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# The trade-off between wiring cost and network topology in white matter structural networks in health and migraine

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The human brain organization of cortical networks has optimized trade-off architecture for the economical minimization of connection distance and maximizing valuable topological properties; however, whether this network configuration is disrupted in chronic migraine remains unknown. Here, employing the diffusion tensor imaging and graph theory approaches to construct white matter networks in 26 patients with migraine (PM) and 26 gender-matched healthy controls (HC), we investigated relationships between structural connectivity, cortical network architecture and anatomical distance in the two groups separately. Compared with the HC group, the patients showed longer global distance connection in PM, with proportionally less short-distance and more medium-distance; correspondingly, the patients showed abnormal global topology in their structural networks, mainly presented as a higher clustering coefficient. Moreover, the abnormal association between these two network features was also found. Intriguingly, the network measure that combined the nodal anatomical distance and network topology could distinguish PM from HC with high accuracy of 90.4%. We also demonstrated a high reproducibility of our findings across different parcellation schemes. Our results demonstrated that long-term migraine may result in a abnormal optimization of a trade-off between wiring cost and network topology in white matter structural networks and highlights the potential for combining spatial and topological aspects as a network marker, which may provide valuable insights into the understanding of brain network reorganization that could be attributed to the underlying pathophysiology resulting from migraine.



## Introduction

The metabolic costs of building and running the brain are generally expensive (~20%) in proportion to the total energy budget of the body (Laughlin and Sejnowski, 2003; Niven and Laughlin, 2008), and that a sparing principle of cost control may require wiring cost minimization involved in the evolution and development of the nervous system (Bullmore and Sporns, 2012). Generally, the cost of functionally resourcing the brain in a three-dimensional anatomical space increases with wiring volume (Bullmore and Sporns, 2012), which is proportional to the physical distance of inter-regional connections (Alexander-Bloch et al., 2013; Bullmore and Sporns, 2012; Vertes et al., 2012). Several studies supported that the distributions of functional and structural connectivity favored high density short distance connections for the economic model of brain organization (Achard and Bullmore, 2007; Bellec et al., 2006; Honey et al., 2009; Salvador et al., 2005). However, integrative brain function depends on a complex wiring diagram within cortical networks that has the small-world property of highly efficient neuronal architecture (Watts and Strogatz, 1998), network modularity of efficient local information processing within modules (Kotter and Stephan, 2003; Sporns et al., 2000), rapid information exchange between modules (He et al., 2009), and the "rich-club" organization of a high-cost, high-capacity backbone for global brain communication (van den Heuvel et al., 2012; van den Heuvel and Sporns, 2011). These complex topologies are largely attributable to the existence of the functional connection of long-distance short-cuts between spatially remote brain regions (Alexander-Bloch et al., 2013), which could

*Abbreviations:* DTI, diffusion tensor imaging; PM, migraine patients; HC, healthy controls; FSGPR, Fast Spoiled Gradient Recalled sequence; TR, repetition time; TE, echo time; FOV, field of view; FDT, FMRIB's Diffusion Toolbox; FSL, FMRIB software Library; FA, fractional anisotropy; FACT, fiber assignment by continuous tracking algorithm; ROIs, region of interests; AAL, automated anatomical labeling atlas; C, average of the clustering coefficient; L, average of the shortest path lengths; Q, modularity; DCS, distance-related connection strength; PH, parahippocampal gyrus; dlPFC, dorsolateral prefrontal cortex; ROC, receiver operating characteristic.

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support efficient parallel information transfer in the cortical networks and be of great advantage to human adaptive behavior (Achard and Bullmore, 2007). Hence, the organization of cortical networks during evolution or development in human brain maturity calls for both low wiring cost and adaptively expensive connections, suggesting that there exists a competitive balance between the economical minimization of the connection distance and maximizing valuable topological properties (Achard and Bullmore, 2007; Alexander-Bloch et al., 2013; Bullmore and Sporns, 2012; Vertes et al., 2012).

Recently, several studies systematically examined relationships between individual topological properties of the cortical network, anatomical distance between interconnected brain regions, and behavioral performance in cognitive tasks (Bullmore and Sporns, 2012). The connection between the anatomically economic and topologically complex of brain network was suggested to serve as a predictor that was associated with normal individual differences in cortical network organization (Alexander-Bloch et al., 2013). Furthermore, integrative information processing and adaptive behavior performance of cortical network function were also enhanced by this optimized trade-off network configuration (Bassett et al., 2009; Kitzbichler et al., 2011). The trade-off principle of the cortical networks organization was presumably shaped by evolutionary constraints and adapted to changing cognitive demands, which may allow for a more general, integrated understanding of the biological mechanisms for cortical network formation. However, disrupted distributions of the normal brain network organization may occur with underlying diseased mental states. For clinical chronic pain, such as migraine, brain structure and function have plasticity and can adapt to a state of frequent cortical overstimulation associated with pain (Apkarian et al., 2011; Davis and Moayedi, 2012), which may give abnormal optimization guidelines to a somewhat selective impact on cortical network characteristics and maintain or reinforce the cognition/emotion of the pain experience (Apkarian et al., 2011; May, 2009). However, few studies considered the abnormal interplay between anatomical and topological perspectives in chronic pain patients' brain networks.

Migraine, as the most common neurological disease, is characterized by recurrent headache attacks of a debilitating condition and has been an important healthcare and social problem for its great influence on the quality of life (May, 2009). Recently, our group found that migraine disrupted the functional organization of cortical networks, and these brain abnormalities occurring in patients with migraine were not limited to the local abnormal central nervous system but to a disruption in the topological organization of intrinsic whole-brain networks (Liu et al., 2011). Functional network organization in migraine is more small-world, more clustered and has less network modularity (Liu et al., 2011). These findings suggested that long-term and high-frequency headache attacks may cause brain connectivity network reorganization, pointing to the underlying learning mechanisms with ongoing central changes for the pain (Farmer et al., 2012). Individual chronic pain conditions may progressively disrupt the cortical network through reduced/strengthened of anatomical distance of pathways or by connectivity shifts in certain brain regions (Liu et al., 2011; Yu et al., 2011), leading to the degradation of network coherence (Farmer et al., 2012), which motivates the hypothesis that development of brain alteration in migraine is associated with both anatomical and topological organization of the cortical network. However, there has been little discussion on the relationship between anatomical aspects of cortical networks and topological abnormalities in migraine.

Since the brain network connections require pathways of myelinated axons to integrate information between different circuits of the brain, white matter properties are essential for evaluating brain structural connectivity shift with continued nociceptive input in migraine. Here, we used diffusion tensor imaging (DTI) tractography and graph theory analysis to investigate the topological changes in the structural connectome of the white matter network in patients with migraine. The Euclidean distance was used to estimate the spatial connected brain regions. Our study focuses exclusively on the relationships between structural connectivity, reorganized cortical network architecture and anatomical distance in migraine. Specifically, we aimed to identify whether migraine disrupts the anatomical distance distribution of brain connections and the topological organization of the cortical network, and if so, whether the altered spatial property of the connection distance was related to abnormal topological properties. Furthermore, with the combination of these two factors, we explored whether the distance-related connection strength could distinguish individuals with migraine from healthy controls.

## Methods and materials

This study was approved by the Medical Ethics Committee of the West China Hospital of Sichuan University and was conducted in accordance with the Declaration of Helsinki. All participants gave their written informed consent after the experimental procedure was fully explained.

### *Participants*

All of the patients fulfilled the ICHD-II criteria. Inclusion criteria for the migraine patients (PM) group were according to ICHD-II migraine without aura criteria (2004): 1) It is a unilateral and/or pulsating headache; 2) headache attacks last 4–72 h (untreated or unsuccessfully treated); 3) There is nausea and/or vomiting, photophobia and phonophobia during headache and 4) headache is disabling. Exclusion criteria were: 1) macroscopic brain T2-visible lesions on MRI scans; 2) existence of a neurological disease; 3) pregnancy or menstrual period; 4) use of prescription medications within the last month; 5) alcohol, nicotine or drug abuse; and 6) claustrophobia. All subjects gave written, informed consent after the experimental procedures had been fully explained.

Twenty-six right-handed PM without aura (female, 34.6.1 ± 4.5 years (mean age ± SD), 12.9 ± 3.4 years (mean migraine duration ± SD)) who did not have any clinical affective disorder were recruited (Table 1). During the past 4 weeks, patients carefully rated the average pain intensity of the attacks (4.1 ± 0.8, 0–10 scale, 10 being the most intense pain imaginable), migraine attack frequency (5.2 ± 2.9 days/month) and migraine attack duration (15.0 ± 7.5 h). Twenty-six age-, education- and gender-matched, healthy, right-handed healthy controls (HC, age 33.3 ± 3.04 years) were recruited from the local community. The controls neither had any headache days per year nor had family members who suffered regularly from a migraine or other headaches.

### *Data acquisition*

This experiment was carried out in a 3.0 Tesla Signa GE scanner with an 8-channel phase array head coil at the Huaxi MR Research Center. For each subject, a high-resolution structural image was acquired by using a three-dimensional MRI sequence with a voxel size of 1 $mm^3$ using an axial Fast Spoiled Gradient Recalled sequence (FSGPR) with the following parameters: repetition time (TR) = 1900 ms; echo time (TE) = 2.26 ms; data matrix = 256 × 256; field of view (FOV) = 256 mm × 256 mm.

**Table 1**
Demographic characteristics of subjects.

| Information | Healthy controls (n = 26) | Patients with migraine (n = 26) | *p*-value |
|---|---|---|---|
| Age (years) | 33.3 ± 3.04 | 34.6 ± 4.5 | >0.05 |
| Education (years) | 11.9 ± 6.3 | 12.9 ± 3.4 | >0.05 |
| Disease duration (years) | N/A | 11.8 ± 5.7 | – |
| Migraine attacks during past four weeks | | | |
| Attack duration (hours) | N/A | 15.0 ± 7.5 | – |
| Attack frequency (times) | N/A | 5.2 ± 2.9 | – |
| Average pain intensity (0–10) | N/A | 4.1 ± 0.8 | – |