

STRUCTURAL CONNECTIVITY WITHIN NEURAL GANGLIA: A DEFAULT SMALL-WORLD NETWORK

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Abstract—Diffusion tensor imaging (DTI) provides a unique contrast based on the restricted directionality of water movement in an anisotropic environment. As such, DTI-based tractography can be used to characterize and quantify the structural connectivity within neural tissue. Here, DTI-based connectivity within isolated abdominal ganglia of *Aplysia californica* (ABG) is analyzed using network theory. In addition to quantifying the regional physical properties of the fractional anisotropy and apparent diffusion coefficient, DTI tractography was used to probe inner-connections of local communities, yielding unweighted, undirected graphs that represent community structures. Local and global efficiency, characteristic path lengths and clustering analysis are performed on both experimental and simulated data. The relevant intensity by which these specific nodes communicate is probed through weighted clustering coefficient measurements. Both small-worldness and novel small-world metrics were used as tools to verify the small-world properties for the experimental results. The aim of this manuscript is to categorize the properties exhibited by structural networks in a model neural tissue to derive unique mean field information that quantitatively describe macroscopic connectivity. For ABG, findings demonstrate a default structural network with preferential specific small-world properties when compared to simulated lattice and random networks that are equivalent in order and degree. © 2016 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: diffusion tensor imaging, structural connectivity, graph theory, small-world networks.

INTRODUCTION

With increasing interest in neural networks and brain organization, the investigation of mathematical properties through either group or graph representatives to assess the connectivity between regions of interest (ROI) continues to be a focal area in the study of neural topology. Graph theoretical analysis recently has become popular for assessing various aspects of connectivity such as asymmetrical human hemispheric networks (Li et al., 2014), aging impact on white matter integrity (Marstaller et al., 2015), reduced global efficiency in mesial temporal lobe epilepsy (mTLE) patients (Xu et al., 2014), increased characteristic path length and lower global efficiency in Alzheimer's patients (Lo et al., 2010), and the small-world network of the cerebral cortex (Sporns and Zwi, 2004). However, one barrier for verifying the credibility of these markers is a reliance on the acquisition resolution and the correlation of attained tracts to biophysical structures and interconnections. With *in vivo* and clinical diffusion tensor imaging (DTI), tractography is largely dependent on the structural connectivity defined by white matter or the functional connectivity defined by the timing of functional magnetic resonance imaging (fMRI)-measurable effects relative to stimulatory events. Taking a structural approach, this study evaluates DTI tractography and employs graph theory in the absence of major white matter tracts.

The network of interest in this study is the structural connectivity in the abdominal ganglion (ABG) of *Aplysia californica*, which is a recognized model for neural tissue including synaptic transmission (Klein and Kandel, 1978), cellular learning and memory (Frost and Kandel, 1995), behavioral conditioning (Vorster et al., 2014), aging (Akhmedov et al., 2013), mathematical modeling of neuronal bursting (Bertram, 1993), electrical coupling of single neurons (Dargaei et al., 2014) and single neuron imaging (Grant et al., 2001; Lee et al., 2015) and spectroscopy (Grant et al., 2000). Using high field DTI, high-resolution tractography analysis was used to generate connecting edges between ROIs within the ABG (Basser et al., 1994). These reconstructed paths are principally tracks that follow the changes in neural fiber orientation that can be detected noninvasively through the DTI technique.

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Abbreviations: ABG, abdominal ganglion of *Aplysia californica*; ADC, apparent diffusion coefficient; ASW, artificial seawater; DTI, diffusion tensor imaging; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; MRI, Magnetic Resonance Imaging; MRM, magnetic resonance microscopy; ROI, regions of interest; WS, Watts–Strogatz.

The simplicity of the one-dimensional analysis in graph theory is the driving force behind its popularity. Although a group theory application would take a multi-dimension approach with consideration for the descriptive geometry of the exhibited paths that connect graph components, many applications that model real networks rely on graph theory. Uses of graph theory are growing and diverse, including various areas such as urban planning (Roberts, 1978), social networks (Newman et al., 2002), and structural and functional connectivity in complex biological networks (Bullmore and Sporns, 2009). In graph approaches, system variables are reduced to cut computational cost and maintain the uniqueness of provided solutions. In addition to the lack of spatial description of the connecting curves, these connections are considered instantaneous. As a result, many of the derived graph properties reveal more about the centrality and clustering of the individual end points at the cost of the spatial and symmetrical feedback of the connections.

For this study, graph properties were derived and compared to lattice and random networks to investigate the small-worldness of the experimental *Aplysia* data. Small-world networks define a category of graphs that maintain a high clustering coefficient C by minimizing the rewiring of graph vertices, but achieve a decrease in the characteristic path length L from small violations of the order in a regular lattice (Watts and Strogatz, 1998). As such, relatively high local and global efficiencies are observed simultaneously in graphs that exhibit small-world properties. One open question in graph theory is how to identify quantitatively a small-world network. Along with efficiency measurements, other metrics have been suggested to quantify the small-worldness of a network. The small-world coefficient σ is used to investigate the graph-clustering ratio with respect to random networks when compared to the path length ratio with respect to a lattice network (Humphries and Gurney, 2008):

$$\sigma = \frac{\gamma}{\lambda} \quad (1)$$

where $\gamma = C/C_{random}$ and $\lambda = L/L_{lattice}$. However, fluctuations in the clustering coefficient for random networks along with variations of the path length in lattice graphs as a function of the graph order and size have been challenges for the small-world coefficient. As a result, σ is mostly an assessment of randomness in a given network.

The novel small-world metric ω is another suggested measurement to identify a graph that exhibits the properties of a small-world network (Telesford et al., 2011):

$$\omega = \frac{L_{random}}{L} - \frac{C}{C_{Lattice}} \quad (2)$$

Despite its limitations, including vulnerability to significant changes in network order and graphs with particular hub distributions, ω is capable of locating a network on the continuum from lattice to random networks. This feature appeals to the aim of using graph theoretical analysis to provide biomarkers and reference data for structural connectivity in neural ganglia.

The size and density of the neurons investigated in this study as well as the high resolution acquired demonstrate that DTI tractography and graph theoretical analysis non-destructively can identify robust networks even within neural structures without significant white matter involvement. As such, this approach, whether in binary form to assess the efficiency of connectivity or in weighted form to display critical vertices related to neuronal density, can be used to identify structural networks that can serve as a framework for functional assessments of data communication within neural tissue and at a cellular level.

EXPERIMENTAL PROCEDURES

Animal model

Aplysia californica were obtained from the NIH/University of Miami National Resource for *Aplysia* (Miami, FL). For all studies, late juvenile *Aplysia* (45–75 g) were examined, and specimens were anesthetized with a paralytic dose of $MgCl_2$ (380 mM applied at 50 mL/100 g animal weight). After gross dissection of nerves and connective tissue, the abdominal ganglion was isolated and fixed for 24 h in 4% paraformaldehyde. The following day, the fixed ganglion was washed three times in fresh artificial seawater (ASW) over 24 h. Freed of any remaining external fibrous tissue, the washed ganglion was placed into a small glass NMR capillary (2.5-mm OD) filled with ASW for scanning.

DTI acquisition

Diffusion data were acquired for ten samples ($N = 10$) at 11.75 T using a 500-MHz widebore vertical magnet located at the FAMU-FSU College of Engineering operated by a Bruker Avance spectrometer (Bruker BioSpin Corp., Billerica MA) and equipped with a triple-axis Bruker Micro2.5 gradient set (peak gradient strength per axis of 1 T/m using 40-A gradient amplifiers). A homebuilt and susceptibility-matched 2.5-mm solenoidal RF coil was utilized for these studies to improve signal-to-noise ratios (Webb and Grant, 1996). Before each run, a shim was performed to maximize homogeneity of the magnetic field, followed by setup scans to assess linewidth and calibrate the RF transmit power and receiver gain. After localizing images, DTI was acquired with the following acquisition parameters: $\Delta = 21$ ms, $\delta = 3$ ms, matrix = 100×100 , TE = 30 ms, TR = 2 s, FOV = 5×5 mm, and slice thickness = 150 μ m.

DTI data were collected over a total acquisition time of 19.5 h using a multi-slice, diffusion-weighted 2D spin echo sequence at a resolution of $50 \times 50 \times 150$ μ m (Fig. 1A–G). A total of 22 pulsed field experiments were used to encode diffusion, with four unweighted data acquisitions equally dispersed among directionally unique and optimally arranged samplings of 18 diffusion-weighted acquisitions whose pulsed field gradient orientation was described by the electrostatic dispersion on the surface of a unit sphere (Jones and Leemans, 2011). The nominal target b value for each directionally encoded DTI acquisi-

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