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Recovery of slow-5 oscillations in a longitudinal study of ischemic stroke patients

C. La[a,b,*], V.A. Nair[b], P. Mossahebi[b], J. Stamm[b], R. Birn[c,e], M.E. Meyerand[a,b,c,d], V. Prabhakaran[a,b,c,e]

[a] Neuroscience Training Program, University of Wisconsin-Madison, Madison, WI 53706, USA
[b] Department of Radiology, University of Wisconsin-Madison, Madison, WI 53792, USA
[c] Department of Medical Physics, University of Wisconsin-Madison, Madison, WI 53705, USA
[d] Department of Bio-Medical Engineering, University of Wisconsin-Madison, Madison, WI 53706, USA
[e] Department of Psychiatry, University of Wisconsin-Madison, Madison, WI 53705, USA

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ABSTRACT

Functional networks in resting-state fMRI are identified by characteristics of their intrinsic low-frequency oscillations, more specifically in terms of their synchronicity. With advanced aging and in clinical populations, this synchronicity among functionally linked regions is known to decrease and become disrupted, which may be associated with observed cognitive and behavioral changes. Previous work from our group has revealed that oscillations within the slow-5 frequency range (0.01–0.027 Hz) are particularly susceptible to disruptions in aging and following a stroke. In this study, we characterized longitudinally the changes in the slow-5 oscillations in stroke patients across two different time-points. We followed a group of ischemic stroke patients ($n = 20$) and another group of healthy older adults ($n = 14$) over two visits separated by a minimum of three months (average of 9 months). For the stroke patients, one visit occurred in their subacute window (10 days to 6 months after stroke onset), the other took place in their chronic window (>6 months after stroke). Using a mid-order group ICA method on 10-minutes eyes-closed resting-state fMRI data, we assessed the frequency distributions of a component's representative time-courses for differences in regards to slow-5 spectral power. First, our stroke patients, in their subacute stage, exhibited lower amplitude slow-5 oscillations in comparison to their healthy counterparts. Second, over time in their chronic stage, those same patients showed a recovery of those oscillations, reaching near equivalence to the healthy older adult group. Our results indicate the possibility of an eventual recovery of those initially disrupted network oscillations to a near-normal level, providing potentially a biomarker for stroke recovery of the cortical system. This finding opens new avenues in infra-slow oscillation research and could serve as a useful biomarker in future treatments aimed at recovery.

1. Introduction

Resting-state fMRI (rs-fMRI) is an imaging technique that is widely implemented in the study of clinical population. This technique allows for the investigation of cortical functional networks without the need of goal-directed behavior. This approach minimizes the influence of known confounding factors associated with goal-oriented task-fMRI design (e.g. attention, motivation, and ability to perform the task as instructed), which can be particularly challenging in clinical populations such as stroke, with patients exhibiting various deficits (e.g. language, attention, and motor). For the purpose of this study, we defined the "resting" condition as a state where neither task participation nor goal-directed behavior is required.

A current approach to rs-fMRI analysis is to study functional connectivity, a measure assessing the correlation, or synchronization, of oscillations among distal regions (Friston et al., 1993). Biswal and colleagues (Biswal et al., 1995) were the first to demonstrate that functionally similar regions presented synchronous fluctuations even in the absence of a task. This approach allows for functionally connected brain regions to be identified and investigated (Biswal et al., 2010; Zuo et al., 2010; Beckmann et al., 2005; Fox & Raichle, 2007; Patriat et al., 2013). In subjects experiencing functional and/or cognitive decline, such as in normal aging, or in clinical populations with neurological disorders, such as patients with Alzheimer's disease (Greicius et al., 2004; Sorg et al., 2007), autism spectrum disorders (Cherkassky et al., 2006; Kennedy & Courchesne, 2008), or schizophrenia (Bluhm et al., 2007; Zhou et al., 2007), synchrony in the intrinsic oscillations between regions have been shown to be disrupted. Detailed reviews on network dysfunction in mental disorder are available in the literature (Broyd et al., 2009; Greicius, 2008). One consistent finding of network impairments is

* Corresponding author at: Wisconsin Institute of Medical Research (WIMR), 1310-L, 1111 Highland Avenue, Madison, WI 53705, USA.
E-mail address: cla@wisc.edu (C. La).

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the disruption of the "default-mode" network. Andrews-Hanna and colleagues (Andrews-Hanna et al., 2007) have shown that connectivity between the anterior and posterior nodes within the DMN system were most severely disrupted by age. Moreover, within-network co-activation (Sorg et al., 2007; Damoiseaux et al., 2008) and functional connectivity density (Tomasi & Volkow, 2012) were also found to be reduced. However, very few studies have investigated the resting-state intrinsic oscillations in stroke outside of the system directly impaired from the injury. Early evidence suggests the occurrence of a comparable reduction of functional connectivity within the DMN following a stroke when stroke lesion did not pertain to regions of the DMN (Tsai et al., 2013; Tuladhar et al., 2013; Park et al., 2014; Wang et al., 2014). The reduction of functional connectivity within the DMN is in addition to the disruption of networks directly affected by the stroke lesion itself (Ward et al., 2003; Saur et al., 2006; Grefkes et al., 2008; Wang et al., 2010; Park et al., 2011; Carter et al., 2012), part of a diaschisis effect (vonMonakow, 1914). However, because of the acute nature of the stroke injury, mechanisms under which the disruption of the DMN system happens may differ.

Synchronicity of the oscillations from distal regions (functional connectivity) is not the only extractable measure from rs-fMRI. Regional homogeneity (ReHo) (Zang et al., 2004) provides a measure of local synchronicity of neighboring voxel fluctuations representing a local coherence of neural firing. Alternatively, voxel-wise amplitude information of the intrinsic low-frequency oscillations (LFOs) can also be obtained by the sum of the amplitude spectra within a specific low-frequency band (i.e. amplitude of low-frequency fluctuation, ALFF) (Yang et al., 2007) and the proportion of low-frequency amplitude spectra in comparison to the spectra over the whole acquired frequency range (i.e. fractional ALFF or fALFF) (Zou et al., 2008). In an ischemic stroke population, Alzheimer's disease population and in subjects with mild cognitive impairment (MCI), these measures have similarly shown decreases within the regions of the DMN (Tsai et al., 2013; Zhang et al., 2012; Liu et al., 2014). Investigations of both regional homogeneity and ALFF address possible mechanisms of synchrony disruption. ReHo could be used to investigate whether the long distance dys-synchrony could be a consequence of localized dys-synchrony within a region, where fluctuations between neighboring voxels no longer coincide (Zang et al., 2004; He et al., 2007). In contrast, a reduction in the long distance correlation between regions of the same network (functional connectivity) due to a decrease in local intrinsic fluctuation amplitude which reduces the signaling of the communicated information in comparison to system noise could be addressed by measures of ALFF and fALFF (Di et al., 2013a). In a more global perspective, various studies have also demonstrated reduced cortical spectral power at the low frequencies in patients with schizophrenia and bipolar disorders within network components (Garrity et al., 2007; Calhoun et al., 2011), showing that amplitude hypothesis is plausible even at the level of the network. Previous work from our group (La et al., 2014; La et al., 2015a) presented comparable findings in an ischemic stroke population following the ischemic injury. The investigation of spectral power in an ischemic stroke population over time allows us to better characterize the longitudinal course. In contrast to schizophrenia or bipolar disorders, which are chronic and more persistent, patients surviving the acute stroke injury often show some level of spontaneous recovery that can be examined in a longitudinal study.

In the investigations of functional intrinsic networks of the DMN and other resting-state networks defined by their synchronous oscillations, there have been few examinations making use of the LFO's amplitude information. Investigations of those amplitude information have been implemented by subdividing the spectra of these spontaneous oscillations into distinct infra-slow frequency ranges (i.e. slow-5: 0.01–0.027 Hz, slow-4: 0.027–0.073 Hz, slow-3: 0.073–0.198 Hz, slow-2: 0.198–0.25 Hz) (Zuo et al., 2010; Buzsáki & Draguhn, 2004; Penttonen & Buzsáki, 2003). Zuo et al (Zuo et al., 2010) found significant slow-4 and slow-5 oscillations to be primarily restricted to gray matter, while slow-2 and slow-3 oscillations were primarily restricted to white matter. Furthermore, they demonstrated that many areas exhibiting maximal low-frequency oscillation amplitudes were regions of the DMN with slow-5 more dominant than slow-4 in these areas in normal healthy young subjects. For this reason, our investigation focuses primarily on the oscillations within the slow-5 range. Furthermore, previous studies from our group demonstrated that a decrease in slow-5 amplitudes contributed to a reduction in slow-5 dominance and the interruption of the balance between slow-5 and slow-4 oscillation in the subacute phase of stroke (La et al., 2014; La et al., 2015a), consistent with the literature describing an extensive change in activity in the slow-5 band after stroke (Zhu et al., 2015). Though the DMN is a common candidate for exploring connectivity changes, the effect of a stroke may extend beyond the boundaries of the DMN. This reduction in slow-5 oscillation amplitude in the subacute stroke group was restricted to subnetworks of the DMN as was observed in the healthy older group, but this reduction also occurred in 'task-positive' networks (La et al., 2015b), suggesting a more generalized deficit of the cortical system following a stroke. With regards to resting-state brain oscillations, we suggest that slow-5 oscillations may play a pivotal role in general network health, but also in network disruption following an acute injury such as a stroke.

In this study, we provided a continuation of this assessment of the slow-5 spectral power, with an investigation of a possible recovery of those oscillations in a longitudinal observational study following a group of ischemic stroke patients from a subacute time-point to a chronic time-point.

2. Methods

2.1. Participants

Twenty stroke patients with mild deficits (mean NIH-Stroke Scale (NIH-SS) score of 1.7) with various stroke lesions were recruited and received MR scans at two different time-points. The lesions of the twenty stroke patients were mostly non-overlapping lesions, with no lesion pertaining to areas of the DMN. A lesion density map, derived from semi-automated segmentation from available T1 BRAVO, Cube T2 FLAIR and Diffusion Weighted Image (DWI) using Jim 7 (Xinapse, http://www.xinapse.com/), is provided in Fig. 1. Fourteen older healthy adults (OHAs) (ages between 50 and 75 years old) were also recruited as controls. Summary participant demographics and visits characteristics are provided in Table 1. More information regarding clinical, demographic, and session information for the 20 enrolled ischemic stroke patients can be found in Supplement material A (Suppl. mat. A). Participants recruited in the study were free of neurological or psychiatric disorders. Participants provided full written informed consent toward participation in compliance with the University of Wisconsin-Madison Health Sciences Institutional Review Board (IRB). Other exclusion criteria included contra-indications to MRI, claustrophobia or pregnancy, and intake of certain types of medications (e.g. antipsychotics, antidepressants, sedative hypnotics, etc.). Participants presented no sign of compromised capacity or ability to consent, as established by neurological examination.

2.2. MRI acquisition

Magnetic resonance images (MRI) were collected at two different time points. For the patients, the first visit (S1) occurred on an average of 3.2 months after stroke onset (between 10 days and 6 months, subacute phase of the stroke) and a second visit (S2) occurred on an average of 8.7 months after the initial visit (chronic phase of the stroke). For our control group of healthy old subjects, the two visits (N1 and N2) were separated on an average of 9.7 months [Table 1]. Neuroimaging data were collected at the University of Wisconsin-Madison, using a 3.0-Tesla GE Discovery MR750 scanner (GE Healthcare, Waukesha, WI)