Commute Time as a Method to Explore Brain Functional Connectomes

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Abstract

Graph theory has been extensively applied to investigate complex brain networks in current neuroscience research. Many metrics derived from graph theory, such as local and global efficiencies, are based on the path length between nodes. These approaches are commonly used in analyses of brain networks assessed by resting-state functional magnetic resonance imaging, although relying on the strong assumption that information flow throughout the network is restricted to the shortest paths. In this study, we propose the utilization of commute time as a tool to investigate regional centrality on the functional connectome. Our initial hypothesis was that an alternative approach that considers alternative routes (such as commute time) could provide further information into the organization of functional networks. However, our empirical findings on the ADHD-200 database suggest that at the group level, the commute time and shortest path are highly correlated. In contrast, at the subject level, we discovered that commute time is much less susceptible to head motion artifacts when compared with metrics based on shortest paths. Given the overall similarity between the measures, we argue that commute time might be advantageous particularly for connectomic studies in populations where motion artifacts are a major issue.

Keywords: ADHD; connectivity; connectome; fMRI; graph-theory

Introduction

DESCRIBING THE BRAIN functional architecture accurately is one of the most important challenges in current neuroscience research (Bullmore and Sporns, 2009; Poldrack and Farah, 2015). This problem is currently formulated based on the prevailing connectomic perspective (Sporns, 2011). When applied to functional magnetic resonance imaging (fMRI) data, the functional connectome concept usually refers to unrestricted resting-state paradigms rather than to classic task-based experiments (Van Den Heuvel and Pol, 2010). Mounting evidence supports the idea that the highly reproducible, intrinsic, functional connectivity (i.e., statistical dependence between local signals measured during resting state) patterns give rise to large-scale networks (Bullmore and Sporns, 2009) whose dynamical organization in turn instantiates complex behaviors and cognition (Bressler and Menon, 2010; Mišić and Sporns, 2016; Sporns et al., 2004). Moreover, the organization of brain structural and functional networks is highly similar, even when different types of measurements are used (Bullmore and Sporns, 2009; Honey et al., 2007).

Graph theory is a suitable and powerful mathematical framework to characterize the organization of both structural

and functional brain networks. Generically, this theoretical approach offers useful and interpretable metrics to describe and summarize the properties of complex networks (Bullmore and Sporns, 2009). Of particular interest to connectomic research, such metrics might be useful to assess the brain's fundamental properties of functional segregation and integration (Sporns et al., 2004). For this purpose, graph theory-based metrics relying on shortest paths between nodes (e.g., local and global efficiencies) have been usually applied (Archard and Bullmore, 2006; Archard et al., 2007; Bassett et al., 2012; Damoiseaux et al., 2008; Wang et al., 2010).

However, the assumption that communication between distinct neural modules is restricted to the shortest paths has been recently challenged (Goñi et al., 2013, 2014). Indeed, this is quite a strong assumption, making the description of network properties incomplete. Considering alternatives through less efficient routes might provide further insights into the organization of brain networks. Random walk and diffusion-based models are the principal alternative approaches to shortest path-based metrics. For instance, Goñi and colleagues (2014) have found that the relationships between structural network and spontaneous functional connectivity are suggestive of diffusion, spreading, or greedy

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routing dynamics (Abdelnour et al., 2014; Goñi et al., 2013; O'Dea et al., 2013; van den Heuvel et al., 2012).

In this study, we sought to evaluate the commute time metric, a random walk-based graph descriptor, to detect dynamical changes in the functional connectome due to development. To the best of our knowledge, no works to date have directly explored the alternative concept of commute time to investigate resting-state fMRI (rs-fMRI)-derived functional networks. In a related field, Dimitriadis and associates (2012) explored the notion of commute time to analyze functional connectivity changes with event-related dynamics in electroencephalograph. Mean commute time was also applied by Meyer and Stephens (2008) and Shen and Meyer (2008), but as a way to parameterize brain states that were in turn used to decode natural and complex stimuli from fMRI signals. Notably, the interpretation of these measures is well established in a general context: the path length metrics were demonstrated to be inversely proportional to the network's efficiency (Latora and Marchiori, 2001, 2003), while commute time is readily interpretable as the inverse of the robustness to edge or node failures (Ellens et al., 2011).

In the current study, we introduce commute time as an alternative metric in functional connectomic research. In addition, we also compared the findings resulting from this metric with the shortest path. Our analyses were based on rs-fMRI data of healthy subjects from the ADHD-200 database, considering replications in seven independent samples. Our hypothesis was that the commute time, in which alternative routes are taken into account, could provide further information into organization of brain networks. Moreover, considering that motion artifacts are one of the most challenging obstacles in fMRI-based connectomic studies involving clinical and pediatric populations, we compared both approaches regarding their susceptibility to such artifacts.

Materials and Methods

In the following, the theoretical foundation of commute time will be presented. Then, we provide empirical comparisons with the shortest path approach by using the ADHD-200 database.

Commute time

In this section, we introduce the main graph of theoretical concepts used to model and analyze rs-fMRI data. For further details on the formulation applied here, see Ellens and associates (2011) and Lyons and Peres (2016). A graph consists of a collection of nodes (which in our case represent the brain's regions) and a collection of edges, each of which joins two distinct nodes (which represent functional connectivity). In many applications, it is natural to assign weights to the edges of a graph (Bullmore and Sporns, 2009). In such case, we say that we have a weighted graph.

Now, we define the notion of a random walk on a weighted graph (Doyle and Snell, 1984; Lovász, 1993). Consider a walk as follows. At each time, we are standing on a node v and want to select another node to move to, we do so by choosing one node at random among the ones directly connected by an edge to v. The probability of choosing a node u is proportional to the weight of the edge uv (i.e., the probability of going from v to u is the weight of the edge uv divided by the total weight of all edges joining v). The com-

mute time between two nodes is the expected number of steps to go from the first node to the second and then come back to the first (Lovász, 1993). One interesting aspect of using random walks is that they tend to linger in areas of the graph that are well connected and rarely go to poorly connected areas.

The commute time may be computed as follows:

- 1. Let A denote the weighted adjacency matrix of G.
- Compute the matrix L=D A, where D is a diagonal matrix such that the entry corresponding to node v is the total weight of the edges joining v.
- 3. Compute the Moore–Penrose pseudoinverse of L. This pseudoinverse can be computed easily by numerical software packages (Ellens et al., 2011). Let L⁺ denote the pseudoinverse.
- 4. Compute the matrix R defined by $R(u,v) = L^+(u,u) + L^+(v,v) 2L^+(u,v)$.
- 5. Compute the matrix $C=t \times R$, where t is the sum of all entries of A. The entry C(u,v) is the commute time from u to v.

Observations. The matrix L is known as the weighted Laplacian of G and it has been extensively studied by the graph theory community (Klein and Randić, 1993; Van Mieghem, 2010). We need to work with the pseudoinverse since the matrix L is not invertible. In the approach we present, we explore a well-known result in the graph theory community that relates the commute time to effective resistance of the edges (Ellens et al., 2011; Klein and Randić, 1993; Lyons and Peres, 2016). Roughly speaking, one considers the graph as an electrical circuit where each edge corresponds to a resistor. The effective resistance values are computed in the matrix R in step 4.

Shortest path calculation

As described in the previous subsection, the commute time calculation is based only on weights specified by the adjacency matrix. Calculation of the shortest path requires the definition of the distance between adjacent nodes. In this study, this distance was defined by $1/|c_{ij}|$, where c_{ij} is the cell at row i and column j of the graph adjacency matrix.

Empirical analysis: ADHD-200 dataset and preprocessing

The rs-fMRI dataset used in this study was acquired by the ADHD-200 Consortium (Milham et al., 2012). Data collection by the ADHD-200 Consortium was conducted with local internal review board approval and data were fully anonymized in compliance with Health Insurance Portability and Accountability Act privacy rules. We considered all healthy subjects of the ADHD-200 competition release and replication analyses considering the seven sites of acquisition.

Data were preprocessed by The Neuro Bureau using the Athena pipeline (www.nitrc.org/plugins/mwiki/index.php/neurobureau:AthenaPipeline). Briefly, the pipeline consists in discarding the first four scans; slice time correction; deobliquing; motion correction; brain masking; coregistration to anatomical image; spatial resampling to $4 \text{ mm} \times 4 \text{ mm} \times 4 \text{ mm}$; regressing out white-matter, cerebrospinal fluid, and motion parameters and trends; and spatial smoothing with Gaussian kernel (full-width-at-half-maximum=6 mm). The

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average time series of 351 regions of interest (ROIs) were extracted considering CC400 functional parcellation (Craddock et al., 2012). For each subject, the head movement amount was estimated by mean frame displacement (Power et al., 2012).

For each subject, the pairwise Spearman (which is more robust to outliers than Pearson) correlation matrix among signals of all 351 ROIs was calculated and absolute values were considered weights of the graph adjacency matrix. To avoid arbitrary choices, no threshold was applied to individual correlation matrices.

In the following analyses, we compare the commute time and shortest path approaches regarding identification of brain functional hubs. We included solely the typical developing participants from seven sites of acquisition to avoid confounders of ADHD. For each subject and each pair of nodes, calculation of commute time was based on correlations at each cell of the graph adjacency matrix, which were considered as input weights.

We first calculated the mean commute time (across connections) for each brain parcel for each subject. Next, the mean of this metric across subjects was calculated to obtain a group-level estimate of the mean commute time for each region. This exact same procedure was applied to the shortest paths. Then, we compared the mean commute time and mean shortest path across the 351 different brain parcels, focusing on investigating the overlap and nonoverlap between the two approaches. In this analysis, we aimed to understand the additional and differential information obtained when using commute time in comparison with shortest path. Finally, since head motion artifact is one of the main issues in functional connectivity analyses, we compare the susceptibility of both methods to the impact of mean frame displacement across scans. Thus, we calculated the single-subject-level correlation between mean frame displacement and mean commute time (and shortest path). Additionally, we performed comparisons between the mean commute time and the degree as a supplementary analysis. This comparison is relevant since the degree is also a graph centrality metric frequently used in connectomic analyses and previous studies. A previous study reported that the mean commute time was biased by the node degree (von Luxburg et al., 2014).

Results

Demographical information is presented in Table 1. On average, children from Oregon Health & Science University were considerably younger, while the ones from NeuroImage were older. Besides, the amount of head motion (frame displacement) was fairly similar at all the sites.

Figure 1 presents the top 10% hub brain regions in each site, identified by ranking regions based on their mean commute time. Note that most hub regions are part of the default mode network (precuneus, posterior cingulate, and ventral medial prefrontal cortex) or control network (dorsal anterior cingulate). Since the hub maps based on mean shortest path or degree approaches would be fairly identical to the map depicted in Figure 1, they were not included.

Contrary to our expectation, the top 10% hub regions mapped using the commute time were almost identical to the ones identified by shortest path length. To further clarify this finding, we built Figure 2 that depicts scatter plots of the acrosssubjects mean commute time and shortest path over all the

TABLE 1. DEMOGRAPHICAL INFORMATION OF THE SAMPLES USED

| Site of acquisition | Ν | Males | Mean age | SD |
|---------------------------------------|-----|-------|----------|-----|
| Peking University | 116 | 71 | 11.7 | 1.7 |
| Kennedy Krieger Institute | 61 | 34 | 10.3 | 1.3 |
| New York Univ. Child Study Center | 98 | 47 | 12.2 | 3.1 |
| University of Pittsburgh | 89 | 46 | 15.1 | 2.9 |
| NeuroImage | 23 | 11 | 17.3 | 2.6 |
| Oregon Health & Science University | 42 | 17 | 8.9 | 1.2 |
| Washington University | 50 | 27 | 11.3 | 3.6 |

SD, standard deviation.

351 regions (each point thus representing a brain parcel), separately by acquisition site. From a practical perspective, this chart unequivocally demonstrates that on average (across subjects), both measures are quite strongly linearly related (Pearson correlation coefficient >0.95 in all sites). In other words, both metrics measure the same phenomena and this was an unexpected finding since they are conceptually different.

Finally, Figure 3 presents box plots of the correlation, each point representing a single subject, between head motion (measured as the mean frame displacement) and the mean (across all brain regions) commute time and shortest path. Note that the shortest path approach was more affected by head motion artifacts in all sites when compared with commute time (p < 0.001 in all sites) since the correlation was different from zero.

Interestingly, the exact same findings of a linear relationship and more robustness against motion artifacts also hold in comparisons between the mean commute time and the mean degree of each brain region (See Supplementary Figs. S1 and S2).

Discussion

In this study, we propose that commute time is a computationally feasible (in terms of processing time) and informative tool to investigate the organization of the functional connectome. In theory, the main advantage of this metric when compared with commonly applied graph theory-based metrics would be that instead of focusing solely on routes based on shortest paths, it considers all possible routes between two regions in a weighted manner. However, contrary to our initial hypothesis, our empirical comparison on the ADHD-200 database suggests that graph analyses based on the mean commute time were, on average, very similar to the ones based on the shortest path. Remarkably, our main finding was that although very similar at the group level (i.e., mean across subjects), the commute time metric was significantly more robust against head motion at the single-subject level.

Identification of main hubs in functional networks is of great importance to enhance our comprehension of brain hierarchical organization. Insightful studies reinforced this relevance both in normal and pathological conditions (Honey and Sporns, 2008; Liu et al., 2008). As expected, in all seven sites, the main hubs identified by using commute time (Fig. 1) were part of the default mode and control networks (Fransson et al., 2011). On the other hand, an accurate



FIG. 1. Top 10% hub brain regions at each site identified by ranking the mean (across subjects) commute time of each area. Color images are available online.

quantification of functional connectivity between brain regions is challenging since head motion artifacts have high impact on this analysis (Power et al., 2012). Our findings suggest that commute time provides a proper ranking of region closeness to brain networks and it is robust against movement artifacts. The reasons for this robustness depend on several factors, but we conjecture that commute time is less sensitive to global changes on edge weights, that is, when the weights of many edges are commonly affected by head motion. In the commute time approach, information flow over the network is modeled based on a random walk. The edge weights define transition probabilities and thus it is less affected by global increases/decreases in these weights.

Regarding the results shown in Figure 3, if correlation between frame displacement and shortest path is positive, this means that head motion artifacts lead to a decrease in overall brain connectivity. Conversely, if correlation is negative, the artifacts impact as an increase in overall connectivity. Both cases should be avoided, and findings reinforce that head motion indeed biases functional connectivity analyses when using the shortest path (and degree). We did not directly investigate the possible reasons for different signs in this correlation, but we speculate that it may be related to the scanning parameters or age. Moreover, Figure 3 demonstrates that the (median) correlation between frame displacement and mean commute time is consistently close to zero. As a consequence, single-subject-level correlations between path length and commute time may not be as high because the former is more affected by motion artifacts. Thus, although path length and commute time approaches reported mostly the same information, our finding is important because often there is interest in conducting correlation analyses between single-subject data (e.g., clinical scales and demographics) and individual ROI metrics. In this setting, commute time should be used to minimize motion confounding.



FIG. 2. Scatter plots between mean (across subjects) commute time and shortest path. Each point corresponds to a brain region.

In addition, head motion levels are usually dependent on age and clinical samples. Thus, our results are of fundamental importance in functional connectomic studies carried out in these populations. The investigation of developmental trajectories of the human connectome is a topic of increasing interest in the scientific community (Cao et al., 2016; Fransson et al., 2011; Huang et al., 2015; Supekar et al., 2009). Younger children usually present a higher level of head motion inside the scanner when compared with older children and adolescents, even in typical samples. On the other hand, hyperkinesia is more frequent in males and a criterion for the ADHD combined type. In addition, clinical populations such as patients diagnosed with Parkinson's disease or Tourette's syndrome also present greater levels of movement during fMRI sessions. Our findings suggest that commute time might be a suitable approach to identify brain hubs in these samples, at least for comparison purposes.

It is important to mention that considering the current state of the literature, head motion confounds cannot be completely ruled out as sources of error. In addition, there is considerable heterogeneity in the age of children and adolescents as well as in acquisition parameters between sites of the ADHD-200 dataset. Despite a loss on methodological reliability, we think that these features reinforce the utility of commute time measures for real-world applications. It is also important to emphasize that our approach, unlike previous efforts using random walk-based metrics (focused on modeling the causal relationship between structural and functional connections), is rather an attempt to find a better phenomenological quantitative descriptor of the functional connectome organization. One further limitation to be mentioned is the definition of graph weights. In the current study, we considered absolute values of functional connectivity coefficients (Spearman's correlation) as the weights between two nodes (brain regions). However, one could argue that positive and negative weights might not result in the same random walks over the graph. While acknowledging that this is a relevant limitation of our study, we remark that there is no consensus on this issue in the current literature. Actually, this is one of the main topics of dispute in the brain network literature, and



FIG. 3. Box plots of the correlation between head motion (frame displacement) and mean (across regions) commute time/ shortest path metrics. Each point corresponds to a subject.

our findings can be later expanded to include alternative random walk approaches.

Commute time provides a graph metric associated with brain functional integration, that is, how coherent is the activity in multiple regions. Future studies on this topic involve the development of novel analytical approaches to investigate brain functional segregation from a random walk perspective, also considering all possible paths and not only the shortest ones. Another interesting open question is how to handle functional connectivity coefficients that are negative when conducting commute analyses. As a conclusion, we argue that commute time, a relatively simple graph theory-derived metric, might be a useful tool to investigate brain connectivity networks, particularly when motion artifacts are of importance.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Figure S1 Supplementary Figure S2

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