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Measuring individual morphological relationship of cortical regions



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Xiang-zhen Kong^{a,c}, Xu Wang^{a,c}, Lijie Huang^{a,c}, Yi Pu^d, Zetian Yang^{a,c}, Xiaobin Dang^{a,c}, Zonglei Zhen^{a,c,*}, Jia Liu^{b,c}

^a State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing 100875, China

^b School of Psychology, Beijing Normal University, Beijing 100875, China

^c Center for Collaboration and Innovation in Brain and Learning Sciences, Beijing Normal University, Beijing 100875, China

^d Department of Cognitive Science, Macquarie University, NSW 2109, Australia

HIGHLIGHTS

• A new metric was proposed to quantify individual morphological relations of regions.

- The new metric is indexed as the similarity of different morphological distributions.
- We estimate the morphological distribution from individual MRI image.
- The metric seemed to have potential application to individual differences studies.

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ABSTRACT

Background: Although local features of brain morphology have been widely investigated in neuroscience, the inter-regional relations in brain morphology have rarely been investigated, especially not for individual participants.

New method: In this paper, we proposed a novel framework for investigating this relation based on an individual's magnetic resonance imaging (MRI) data. The key idea was to estimate the probability density function (PDF) of local morphological features within a brain region to provide a global description of this region. Then, the inter-regional relations were quantified by calculating the similarity of the PDFs for pairs of regions based on the Kullback–Leibler (KL) divergence.

Results: For illustration, we applied this approach to a pre-post intervention study to investigate the longitudinal changes in morphological relations after long-term sleep deprivation. The results suggest the potential application of this new method for studies on individual differences in brain structure.

Comparison with existing methods: The current method can be employed to estimate individual morphological relations between regions, which have been largely ignored by previous studies.

Conclusions: Our morphological relation metric, as a novel quantitative biomarker, can be used to investigate normal individual variability and even within-individual alterations/abnormalities in brain structure.

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1. Introduction

Most studies on brain morphology have focused on local morphological features with either voxel/vertex-based or region-based approaches (e.g., Ashburner and Friston, 2000). These local features

* Corresponding author at: Room 405, Yingdong Building, 19 Xinjiekouwai St, Haidian District, Beijing 100875, China. Tel.: +86 10 58806154; fax: +86 10 58806154.

E-mail address: zhenzonglei@bnu.edu.cn (Z. Zhen).

http://dx.doi.org/10.1016/j.jneumeth.2014.09.003 0165-0270/© 2014 Elsevier B.V. All rights reserved. have been considered to reflect clinical conditions (Li et al., 2012), development (Franke et al., 2012), plasticity (Wei et al., 2013), and individual differences in various tasks (Kanai and Rees, 2011). However, inter-regional relations of local brain morphology (referred to as the morphological relations) in individuals have seldom been explored, although they could provide exclusive useful information about the inter-regional associations that are not evident from local morphological measures.

Thus far, several approaches have been proposed for quantifying morphological relations, all of which are based on the co-variance of regional gray matter morphology with magnetic resonance



Fig. 1. Flowchart for the estimation of inter-regional morphological relation using gray matter measures from individual MRI data. (a1) MR images were segmented to create gray matter (GM) images. (a2) GM images for each individual were normalized to the standard template in MNI152 space, and then modulated and smoothed for further analysis. (b) Brain parcellation and estimation of regional probability density functions (PDFs). (c) Similarity between PDFs from different brain regions was quantified with KLS.

imaging (MRI) scans. For instance, the relations are characterized by considering the co-variance between averaged regional morphological measures (i.e., cortical thickness or volume) across participants (Mechelli et al., 2005). However, this method can only be used when we have relatively large number of participants, which limits its application to investigating normal individual variability and, particularly, to identifying within-individual brain structural alterations or abnormalities related to morphology. More recently, Tijms et al. (2012) have proposed an insightful method that allows the construction of morphological relations for a single participant. In such an approach, morphological relation is defined as the correlation between two sets of 27 voxels separately from two rigid cubes. However, this approach does not take into account the complexity of the cerebral cortex structure, which often exhibits remarkable variability across participants in terms of the shape and size of a particular region. More importantly, the rigid extraction of those small cubes might not optimally correspond to functionally/anatomically homogeneous regions of the brain (Tijms et al., 2012).

In this paper, we introduce a novel framework to associate the morphological information of two brain regions without the limitations mentioned above. By estimating the similarity of their morphological distributions, our approach is able to quantify the inter-regional relations within each participant. Technically, morphological distributions can be accurately estimated from the intensity values of voxels within a specified brain region from MRI data. Since the estimated distributions provide a full description of this region, the similarity in the morphological distributions can provide a plausible way of quantifying its inter-regional relations. In this work, the relation was captured via a similarity measurement based on Kullback-Leibler (KL) divergence. This framework can be applied with various local characteristics of the gray matter (e.g., cortical thickness, area, and volume). More importantly, the novel approach has a competitive advantage in that it allows for the quantification of morphological relations for a single participant. Due to this advantage, the method opens up a new avenue for investigating intra- and inter-individual differences in the brain's structural organization with individual MRI data.

In the following sections, we first describe our new method in detail, followed by an illustration of this approach with a pre-post study on the effects of sleep deprivation (SD) on brain structure. Our experiment specifically focused on the morphological relations between the thalamus and multiple ipsilateral association cortical regions. We chose the thalamus because it acts as the gate of nearly all incoming information to the cortex and plays an important role during natural sleep (Blethyn et al., 2006). In addition, a previous study (Liu et al., 2014) has shown that SD has a significant effect on the thalamus.

2. Methods

As shown in Fig. 1, our approach can be summarized in the following three steps:

- (a) Computing local morphological features for each voxel in the brain.
- (b) Brain parcellation and estimation of the morphological distributions of each region.
- (c) Quantifying the relation between the morphological distributions of each pair of compared regions.

As detailed below, Step (a) is done with an automatic neuroimaging technique called voxel-based morphometry (VBM) (Ashburner and Friston, 2000). Steps (b) and (c) are the main contributions of the present paper, and will be described in detail.

2.1. Step a: morphometry computation

The MRI data was preprocessed using VBM (Ashburner and Friston, 2000) implemented in Statistical Parametric Mapping version 8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm/). VBM is an automatic whole-brain neuroimaging analysis technique that allows the quantification of local morphological features from individual MRI data. First, the MRI data for each participant was checked manually by two experienced experts to ensure that it contained no scanning artifacts. Second, gray matter (GM) images were obtained by segmenting individual MRI data using the unified segmentation tools in SPM8. Then, the GM images of each participant were normalized to the study-specific template in MNI152 space using the Diffeomorphic Anatomical Registration Through Exponential Lie Algebra (DARTEL) approach (Ashburner, 2007). Next, to preserve the tissue volume after warping, voxel values in individual GM images were modulated by multiplying the Jacobian determinants derived from the normalization. Finally, all modulated GM images were smoothed individually with an 8-mm full-width at half-maximum (FWHM) Gaussian kernel. Then the smoothed and modulated GM images, consisting of morphological intensity information of each voxel that was comparable across all participants, were used for further analyses.

2.2. Step b: brain parcellation and estimation of regional probability density functions (PDFs)

Regions of interest (ROIs) can be obtained from brain parcellation based on prior atlases. Here, we used the Automated Anatomical Labeling atlas (AAL) (Tzourio-Mazoyer et al., 2002). Additionally, Step (a) gave a scalar quantifying the morphological intensity of gray matter at each voxel within each ROI. For each ROI, the PDF of these values was then estimated using kernel density estimation (KDE) (Bowman and Azzalini, 1997). In this paper, the *gaussian_kde* function implemented in the SciPy package (http://www.scipy.org/) was used. The kernel width was not set manually but adaptively estimated from the data using Scott's rule (Scott, 1992). Here, it is plausible to quantify the morphological relations between brain structures with the PDFs of their regional morphology.

2.3. Step c: similarity between morphological distributions from different brain regions

In this step, we defined the morphological relation as the statistical similarity between the two PDFs of two brain regions, which was inspired by a similar concept recently proposed for combining surface and its connecting fiber geometry (Savadjiev et al., 2013). Technically, the KL divergence is a natural method for estimating the dissimilarity/similarity between two probability distributions. In our approach, a similarity measurement based on the symmetric KL divergence was employed to quantify the similarity of two PDFs of local brain regions.

The description of the KL divergence measurement is as follows:

$$\operatorname{KL}(p,q) = \int_X \left(p(x) \log\left(\frac{p(x)}{q(x)}\right) + q(x) \log\left(\frac{q(x)}{p(x)}\right) \right) \tag{1}$$

where *p* and *q* are the two PDFs. The KL divergence can be converted to a similarity measurement using the following equation:

$$KLS(p,q) = e^{-KL(p,q)}$$
⁽²⁾

The KLS ranges from 0 to 1, where 1 is for two identical distributions. This similarity measurement has been used in previous studies to quantify the similarity of documents from word frequency distributions (Hazen, 2010). Given two morphological PDFs of a pair of brain regions, we used the similarity index KLS to quantify the morphological connection between them.

3. Subjects and data acquisition

Here we used a pre-post intervention study on the effects of SD on brain structure to illustrate our method. Eight healthy college students (mean age = 24.83, standard deviation = 2.88; right-handed; all males) were recruited for the SD study. The experimental protocol was approved by the Institutional Review Board (IRB) of Beijing Normal University, and written informed consent was obtained from all participants before the investigation. The SD experiment $(72\pm0.8h)$ was conducted in the local SD laboratory. A high-resolution T1-weighted MRI data was acquired for each participant on a 3.0-T scanner (Siemens Medical) using a high-resolution 3D magnetization-prepared rapid acquisition of gradient echoes (MPRAGE) sequence with the following parameters: resolution, $1.0 \text{ mm} \times 1.0 \text{ mm} \times 1.33 \text{ mm}$; TR/TE/TI, 2530/3.39/1100 ms; flip angle, 7°; FOV 256×256 . All the participants finished two sessions of MRI scanning before and after the total SD. As a control, we performed MRI for eight age- and sexmatched participants (mean age = 24.75, standard deviation = 2.05; all males) with a pre-post procedure, but without SD. These data was obtained on the same scanner with the same sequence as in the SD group.

4. Data analysis

Previous studies have demonstrated the effects of SD on psychological measures and neural systems alike. For example, sleep loss has been shown to reduce performance on a broad range of tasks (Alhola and Polo-Kantola, 2007). A recent study has showed that long-term SD significantly reduces the thalamic gray matter volume (Liu et al., 2014). Given the reciprocal relationship between the thalamus and cortex (Kaas, 1999), we hypothesized that some morphological connections between the thalamus and ipsilateral cortical regions would change after SD. In this study, we focused on thalamic connections with the parietal, temporal, and prefrontal heteromodal association cortices, which play a central role in receiving convergent inputs from multiple cortical regions and are considered to be involved in more complex and integrated cognitive activities (Mesulam, 2000).

Here, we identified bilateral thalamic and association cortical regions of interest (10 for each hemisphere) with the widely used AAL atlas (Tzourio-Mazoyer et al., 2002). For each hemisphere, these cortical regions included the superior frontal gyrus (SFG), middle frontal gyrus (MFG), inferior frontal gyrus pars triangularis (IFGtri), medial superior frontal gyrus (SFGmed), lingual gyrus (LING), inferior parietal lobule (IPL), supramarginal gyrus (SMG), angular gyrus (ANG), precuneus (PCUN), and superior temporal gyrus (STG). The morphological relations were calculated for each scan and each hemisphere in each individual. A paired-samples *t*-test was used to investigate possible changes of the thalamocortical morphological relations in the pre-post procedure for the SD and control groups separately. Data normality was confirmed using the Shapiro–Wilk test (Shapiro and Wilk, 1965).

False discovery rate (FDR) correction for multiple comparisons (as described in Huang et al., 2013, see also Hastie et al., 2009) was used to control the false positive rate. Differences with a corrected p value of <0.05 were considered statistically significant. An independent-samples *t*-test was further used to examine whether the observed SD-induced changes in the experimental group were significantly larger than the pre-post changes in the control group.

5. Results

To test our hypothesis, the ipsilateral thalamocortical morphological relations (i.e., values of KLS for each pair of brain regions) were first quantified with our proposed method for each hemisphere in each individual. Then, a paired-samples *t*-test was used to investigate the changes in the relation metrics before and after SD (i.e., pre-SD versus post-SD) to find out the possible effects of SD on the thalamocortical morphological relations.

For the pre-post comparisons, analyses were performed separately for each hemisphere; that is, only ipsilateral thalamocortical relations were considered. The changes in the right hemisphere were not significant (p > 0.05, FDR corrected), so we focused on the changes in the left hemisphere. We observed specific changes in two morphological relations that survived multiple comparisons correction (p < 0.05, FDR corrected) in the left hemisphere: the relation between the thalamus and angular gyrus (THA-ANG₋L) (Fig. 2) and the relation between the thalamus and lingual gyrus (THA-LING_L) (Fig. 2). Specifically, the morphological relation was significantly weakened between the thalamus and lingual gyrus [mean KLS: 0.606 reduced to 0.428; t(7) = -3.54, p = 0.0095], while it was enhanced between the thalamus and angular gyrus [mean KLS: 0.793 increased to 0.867; t(7) = 4.45, p = 0.0030]. These results are shown in Fig. 2b. In addition, the Shapiro-Wilk normality test showed that the SD-induced changes in THA-ANG_L and THA-LING_L were both normally distributed: W=0.91, p=0.32; and W = 0.94, p = 0.62, respectively, suggesting the validity of the statistical tests above.

As expected, the control group without SD showed no significant pre-post differences in the thalamocortical relations in either hemisphere (p > 0.05, FDR corrected). Furthermore, we found that the observed SD-induced changes were significant larger than the



Fig. 2. Effects of sleep deprivation (SD) on the morphological relations. (a) SD-induced changes in a typical participant. The *x*-axis is the gray matter intensity. The red circles point out obvious changes. (b) Significant alterations related to SD (p < 0.05, FDR corrected). THA-LING_L: thalamus-lingual gyrus in the left hemisphere; THA-ANG_L: thalamus-angular gyrus in the left hemisphere. * indicates p < 0.01, ** indicates p < 0.005, two-tailed. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

pre-post changes in the control group [THA-ANG_L: t(7)=2.5, p=0.02; THA_LING_L: t(7)=2.9, p=0.01].

Taken together, we found that there were significant SDinduced changes and that the change in the morphological relation between the thalamus and angular gyrus was relatively more evident. Given that the angular gyrus has been shown to be involved in multiple functions (Seghier, 2013) including memory retrieval and attention, the SD-induced alteration appears to be related to the decline in cognitive performance caused by sleep loss (Alhola and Polo-Kantola, 2007). Essentially, these results suggest the potential application of the new approach to studies of individual differences.

6. Discussion

Here, we introduced a novel approach for quantifying the inter-regional relation between morphological distributions with MRI data. More importantly, the approach allows the quantification of inter-regional relations for each individual participant. This new morphological relation metric could be informative in many contexts in neuroscience, such as in studies on normal neurodevelopment or on single brain structure abnormalities due to neurological diseases. Our preliminary results suggest that the cognitive performance decline caused by long-term SD might be reflected in the morphological connection changes between different brain regions. Additionally, these findings illustrate the potential application of our proposed method.

It is noteworthy that, in this study, the relation was quantified with the similarity of distributions in local brain morphology. To our knowledge, this is the first study to measure inter-regional relations with regional morphological distribution information. Previous approach constructed the morphological relations using the co-variances of averaged cortical measures (e.g., cortical thickness and gray matter volume) between different brain regions across participants (Bassett et al., 2008; Chen et al., 2008; He et al., 2007). But, with such an approach, a relatively more complicated procedure (e.g., permutation test) has to be used to make statistical inference, because we can obtain only one measure for a relatively large group. Unlike such an approach, ours provides more flexibilities to researchers. As we can see that we can get one measure for each of the participants, this method can be applied to studies on individual differences, where plentiful statistical methods (e.g., Pearson correlation, multiple regression, two samples *t*-test, paired *t*-test, and analysis of variance) can be used. This opens up an avenue for investigating individual variability in brain structure, especially for identifying brain abnormalities in each individual patient. More importantly, given that MRI scanning is conventionally performed and is not as sensitive as other imaging modalities to the confounding artifacts, such as the motion artifacts in diffusion MRI (dMRI) (Kong, 2014; Ling et al., 2012) and functional MRI (fMRI) (Kong et al., 2014; Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012), our proposed method could provide a novel perspective for understanding individual variability and clinical conditions. For example, this method could provide a more comprehensive view for automatically identifying brain abnormalities in a single-participant's brain.

The physiological meaning underlying inter-regional morphological relations is complex and not completely understood yet. One possible explanation for morphological relations is from the axon tension theory (Van Essen, 1997), which predicts that anatomically connected areas are pulled by a mechanical force, resulting in similar morphological properties. An alternative explanation is that regions with similar morphological distributions might reflect coordination between areas in development (Alexander-Bloch et al., 2013; Lerch et al., 2006) and learning (Draganski et al., 2004; Mechelli et al., 2004). Thus, from these points of view, one could speculate that the inter-regional morphological relations provide a proxy for the structure of neuronal circuits. In addition, the morphologically related regions might also share similar distributions of major cell classes (such as neurons, oligodendrocytes, and astrocytes) and gene expression (Hawrylycz et al., 2012). The exact biological underpinning of the morphological relations will be an important topic for future studies.

It is intriguing to note that significant changes in the thalamocortical relations were found only in the left hemisphere. There are two possible reasons for this lateralization of SD-induced effects. First, the left and right thalamus may function differently during sleep. Previous studies have found that the thalamocortical network is involved in the transitional state from wakefulness to sleep (Timofeev, 2011), and that the left and right thalamus show guite different changing courses over different stages of sleep (Spoormaker et al., 2010). For example, when shifting from an early sleep stage to slow-wave sleep, the left thalamus has a differential connection with 50 regions, whereas the right thalamus has only 22 connections changed (Spoormaker et al., 2010). Second, the left thalamus might be more vulnerable to the effects of long-term sleep loss. Previous studies have found that patients having depression with sleep loss showed abnormal decreases in the relative cerebral metabolic rate of glucose in the left thalamus during the transition from wakefulness to sleep (Germain et al., 2004). Overall, the left-lateralized SD-induced effects on the morphological relation could be explained, at least in part, by the different function and vulnerability of the left and right thalamocortical networks.

Finally, given the simplicity and straight-forwardness of our framework, it can be extended in several ways. Firstly, local cortical measures other than gray matter volume can be used, such as the cortical thickness or surface area. The approach could also be

applied to measuring the human brain at the cellular level, such as in the only ultrahigh-resolution brain model developed thus far, BigBrain (Amunts et al., 2013). We refer to a study under this framework as a Distribution Based Inter-regional Relation (DBIR) study. Additionally, in the future, we will perform an investigation over a parcellation of the entire cerebral cortex, which will then be incorporated into a network analysis framework in order to detect global patterns of changes with powerful graph theoretic tools.

There are some limitations of this study. First, the exact physiological meaning of the individual morphological relation metric is still unclear. Further studies combining different techniques (such as fMRI, dMRI, single-cell recording, and gene expression data) are needed to explore the underlying mechanism. Nevertheless, this metric does show considerable individual differences in morphological features and high sensitivity to longitudinal changes. Second, the number of SD participants was relatively small. Further studies in a larger cohort are needed to verify these preliminary findings.

In summary, we propose a novel approach for quantifying interregional morphological relations within an individual participant and illustrate its potential application through a pre-post intervention study. Further studies are needed to investigate the underlying physiological meaning of the morphological relation metric, and its convergence or divergence with anatomical connections and functional connectivity.

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