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INVESTIGATING UNIVARIATE TEMPORAL PATTERNS FOR INTRINSIC CONNECTIVITY NETWORKS BASED ON COMPLEXITY AND LOW-FREQUENCY OSCILLATION: A TEST–RETEST RELIABILITY STUDY

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Abstract—Intrinsic connectivity networks (ICNs) are composed of spatial components and time courses. The spatial components of ICNs were discovered with moderate-to-high reliability. So far as we know, few studies focused on the reliability of the temporal patterns for ICNs based their individual time courses. The goals of this study were twofold: to investigate the test–retest reliability of temporal patterns for ICNs, and to analyze these informative univariate metrics. Additionally, a correlation analysis was performed to enhance interpretability. Our study included three datasets: (a) short- and long-term scans, (b) multi-band echo-planar imaging (mEPI), and (c) eyes open or closed. Using dual regression, we obtained the time courses of ICNs for each subject. To produce temporal patterns for ICNs, we applied two categories of univariate metrics: network-wise complexity and network-wise low-frequency oscillation. Furthermore, we validated the test–retest reliability for each metric. The network-wise temporal patterns for most ICNs (especially for default mode network, DMN) exhibited moderate-to-high reliability and reproducibility under different scan conditions. Network-wise complexity for DMN exhibited fair reliability (ICC < 0.5) based on eyes-closed sessions. Specially, our results supported that mEPI could be a useful method with high reliability and reproducibility. In addition, these temporal patterns were with physiological meanings, and certain temporal patterns were correlated to the node strength of the corresponding ICN. Overall, network-wise temporal patterns of ICNs were reliable and informative and could be complementary to spatial patterns of ICNs for further study.

Key words: resting state fMRI, test–retest reliability, complexity estimators, intrinsic connectivity networks, low-frequency oscillation.

INTRODUCTION

The human brain is known to be organized into dynamic, intrinsic functional networks (Fox et al., 2005), namely resting state functional connectivity networks or intrinsic connectivity networks (ICNs). ICNs represent spatially coherent spontaneous fluctuations of the functional magnetic resonance imaging (fMRI) signals (Zuo et al., 2010b). About 20 ICNs were discovered and confirmed with high consistency (Damoiseaux et al., 2006; Smith et al., 2009; Biswal et al., 2010; Zuo et al., 2010b). The ICNs were related to certain physiological and behavioral meanings (Smith et al., 2009; Laird et al., 2011), as well as personality (Lei et al., 2013; Markett et al., 2013). Therefore, previous studies suggested that ICNs can be potential biomarkers for brain-related disorders research (Blautzik et al., 2012; Washington et al., 2013), and it is necessary to rigorously evaluate test–retest reliability of ICN measures (Guo et al., 2012).

There are two kinds of properties for ICNs to be evaluated, spatial patterns and temporal patterns (Beckmann et al., 2009). The spatial patterns for ICNs have been discovered with moderate-to-high test–retest reliability and reproducibility (Zuo et al., 2010b; Guo et al., 2012). The reliability and reproducibility of the spatial components were also confirmed with cross-validation using a meta-level method (Wisner et al., 2013). Specially, default mode network (DMN) (Raichle et al., 2001; Raichle and Snyder, 2007) was discovered with high reproducibility and inter-rater selection reliability (Franco et al., 2009; Meindl et al., 2010; Zuo et al., 2010b). To the best of our knowledge, most studies were focused on the spatial patterns of ICNs. The temporal patterns of ICNs might be meaningful in temporal dynamics for three reasons: (1) technically, the conventional spatial-independent component analysis (ICA) is not truly spatial independent and usually results in anatomically overlapping components, either because of limited spatial resolution of the data, or because an anatomical region truly is a part of two or more components (Beckmann et al., 2005; Smith et al., 2012);

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Abbreviations: ALFF, Amplitude of Low-Frequency Fluctuations; CCC, concordance correlation coefficient; DE, differential entropy; DMN, default mode network; EPI, echo-planar imaging; fALFF, fractional ALFF; fMRI, functional magnetic resonance imaging; ICA, independent component analysis; ICC, interclass correlations; ICNs, intrinsic connectivity networks; ICs, independent components; mEPI, multi-band EPI; MPRAGE, magnetization-prepared rapid acquisition with gradient echo; NIRS, near infrared spectroscopy; RE, Renyi entropy; SE, sample entropy; TE, Tsallis entropy; TR, Repetition Time; WE, wavelet entropy.

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(2) mathematically, a previous study suggested group ICA estimated sparse components rather than independent components (ICs) (Daubechies et al., 2009); (3) physiologically, the individual time courses for each ICNs represented the average spontaneous fluctuation within the corresponding spatial map of ICN (Smith et al., 2009). Moreover, one recent study reported that the long memory measured by Hurst exponent in the individual time course of DMN was correlated with personality (Lei et al., 2013). Another study reported that the time courses of ICNs were highly correlated with systemic low-frequency oscillation detected by near infrared spectroscopy (NIRS) with consistency and reproducibility (Tong et al., 2013). Therefore, the temporal patterns of ICNs might be informative with physiological meanings and the test–retest reliability analysis could be beneficial to these temporal measures.

Dual regression (Beckmann et al., 2009; Filippini et al., 2009) and ICA (Calhoun et al., 2001; Beckmann et al., 2005) are the two techniques to investigate the spatial and temporal patterns for ICNs. The limitations of ICA-based studies were that a manual procedure was always required to select the component maps for ICNs (Calhoun et al., 2001) and was not convenient for comparison of different metrics and studies (Guo et al., 2012). To address the above problems of ICA-based ICN investigations, dual regression was introduced to investigate the spatial–temporal patterns for ICNs (Beckmann et al., 2009; Filippini et al., 2009). Dual regression results in a set of subject-specific spatial maps and corresponding time series for each ICN (Beckmann et al., 2009; Filippini et al., 2009; Zuo et al., 2010b). One advantage of dual regression is that no manual selection of ICNs is required, since a set of spatial maps from the group-average analysis was used as input template (Beckmann et al., 2009; Filippini et al., 2009). Dual regression has been applied in many brain network researches (Filippini et al., 2009; Zuo et al., 2010b; Washington et al., 2013). However, few studies focused on the temporal patterns of ICNs using dual regression.

There were two categories of univariate temporal patterns: signal complexity and low-frequency fluctuations, which could be applied to investigate time courses of fMRI signals. (1) Complexity estimators: complexity is a measurable metric for time series and has been applied in assessment of biomedical signals (Andino et al., 2000). Nonlinear complexity algorithms for time series analysis can lead to a thorough understanding of the signal, and have been applied to research of brain complexity (Fernández et al., 2012). Entropy-related complexity estimators have been well established for studies of schizophrenia (Bassett et al., 2012; Fernández et al., 2012), and normal aging (Liu et al., 2012; Yang et al., 2013). Moreover, a pairwise maximum entropy model was established for brain network analysis (Watanabe et al., 2013). Specially, a fractional-related metric named Hurst exponent has been applied in neuroscience to measure the long memory of time signals in the brain (Bullmore et al., 2001; Lai et al., 2010; Lei et al., 2013); (2) Amplitude of Low-Frequency Fluctuations (ALFF): ALFF was the most studied voxel-wise metric of the brain and were broadly utilized to study the basic of brain, since slow fluctuations are one of the fundamental characteristics of the resting brain (Biswal et al., 1995; Zang et al., 2007). Alternatively, fractional ALFF (fALFF) was introduced for resting state fMRI studies (Zou et al., 2008). With complexity estimators and ALFF/fALFF, the oscillation of the brain can be quantified in voxel-wise level and regional-wise level (Yan et al., 2009; Zuo et al., 2010a; Zhang et al., 2011; Bassett et al., 2012). However, the network-wise entropy and low-frequency fluctuations for oscillation of ICNs remain unexplored.

In this study, we test the hypothesis that the temporal patterns of ICNs possess moderate-to-high reliability, and these temporal patterns are informative. To test this hypothesis, we represented univariate metrics derived from complexity and low-frequency fluctuations to measure the temporal patterns for ICNs, and analyzed their reliability under different scan conditions based on three datasets: (a) short- and long-term scans, (b) multi-band echo-planar imaging (mEPI), and (c) eyes open or closed. First, all of the original raw fMRI data were preprocessed and normalized. Then, the time course of each individual ICN was extracted based on the first step of dual regression. Third, the univariate metrics of temporal patterns for each ICN were computed. Finally, the test–retest reliability and reproducibility of oscillating ICNs were analyzed based on the proposed temporal patterns. In addition, a correlation analysis was performed based on these univariate metrics and bivariate properties for each time course of ICN to enhance interpretability.

EXPERIMENTAL PROCEDURE

Test–retest datasets

Three publicly available datasets were obtained from the 1000 Functional Connectomes Project (http://www.nitrc.org/projects/fcon_1000/). The three dataset are: (a) short- and long-term scans (nyu_trt), (b) mEPI (eNKI, enhanced Nathan S. Kline Institute) and (c) eyes open or closed (Beijing_eoec). The detailed scan parameters are listed as follows:

(a) *Short- and long-term scans (nyu_trt)*. This dataset was collected from a Siemens Allegra 3.0 T scanner according to protocols approved by the institutional review boards of the NYU School of Medicine. This dataset includes 25 individuals. Three resting-state scans were obtained for each participant. Each scan consisted of standard EPI functional volumes (Repetition Time (TR) = 2000 ms, 3 mm isotropic voxels, 6.5 min). Scans 2 and 3 were conducted in a single-scan session, 45 min apart, and were 5–16 months (mean 11 ± 4) after scan 1. An magnetization-prepared rapid acquisition with gradient echo (MPRAGE) structural image was obtained for each participant during each scan. All subjects were asked to relax and remain still with eyes open during the scan (Shehzad et al., 2009; Zuo et al., 2010b).