Magnetic Resonance Imaging 32 (2014) 359–365

Contents lists available at ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.mrijournal.com

A study on small-world brain functional networks altered by postherpetic neuralgia☆

Yue Zhang [a,1], Jing Liu [b,1], Longchuan Li [c,d], Minyi Du [e], Wenxue Fang [e], Dongxin Wang [e], Xuexiang Jiang [b], Xiaoping Hu [d], Jue Zhang [a,*,2], Xiaoying Wang [b,**,2], Jing Fang [a]

[a] College of Engineering, Peking University, Beijing, China
[b] Department of Radiology, Peking University First Hospital, Beijing, China
[c] Marcus Autism Center, Emory University School of Medicine, Atlanta, GA, USA
[d] Biomedical Imaging Technology Center, Department of Biomedical Engineering, Georgia Institute of Technology/Emory University, Atlanta, GA, USA
[e] Department of Anesthesiology, Peking University Fist Hospital, Beijing, China

ARTICLE INFO

Article history:
Received 15 December 2012
Revised 16 December 2013
Accepted 23 December 2013

Keywords:
Small-world
Brain functional networks
Resting-state fMRI
Chronic pain
Postherpetic neuralgia

ABSTRACT

Understanding the effect of postherpetic neuralgia (PHN) pain on brain activity is important for clinical strategies. This is the first study, to our knowledge, to relate PHN pain to small-world properties of brain functional networks. Functional magnetic resonance imaging (fMRI) was used to construct functional brain networks of the subjects during the resting state. Sixteen patients with PHN pain and 16 (8 males, 8 females for both groups) age-matched controls were studied. The PHN patients exhibited decreased local efficiency along with non-significant changes of global efficiency in comparison with the healthy controls. Moreover, regional nodal efficiency was found to be significantly affected by PHN pain in the areas related to sense (postcentral gyrus, inferior parietal gyrus and thalamus), memory/affective processes (parahippocampal gyrus) and emotional activities (putamen). Significant correlation ($p < 0.05$) was also found between the nodal efficiency of putamen and pain intensity in PHN patients. Our results suggest that PHN modulates the local efficiency, and the small-world properties of brain networks may have potentials to objectively evaluate pain information in clinic.

1. Introduction

Living with chronic pain significantly impacts one's quality of life negatively. Peripheral neuropathic pain (PNP), originated from injury or dysfunction of peripheral nerves, has been revealed to cause a change of connections among central neurons [1–3]. As a common type of PNP, postherpetic neuralgia (PHN) is caused by the reactivation of the varicella zoster virus, which travels along nerve cells and produces pain in the infected region [4]. In fact, PHN is a prototypical human chronic neuropathic condition exhibiting multiple signs of peripheral and central neuropathy [5]. Several studies have explored the effects of PHN pain on brain activity using functional magnetic resonance imaging (fMRI) [6–8]. Their results showed that brain activations with spontaneous PHN pain involved affective, sensory-discriminative (thalamus, primary and secondary somatosensory, insula and anterior cingulated cortices), emotion, hedonics, reward, and punishment areas (ventral striatum, amygdala, orbital frontal cortex and ventral tegmental area). Most of these activations (except insula) decreased after treatment by Lidoderm [6]. Also the functional connectivity between several regions and putamen was altered in PHN patients [7]. Moreover, compared with healthy subjects, increased cerebral blood flow (CBF) in striatum, thalamus, primary somatosensory cortex (S1), insula, amygdala, and inferior parietal lobule, and decreased CBF in the frontal cortex were found in PHN patients. The functional connectivities involving the left caudate, left insula, left S1, and right thalamus based on CBF measurements were altered by PHN [8]. However, the fMRI study on PHN pain is still limited.

To date, there have not been any studies examining PHN-related alterations of functional connectivities using the graph theoretical approach. The graph theoretical approach, a powerful data reduction tool, can characterize the entire functional connectivity pattern among all brain regions and capture the topological

☆ Conflicts of interest: There are no conflicts of interest for any author.

* Correspondence to: Jue Zhang, College of Engineering, Peking University, 5 Yiheyuan Rd, Beijing 100871, P.R. China. Tel.: +86 106 275 5036; fax: +86 106 275 3562.

** Correspondence to: Xiaoying Wang, Department of Radiology, Peking University First Hospital, No. 8, Xishiku Street, Xicheng District, Beijing 100034, P.R. China. Tel.: +86 108 357 2705.

E-mail addresses: zhangjue@pku.edu.cn (J. Zhang), cjr.wangxiaoying@vip.163.com (X. Wang).

[1] These co-first authors contributed equally to this work.
[2] These corresponding authors contributed equally to this work.

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http://dx.doi.org/10.1016/j.mri.2013.12.016

measures of the functional brain networks [9]. It can measure the core features of a complex brain network that spans the entire regions in contrast to the seed-based functional connectivity analysis [7,8], which merely takes into account of the functional connectivity with a few predefined regions of interest (ROI). Previous investigations [9] have shown that the graphs with dense local connections and few long connections can be characterized as small-world networks by graph theoretical approaches. More recent studies have revealed that the small-world topologies exist in large-scale functional brain networks of humans. Also there is increasing evidence demonstrating that the small-world properties of brain networks are affected by normal aging, external stimulations or brain diseases [10–14]. Thus as an attractive technique to characterize complex networks by providing quantitative parameters, the small-world analysis of brain functional networks is used to investigate the effects of PHN pain on the properties of small-world in this study. More specifically, the study focused mainly on functional networks based on spontaneous low-frequency fluctuation (LFF) using fMRI data acquired during the resting state [10,13]. Given that functional connectivity between different brain regions was altered by PHN pain [7,8], we hypothesized that the properties of small-world would be altered by PHN pain, and such alteration could be detected and quantified using graph theoretic approaches.

2. Materials and methods

2.1. Subjects

This study was approved by the local ethics committee. All subjects provided informed written consent, in line with the Declaration of Helsinki. Thirty-five right-handed subjects (16 patients suffering from PNH and 19 control healthy subjects) participated in the study. PHN pain was localized on the left side of body region for all the patients (Table 1). All subjects were free to withdraw from the experiment at any time. No subjects had a history of psychiatric or neurological disorder. All subjects were requested to report their emotional status verbally before the experiment, including anger, anxiety and depression. Only the subjects who had no feelings of anger, anxiety or depression were included in this study. Data from 16 patients and 16 controls were analyzed (8 males, 8 females in both groups, 3 controls with maximum displacement in any direction larger than 1.5 mm or head rotation larger than 1.5° were excluded due to too excessive head motion). Eight male patients and eight male healthy controls were the same as in the previous study of our group [8]; another eight female patients and eight female healthy controls were recruited for this study. Compared to the previous investigation [8], this study focused on analyzing the blood oxygenation level dependent (BOLD) data instead of CBF data [8].

Table 1
Clinical characteristics of patients with postherpetic neuralgia.

Patients	Age(y)/gender	Location of lesion	Pain duration	Visual analog scale
1	70/M	Left T3–T5	6	9
2	71/M	Left T6–T10	3	7
3	71/M	Left L2–L3	8	9
4	59/M	Left T2–T5	2	7
5	73/M	Left T3–T5	24	8
6	73/M	Left T7–T11	11	7
7	62/M	Left T6–T8	6	8
8	66/M	Left T2–T9	14	8
9	52/F	Left T4–T6	4	8
10	56/F	Left T3–T6	6	8
11	76/F	Left T9–T12	8	9
12	76/F	Left L2–L3	22	7
13	80/F	Left T5–T8	7	6
14	75/F	Left T2–T5	15	7.5
15	59/F	Left T9–T12	11	6.5
16	71/F	Left T5–T8	3	6.5

M = male; F = female; T = level of thoracic vertebrae; L: level of lumbar vertebrae; S: level of sacral vertebrae.

Clinical symptoms of patients were assessed using a mechanical visual analog scale (VAS), with a range from 0 (no pain) to 10 (the highest tolerable pain) for rating the pain intensity levels [6–8]. The pain intensities of the patients ranged from 6 to 9 on VAS (average score: about 7.6 points). The average age of the PHN patients was 68.1 (range 52–80) years and that of the healthy controls was 68.6 (range 52–79) years, there was no difference in age between the two groups (two-tailed t-test, $p = 0.78$). The durations of persistent pain were longer than 2 months for all patients (2–24 months with an average of 9.4 months). All subjects underwent neurological and psychological examinations as well as standard MR brain scanning. During the time of scanning, greatest care was taken to avoid evoking pain.

2.2. Experimental design

During the MR scanning, all subjects were instructed to keep their eyes closed and mind clear, and to remain awake. The scan time was 8.4 minutes for all subjects. All 16 patients were scanned before treatment.

2.3. Image acquisition

All MRI experiments were performed on a General Electric 3 T Signa system (GE Medical Systems, Waukesha, WI) with a standard head coil. Functional data were acquired using a double readout spiral-out sequence with simultaneous gradient-echo BOLD and CBF acquisitions, at short and long TEs, respectively [15]. This sequence interleaved pulsed ASL (Arterial Spin Labeling) acquisitions with slab-selective and non-selective inversion using PICORE (proximal inversion with a control for off-resonance effects) tagging [16] and QUIPSS II (quantitative imaging of perfusion using a single subtraction), which applied saturation pulses to the tagging region to eliminate variable transit time effects [15]. Both readouts utilized slice thickness/gap (THK) of 8.0/2.0 mm with 3.6×3.6 mm^2 in-plane resolution, a 230-mm^2 field of view (FOV) with a 64×64 acquisition matrix, a repetition time (TR) of 3000 ms and a 90° flip angle. Following inversion, the saturation pulse lasted 700 ms, and there was an 800-ms delay between saturation and excitation. CBF/BOLD readouts were acquired at TEs of 3.1/30 ms, respectively, covering 10–12 axial slices of the whole cerebrum. The data set consisted of 168 functional contiguous axial images.

For anatomical imaging, a 3D gradient-echo T_1-weighted sequence (TR/TE: 25/4 ms; FOV: 230 mm^2; THK of 2.0 mm with no gap, resolution: 1×1 mm^2) was run.

2.4. Data analyses

SPM5 (Wellcome Department, University College of London, UK) and MATLAB were used for data processing. Only the BOLD data were analyzed in this study. After discarding the first eight images to allow for the longitudinal magnetization to reach steady state and subject acclimation, the remaining 160 functional images were first corrected for the acquisition time delay among different slices and motion, then coregistered with the corresponding anatomical image to facilitate transformation to Montreal Neurological Institute (MNI) space and resampling of functional images