Postherpetic neuralgia alters small-world brain functional networks

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Introduction: Living with chronic pain impacts one's life quality negatively. 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 [1]. In fact, PHN is a prototypical human chronic neuropathic condition for exhibiting multiple signs of peripheral and central neuropathy [2]. Several studies have explored the effects of PHN pain on brain activity using functional magnetic resonance imaging [3,4,5]. Their results showed that brain activations with spontaneous PHN pain included affective, sensory-discriminative, emotion, hedonics, reward, and punishment areas [3]. Also the connectivity between several regions and putamen was altered by PHN patients [4]. Up to now, however, there is no investigation concerning topological organization of functional networks in the whole brain related to PHN pain. The small-world networks is an attractive model to describe complex networks by providing quantitative parameters [6], given that functional connectivity between different brain regions was modulated by PHN [4,5], we hypothesized that the properties of small-world would be modulated by PHN pain.

Materials and Methods: Thirty-two right-handed subjects (16 patients suffering from PNH and 16 control healthy subjects) participated in the study (8 males, 8 females for both groups). The average age of the PHN group was 68.1 (range 52-80) and that of the healthy controls was 68.6 (range 52-79) years old (two tailed t-test, $p = 0.78$). PHN pain was localized on the left side of body region for the 16 patients. All of these patients were assessed using a mechanical Visual Analog Scale (VAS), with a range from 0 (no pain) to 10 (the highest tolerable pain) to rate the pain intensity levels [3,4,5]. The sixteen patients were with pain intensities ranged from 6 to 9 on VAS (average score: about 7.6 points). The durations of persistent pain were longer than two months for all patients. During the time of scanning, the greatest care was taken to avoid the situation that might trigger evoked pain. During the MR scanning, all subjects were instructed to keep their eyes closed, minds clear, and awakening remained. The scan time was 8.4 minutes for all subjects.

All MRI experiments were performed using a General Electric 3T 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 blood oxygenation level dependent (BOLD) and cerebral blood flow (CBF) acquisitions, at short and long TEs, respectively [7,8]. Both readouts utilized slice thickness / gap (THK) of 8.0 / 2.0 mm with 3.6 x 3.6 mm^2 in-plane resolution, using a 230 mm^2 field of view (FOV) with a 64 x 64 acquisition matrix, a repetition time (TR) of 3000 ms and a 90° flip angle. CBF/BOLD readouts were acquired at TEs of 3.1/30 ms, respectively, covering 12 axial slices of the whole cerebrum. The set consisted of 168 functional contiguous axial images.

Only the BOLD data were analyzed in this study. After discarding the first 8 images, the remained 160 functional images were first corrected for the acquisition time delay among different slices and motion corrected, then coregistered with the corresponding anatomical image to facilitate transformation to Montreal Neurological Institute (MNI) space and resampling of functional images to isotropic 2*2*2 mm^3 voxels. Several sources of spurious variances (six motion parameters, the signal averaged from the region in cerebrospinal fluid, and the signal averaged from the region in the white matter) were further removed by multiple linear regression analysis. The data were detrended and temporally filtered by band-pass (0.01~0.08 Hz).The data sets preprocessed above were divided into 90 regions of interest (ROIs) (45 for each hemisphere) according to the AAL-atlas [9]. The mean time series of each region were then obtained by averaging the time series of all voxels in that area. The Pearson correlation coefficients between every possible pair of the regional residual time series were calculated, and a 90*90 correlation matrices were obtained for each subject. Finally, each absolute correlation matrix was thresholded into an undirected binary graph (network) for further analysis by graph theoretical approaches with the nodes describing brain regions and the edges describing the links between the regions.

In the study, the network cost (from 0 to 1, with an incremental interval of 0.01) was used for threshold measurement [10,11]. Several small-world parameters of the networks were obtained, including global efficiency (E_{glob}), local efficiency (E_{loc}), integrated regional nodal efficiency (i.e. the area under the curve with the cost ranged from 0 to 1 for regional nodal efficiency) [12,13]. To estimate the small-world properties, 100 degree-matched random networks were generated.

Results: At a wide range of cost threshold, the brain networks of the PHN group demonstrated lower local efficiencies compared with the healthy controls (0.26<= cost <= 0.36, 0.39, 0.50,0.52,0.53, 0.55<=cost<=0.76, 0.79, 0.83,black asterisks in Fig1, two-sample two-tailed t-test ,$P < 0.05$), whereas there was no significant difference in E_{glob} between the two groups. The PHN case also demonstrated significant decreases of integrated nodal efficiency in the bilateral paraHippocampal gyrus, fusiform gyrus and left thalamus and increases in the right postcentral gyrus, putamen and left inferior parietal gyrus and inferior temporal gyrus in comparison with the healthy controls (two-sample two-tailed t-test,FDR corrected $p<0.05$). Moreover, The correlations between integrated nodal efficiencies and VAS were evaluated, by comparing only the nodes with significant difference between PHN and healthy controls. It can be observed that the integrated nodal efficiencies of right putamen ($r = 0.7136, p = 0.0019$) and left inferior temporal gyrus ($r = 0.6205, p = 0.0103$) were significantly positively correlated with VAS (FDR corrected $p <0.05$, Fig 2). No significant correlation was found between any topological properties and age or the duration of persistent pain for the PHN group.

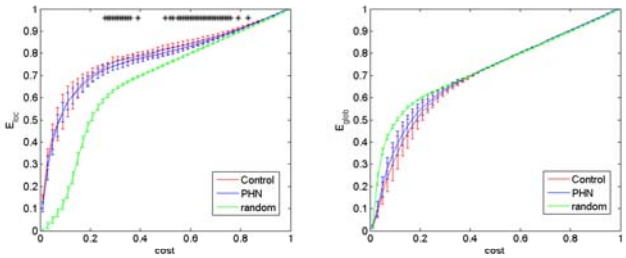

Fig 1. The E_{loc} and E_{glob} for the random, PHN and healthy controls brain networks as a function of the cost.

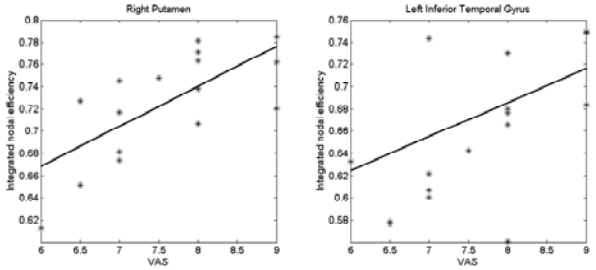

Fig 2. The correlations between integrated nodal efficiency of putamen and inferior temporal gyrus and VAS for the PHN pain.

Discussion and Conclusion: In summary, Our graph theoretic study of brain functional networks in PHN demonstrated decreased local efficiency combined with non-significantly changed global efficiency in PHN. Moreover, the nodal efficiencies in several regions were altered by PHN, including postcentral gyrus, inferior parietal gyrus, thalamus, paraHippocampal gyrus and putamen that are related to sensory, memory, affective and emotional processes. We also found significant positive correlations between the nodal efficiency of putamen and pain intensity in PHN. Our results suggested that the local efficiency of the whole-brain networks and nodal efficiencies of several brain regions were altered by PHN, providing further evidences for brain functional dysfunctions associated with PHN.

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