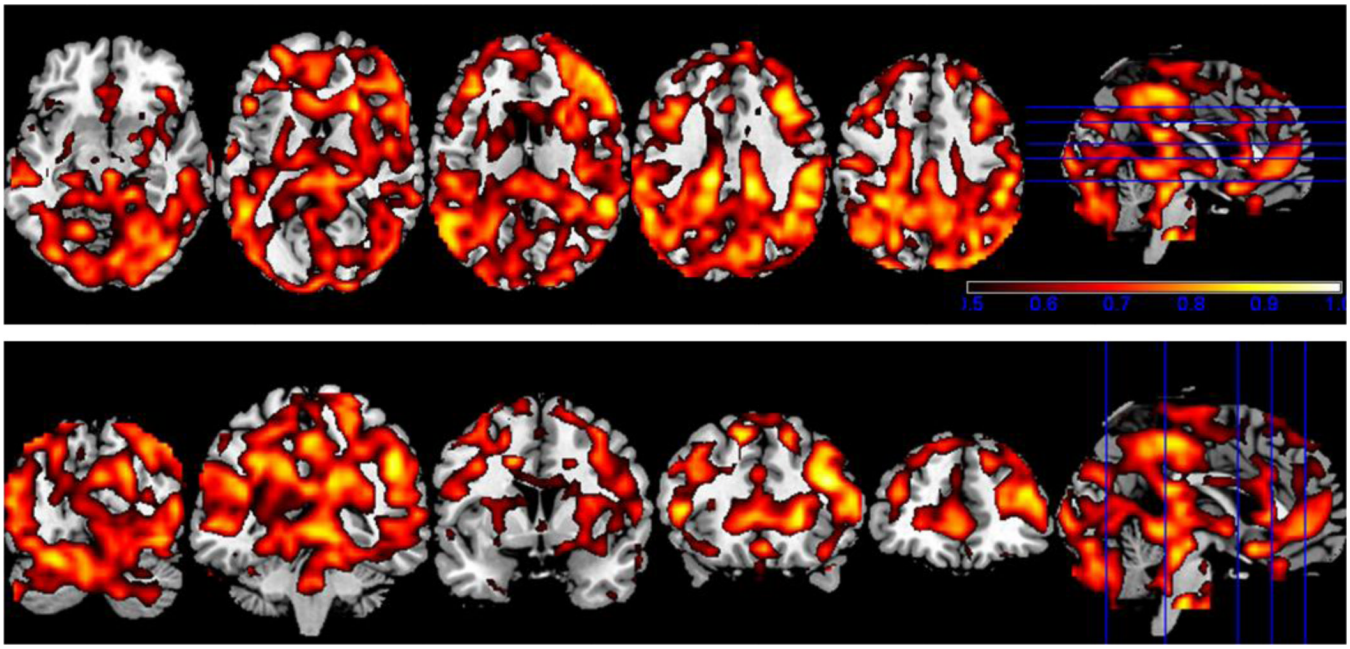

Figure 1.
The ICC image thresholded at 0.5 or greater overlaid on the MNI template brain, in both axial and coronal views. The color bar covers from red (ICC = 0.5) to white (ICC =1).