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# Comparing connectivity pattern and small-world organization between structural correlation and resting-state networks in healthy adults

S.M. Hadi Hosseini [a,*], Shelli R. Kesler [a,b]

[a] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA
[b] Stanford Cancer Institute, Palo Alto, CA, USA

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ABSTRACT

In recent years, coordinated variations in brain morphology (e.g. volume, thickness, surface area) have been employed as a measure of structural association between brain regions to infer large-scale structural correlation networks (SCNs).
However, it remains unclear how morphometric correlations relate to functional connectivity between brain regions. Resting-state networks (RSNs), derived from coordinated variations in neural activity at rest, have been shown to reflect connectivity between functionally related regions as well as, to some extent, anatomical connectivity between brain regions. Therefore, it is intriguing to investigate similarities between SCN and RSN to help identify how morphometric correlations relate to connections defined by resting-state connectivity. We investigated the similarities in connectivity patterns and small-world organization between SCN, derived from correlations of regional gray matter volume across individuals, and RSN in 36 healthy individuals. The results showed a significant similarity between SCN and RSN (60% for positive connections and 40% for negative connections) that might be explained by shared experience-related functional connectivity underlying both SCN and RSN. Conversely, the small-world parameters of the networks were significantly different, suggesting that SCN topological parameters cannot be regarded as a substitute for topological organization in resting-state networks. While our data suggest that using structural correlation networks can be useful in understanding alterations in structural associations in various brain disorders, it should be noted that a portion of the observed alterations might be explained by factors other than those reflecting resting-state connectivity.


## Introduction

Coordinated variations in brain morphology (e.g. volume, thickness, surface area) have been recently employed as a measure of structural association between brain regions to infer large-scale structural correlation networks (SCNs) (Bassett et al., 2008; Bernhardt et al., 2011; Chen et al., 2008, 2011; Fan et al., 2011; Guye et al., 2010; He and Evans, 2010; He et al., 2007, 2008, 2009a; Hosseini et al., 2012a, 2012b; Lerch et al., 2006; Lv et al., 2010; Raj et al., 2010; Sanabria-Diaz et al., 2010; Sun et al., 2012; Wu et al., 2012; Zhou et al., 2011). Alterations in the arrangements of these networks have been associated with normal aging (Chen et al., 2011; Sun et al., 2012; Wu et al., 2012), multiple sclerosis (He et al., 2009a), Alzheimer's disease (He et al., 2008; Zhou et al., 2011), schizophrenia (Bassett et al., 2008) and epilepsy (Bernhardt et al., 2011; Raj et al., 2010). However, it remains unclear how morphometric correlations relate to actual anatomical and/or functional connectivity between brain regions.

These morphometric correlations might reflect anatomical connectivity, as axonally connected regions are believed to be influenced by common developmental, trophic and maturational effects (Bernhardt et al., 2011; Cheverud, 1984; Wright et al., 1999; Zhang et al., 2000). This idea is supported by a number of studies that suggest consistencies between networks constructed from morphometric correlations of cortical volume, thickness, and surface area data with those constructed from white matter tract-based data (Bernhardt et al., 2008; He et al., 2007; Lerch et al., 2006; Sanabria-Diaz et al., 2010). Further evidence is provided by a recent study that reported 40% similarity between cortical thickness correlations and diffusion tensor imaging (DTI)-derived anatomical networks (Gong et al., 2012).

Alternatively, morphometric correlations might also be influenced by functional connectivity as functional specialization, through practice, skill acquisition and training, can cause changes in underlying anatomy (experience-related plasticity) (Duan et al., 2012; Gaser and Schlaug, 2003a; Halwani et al., 2011; Maguire et al., 2000, 2006; Rykhlevskaia et al., 2008; Sluming et al., 2002). This possibility is supported by neuroimaging evidence showing, for example, increased gray matter volume in motor, auditory and visual–spatial brain regions in professional musicians in response to long-term skill acquisition (Gaser and Schlaug, 2003a, 2003b), enhanced integration of striatal network in chess

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, 401 Quarry Rd., Stanford, CA 94305-5795, USA. Fax: +1 650 724 4794.
*E-mail addresses:* hosseiny@stanford.edu, hadi.hosseini@gmail.com (S.M.H. Hosseini).

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experts (Duan et al., 2012), increased gray matter density in Broca's area in orchestra musicians (Sluming et al., 2002), and increased hippocampal gray matter volume in taxi drivers (Maguire et al., 2000, 2006; Woollett and Maguire, 2011).

Resting-state networks (RSNs) (Biswal, 2012; Biswal et al., 1995), derived from coordinated variations in neural activity at rest, have been shown to reflect connectivity between functionally related regions (Biswal et al., 2010; Greicius et al., 2009). Recent data show that resting-state functional connectivity not only reflects functional connectivity mediated by indirect anatomical connections and experience-related functional plasticity, but also represents, to some extent, the underlying anatomical connectivity between brain regions (Damoiseaux and Greicius, 2009; Honey et al., 2009; Luo et al., 2012; Skudlarski et al., 2008; van den Heuvel et al., 2009a). The gold standard for extracting anatomical connectivity involves invasive retrograde/anterograde tract tracing that cannot be done in the living human (Bernhardt et al., 2011). However, a significant agreement has been demonstrated between a majority of common resting-state connections and known anatomical fiber tracts in monkeys (Mantini et al., 2011; Shen et al., 2012). Thus, it is intriguing to investigate similarities between SCN and RSN to help identify how morphometric correlations relate to functional connections defined by resting-state connectivity.

In the present report, we aimed to identify the similarities between SCN, derived from correlations of regional gray matter volume across individuals and RSN in healthy adults. SCN was represented by a set of nodes that correspond to brain regions and a set of edges (connections) that correspond to statistical correlations in gray matter volume between brain regions, across individuals (He et al., 2007; Hosseini et al., 2012b). RSNs were represented by the same set of nodes while their edges were quantified by computing the statistical correlation between time series of different brain regions (Bassett et al., 2012; Buckner et al., 2009; He et al., 2009b; Liao et al., 2010;Tian et al., 2011; van den Heuvel et al., 2009a; Wang et al., 2009a, 2009b). Thresholding the obtained correlation matrices at an absolute threshold results in networks with different numbers of nodes and connections that might influence the network measures and limit interpretation of comparison findings (van Wijk et al., 2010). Therefore, many recent studies involving brain networks binarize the correlation matrices at fixed network densities (number of existing edges to the number of possible edges in the network) and compare the binary networks across a range of densities (Alexander-Bloch et al., 2013a, 2013b; Bassett et al., 2012; Bernhardt et al., 2011; Bruno et al., 2012; Fan et al., 2011; He et al., 2009a; Hosseini et al., 2012a, 2012b; Sanabria-Diaz et al., 2010; Wang et al., 2010; Wu et al., 2012).

Similarities between two networks can be assessed either by comparing the similarity of their connections or by comparing their organizational properties. The most direct way of comparing connections in networks with the same size is to find their distances. The distances between two binary networks are usually calculated using the Hamming distance ($S_{hd}$), which measures the number of addition/deletion operations required to make two networks the same (van Wijk et al., 2010). While Hamming distance gives an accurate estimate of similarity between network connections, it overestimates the similarity if the networks are sparse (Fig. 1). Therefore, we also used a normalized distance metric ($S_{norm}$) that accounts for large baseline correlations between networks (Costa et al., 2007).

We also compared the organizational properties of SCN and RSN to assess their similarities in terms of information processing potential. Previous studies have shown that SCNs and RSNs follow small-world architecture in healthy individuals (Bassett et al., 2008, 2012; Fan et al., 2011; He et al., 2009a; Hosseini et al., 2012a, 2012b, 2013; Wu et al., 2012), an architecture that provides optimal balance between local and global information processing in the network (Amaral et al., 2000; Bassett and Bullmore, 2006; Latora and Marchiori, 2001; Watts and Strogatz, 1998). Therefore, we compared the organizational properties of SCN and RSN by directly measuring their small-world characteristics at the global level as well as their connectedness properties at the regional level.

A recent study by Alexander-Bloch and colleagues examined the convergence of SCN constructed from cortical thickness data and RSN in healthy individuals and reported a significant correlation between the two networks (Alexander-Bloch et al., 2013a, 2013b). However, they constructed SCN for cortical thickness data and did not include the subcortical regions. In the present study, we used regional volume data to construct SCN since they contain information regarding both thickness and surface area and thus reflect a summary effect of interaction between brain regions. Using regional volume data also allowed us to compare SCN and RSN that include both cortical and subcortical regions. In addition, the current study expands the previous findings by comparing the similarities and small-world indices between SCN and RSN across a large range of density thresholds. Finally, we tested the reproducibility of our findings by comparing RSN and SCN of the same subjects across two time points.

We expected a degree of similarity between SCN and RSN that might be explained by the shared influence of both anatomical connectivity and experience-related plasticity. We also expected a higher small-world index in RSN compared to SCN since functional networks require rapid transitions and reconfigurations and would allow higher rates of information processing.

## Materials and methods

### Participants

We enrolled 36 healthy adults (age 20–39 years old, mean age 28.4) in the study (Table 1). Participants were excluded for any history of medical, neurologic or psychiatric conditions or MRI contraindications. The Stanford University Institutional Review Board approved the study. This study was conducted according to the principles expressed in the Declaration of Helsinki. All participants provided written informed consent.

### MRI data acquisition

MRI scanning was performed on a GE Discovery MR750 3.0 T whole body scanner (GE Medical Systems, Milwaukee, WI). High-resolution T1-weighted images were acquired with 3D spoiled gradient recall pulse sequence using the following parameters: TR = 8.5 ms, TE = 3.396, TI = 400 ms, flip angle = 15°, FOV = 220 mm, number of excitation = 1, acquisition matrix = 256 × 192, slice thickness = 1.6. Totally, 124 contiguous coronal slices were obtained with in-plane resolution of 0.859 mm × 0.859 mm. Resting-state functional MRI data was acquired, in the same session, while participants rested in the scanner with their eyes closed using a T2* weighted gradient echo spiral pulse sequence: relaxation time = 2000 ms, echo time = 30 ms, flip angle = 80° and 1 interleave, field of view = 220 mm, slice thickness = 4 mm, spacing = 1 mm, matrix = 64 × 64, in-plane resolution = 3.125. Number of data frames collected was 216 with a total scan time of 7:12 min. An automated high-order shimming method based on spiral acquisitions was employed to reduce field heterogeneity (Glover and Lai, 1998).

### Image preprocessing

Anatomical image preprocessing was performed using Statistical Parametric Mapping 8 (SPM8; Wellcome Department of Cognitive Neurology, London, UK) (Friston, 2007) as described in detail in our previous publications (Hosseini et al., 2012a, 2012b). The anatomical images were segmented into gray matter (GM), white matter, and cerebrospinal fluid images based on the ICBM Tissue Probabilistic Maps (http://www.loni.ucla.edu/ICBM/ICBMTissueProb.html). A study-specific a priori probability map of GM was created from the modulated spatially normalized



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