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Determining Disease Evolution Driver Nodes in Dementia Networks

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ABSTRACT

Imaging connectomics emerged as an important field in modern neuroimaging to represent the interaction of structural and functional brain areas. Static graph networks are the mathematical structure to capture these interactions modeled by Pearson correlations between the representative area signals. Dynamical functional resting state networks seen in most fMRI experiments can not be represented by the classic correlation graph network. The changes in brain connectivity observed in many neuro-degenerative diseases in longitudinal data series suggest that more sophisticated graph networks to capture the dynamical properties of the brain networks are required. Furthermore, certain brain areas seem to act as "disease epicenters" being responsible for the spread of neuro-degenerative diseases. To mathematically describe these aspects, we propose a novel framework based on pinning controllability applied to dynamic graphs and seek to determine the changes in the "driver nodes" during the course of the disease. In contrast to other current research in pinning controllability, we aim to identify the best driver nodes describing disease evolution with respect to connectivity changes and location of the best driver nodes in functional ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography (¹⁸FDG-PET) and structural Magnetic Resonance Imaging (MRI) connectivity graphs in healthy controls (CN), and patients with mild cognitive impairment (MCI), and Alzheimer's disease (AD). We present the theoretical framework for determining the best driver nodes in connectivity graphs and their relation to disease evolution in dementia. We revolutionize the current graph analysis in brain networks and apply the concept of dynamic graph theory in connection with pinning controllability to reveal differences in the location of "disease epicenters" that play an important role in the temporal evolution of dementia. The described research will constitute a leap in biomedical research related to novel disease prediction trajectories and precision dementia therapies.

Keywords: Graph Theory, Dynamic Graph, Disease Epicenters, Pinning Observability, Dementia

1. INTRODUCTION

Novel mathematical concepts such as graph theoretical techniques can capture the brain connectivity and its topology.¹⁻³ These graph networks are mostly based on Pearson correlation and are capturing either the structural and/or functional brain connectivity. From these graphs, new descriptors can be derived to quantify induced changes in topology or network organization, or serve as theory-driven biomarkers to predict dementia at the level of the individual patient. Most graph networks applied to dementia research, even for longitudinal data are static graph networks, which cannot capture the dynamical processes governing the temporal evolution of dementia. Therefore, a new paradigm in dementia research - dynamical graph networks - is required to advance this field and overcome the obstacles posed by static graph theory in terms of disease prediction, evolution,

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and its associated connectivity changes. We pioneered the fusion of modern dynamic graph network theory and modeling strategies at different time scales with pinning control of complex neural networks in brain connectivity networks.⁴ Tahmassebi et al.^{5,6} established a transformational paradigm in dementia research investigating disease evolution and treatment response at the patient level revealing several central mechanism in a network that drives alterations in dementia. We modeled and analyzed functional connectivity networks in dementia as two-time scale sparse dynamic graph networks with hubs (clusters) representing the fast sub-system and the interconnections between hubs and the slow sub-system. Alterations in brain function as seen in dementia can be dynamically modeled by determining the clusters in which disturbance inputs have entered and the impact they have on the large-scale dementia dynamic system. Controlling regions in dementia networks represent key nodes to control the dynamics of the network. It seems to be crucial to understand how this complex network is controlled to enable an understanding of the progressive abnormal neural circuits in dementia. Figure 1 demonstrates the schematic presentation of an unweighted-undirected graph of complex networks in brain.

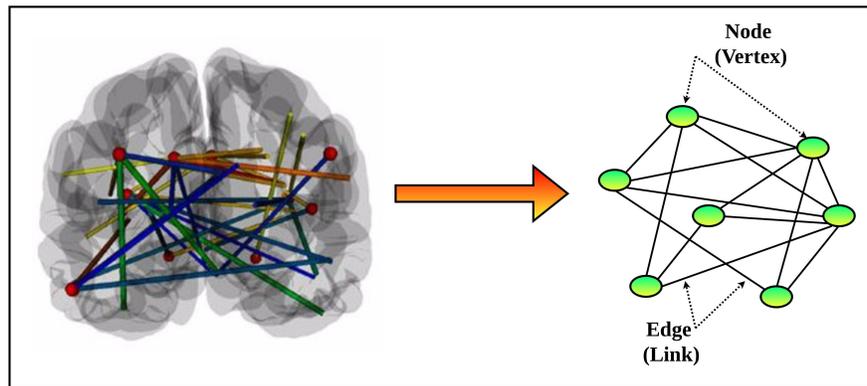


Figure 1. Schematic illustration of unweighted-undirected graph of complex networks in brain. Nodes or vertices can be brain regions or voxels. Edges or links are the functional or structural connections between nodes.⁷

While static graph analysis revealed the loss of strong connections in dementia patients compared to healthy controls, the dynamic graph analysis revealed different slow modes between dementia patients and connectivity networks in healthy controls. The connectivity networks in healthy controls have smaller eigenvalues than in dementia patients for both functional and structural data and those eigenvalues remain operative. The contribution of the larger eigenvalues over time decreases quickly and the range of the eigenvalues for each subject represents an important biomarker for disease prediction.

To further contribute to the theoretical progress of the analysis of the dynamical behavior in dementia, we propose a new research avenue based on pinning controllability and selection of the best driver nodes in connectivity graphs that show a transaction from normal subjects to Alzheimer's subjects. We will address this issue by choosing a technique recently developed by Moradi Amani et al.⁸ in pinning control and apply it to the analysis of these networks.

Brain networks represent an important model for a large-scale system and its associated aspect of synchronization across many neural ensembles has been shown to play a key role in the evolution of neuro-degenerative diseases.⁹⁻¹³ Among the many research topics on brain networks, synchronization control has been of particular interest to computational neuroscience and control engineering.¹⁴⁻¹⁶ Global pinning synchronization was first studied by Wang and Chen¹⁷ in 2002, but nowadays one very interesting research initiative in this area is pinning observability of complex networks.¹⁸

The research described in this paper can be viewed as part of the ongoing interest in pinning observability applied to brain network where the nodes of the neural network are coupled linearly and diffusively. The problem considered here is the duality of the "pinning control" problem¹⁹⁻²¹ and the goal is to observe the entire state of the neural network just from information available at only a subset of nodes. This "pinning observer" problem

has been recently formulated by Yu et al.¹⁸ and the work described in this paper extends the results presented by Moradi Amani et al.⁸ by analyzing the functional (¹⁸FDG-PET) and the structural (MRI) connectivity graphs²² for CN, MCI and AD patients. By applying the new concept of "pinning observability", we observe a small number of neurons such that the states of the other neurons can be recovered. Identifying the best driver nodes - those that give the fastest synchronization to the reference state - has been a challenge in pinning control research and has been for the first time proposed by Moradi Amani et al.⁸ In the present paper, we apply this novel concept of pinning controllability to the important requirement of identifying the best driver nodes with functional (¹⁸FDG-PET) and structural (MRI) connectivity graphs²² for CN, MCI, and AD patients.

2. DETERMINING THE MOST INFLUENTIAL NODES IN PINNING CONTROLLABILITY OF CONNECTIVITY NETWORKS

We consider an undirected and unweighted network (\mathbf{V}, \mathbf{E}) with the set of N nodes (or vertices) \mathbf{V} and a set of edges \mathbf{E} . Each node is assumed to be a dynamical system with the following dynamical equation:

$$\frac{dx_i}{dt} = F(x_i) - \sigma \sum_{j=1}^N l_{ij} H x_j \quad (1)$$

where $x_i \in R_n$ is the n -dimensional state vector, $F : R_n \rightarrow R_n$ defines the individual systems dynamical equation, which is considered identical for all nodes in this paper, and σ represents unified coupling strength. $L = [l_{ij}] = D - A$ is the Laplacian matrix of the graph (\mathbf{V}, \mathbf{E}), where \mathbf{A} is the adjacency matrix and \mathbf{D} is a diagonal matrix of nodes degrees. Non-zero elements of \mathbf{H} determine the coupled elements of the oscillators. The pinning control objective is to synchronize all nodes to the following desired state (i.e. $x_1(t) = x_2(t) = \dots = x_N(t) = s(t)$):

$$\frac{d(s(t))}{dt} = F(s(t)) \quad (2)$$

In order to pin the dynamical network to this reference, the following control system should be designed:

$$\frac{dx_i}{dt} = F(x_i) - \sigma \sum_{j=1}^N l_{ij} H x_j + \beta_i u_i \quad i = 1, 2, 3, \dots, N \quad (3)$$

where u_i is the control signal and $\beta_i = 1$ for driver nodes, otherwise $\beta_i = 0$. The system can be linearized over an equilibrium point x_e as follows:

$$\frac{dz_i}{dt} = [DF(x_e) - \sigma \lambda_i H] z_i + \beta_i u_i \quad i = 1, 2, 3, \dots, N \quad (4)$$

where \mathbf{D} stands for the Jacobian, λ_i is the i^{th} eigenvalue of the Laplacian matrix of the graph. In order to find the node with the most influence on pinning controllability, we restate the following definition and lemma.⁸

Definition: For each node i of the undirected network (\mathbf{V}, \mathbf{E}), the Eigenratio Sensitivity Index (**ESI**) is defined as:

$$ESI(i) = [x_N^i]^2 \quad (5)$$

where x_N^i represents the i^{th} element of x_N , the eigenvector corresponds to the largest eigenvalue of the Laplacian matrix (λ_N).

Lemma 1: In the undirected network (\mathbf{V}, \mathbf{E}), the node with maximum ESI has the strongest influence on pinning controllability of complex network.⁸

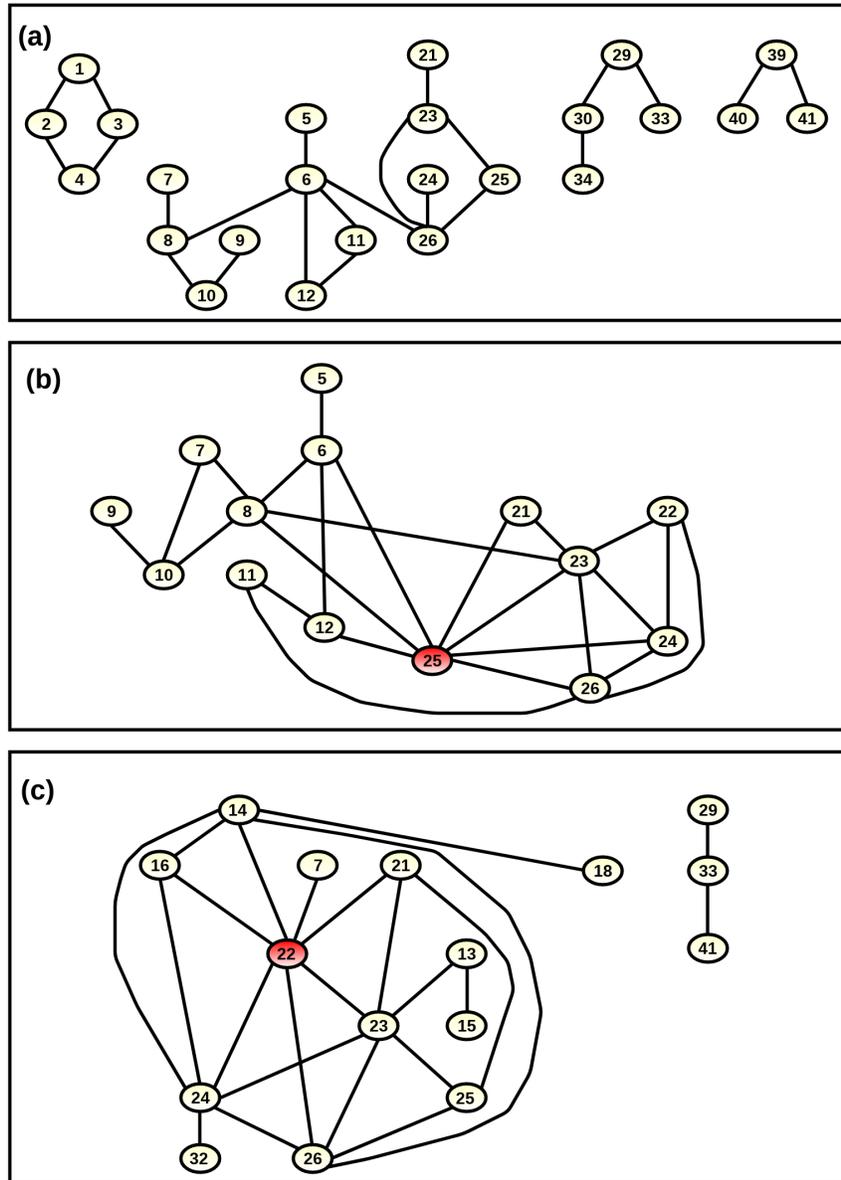


Figure 2. The most influential driver nodes (shown in red) in functional connectivity graphs for (a) CN, (b) MCI and (c) AD. Re-drawn from Ortiz et al.²²

3. LOCATION OF THE MOST INFLUENTIAL NODES IN STRUCTURAL AND FUNCTIONAL CONNECTIVITY GRAPHS

We apply the theoretical results on functional (¹⁸FDG-PET) and structural (MRI) connectivity graphs²² for CN, MCI, and AD patients. These data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI)*database. For the structural MRI data, the connections in the graph show the inter-regional covariation of gray matter volumes in different areas while for the functional PET data, the connections do not show the correlation in activity but in the glucose uptake between different regions. Ortiz et al.²² considered only 42 out

*<https://adni.loni.usc.edu/>

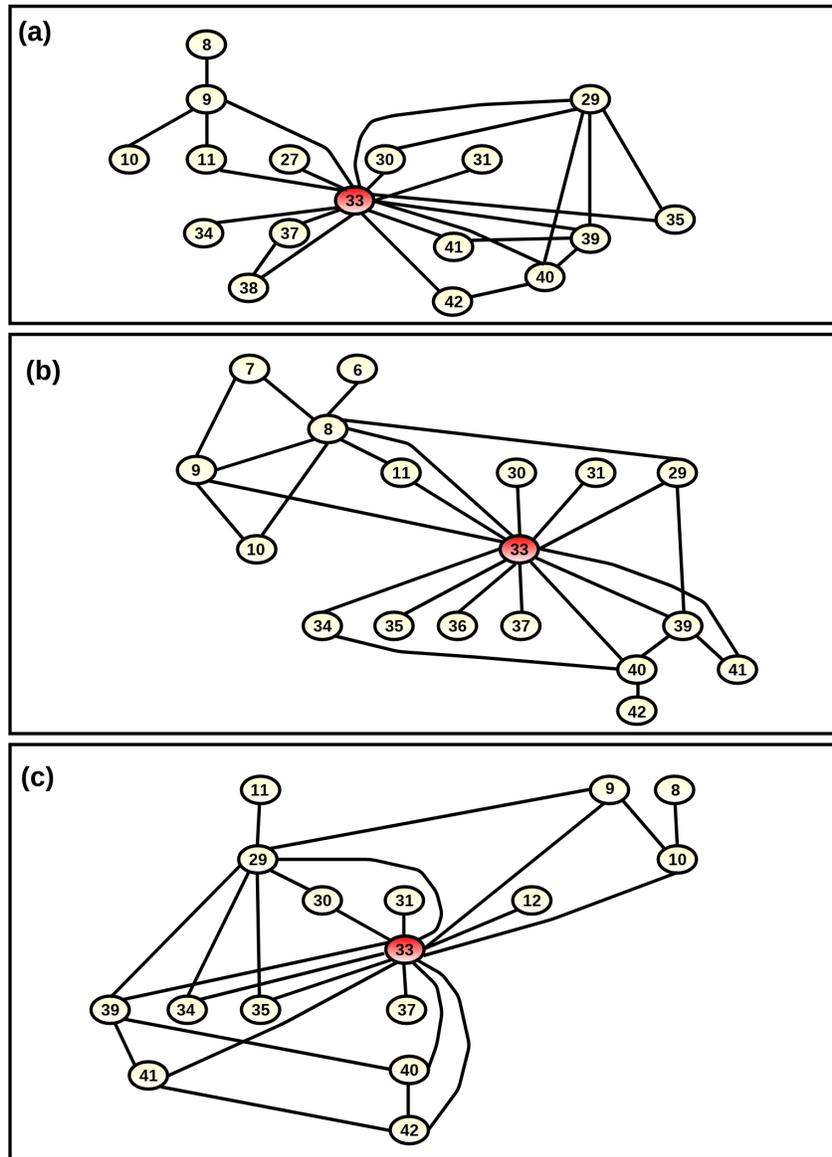


Figure 3. The most influential driver nodes (shown in red) in structural connectivity graphs for (a) CN, (b) MCI and (c) AD. Re-drawn from Ortiz et al.²²

of the 116 from the AAL in the frontal, parietal, occipital, and the temporal lobes. The nodes in the graphs represent the regions while the links show if a connection is existing between these regions or not. We have considered undirected and unweighted graphs previously presented by Ortiz et al.²² and have applied the ESI metric on these graphs. Except for the functional connectivity graph for CN, we were able to apply the ESI metric on all the other graphs. We considered the biggest connected graph in the functional connectivity graph for AD. Figure 2 shows the most influential driver nodes found on the functional connectivity graph. For CN due to the disconnectivity of the graph, we were not able to theoretically determine the best driver nodes. For MCI the best driver node is located in the inferior left occipital lobe (Occipital-Inf-L), and for AD in the superior right occipital lobe (Occipital-Sup-R). Early-onset AD is characterized by changes in the functional connectivity in the occipital lobe. Figure 3 shows the most influential driver nodes found on the structural connectivity graph.

For all three networks, we found that the most influential node is located in the temporal lobe (Temporal-Pole-Mid-L). These results are in agreement with the clinical findings which show that the MCI patients who are at risk to develop AD show medial temporal lobe atrophy. The detection of this important driver node being at the same time the most influential one may represent an important biomarker of the diagnosis of AD and its transition from MCI to AD.

4. DISCUSSION

We analyzed structural and functional connectivity graphs in normal CN, MCI and AD patients to determine the most influential driver nodes or so-called "disease epicenters". The new paradigm of pinning controllability borrowed from modern graph control theory applied to the study of the evolution of dementia is a novel and simple tool that can be used in dementia diagnosis. The location of the most influential driver node provides the scientific community with a novel biomarker that can be employed in differentiating dementia types and to monitor disease evolution. Initial results were in good agreement with preliminary clinical findings. While static graph theory shows the changes in graph measures at certain points in time and the differences between AD patient and CN, the derived results may have important implication in the discovery of relevant biomarkers leading to an improved understanding and controlling of the evolution of dementia that consequently can aid in the development of therapeutic interventions. Thus, by applying pinning controllability in disease connectivity networks, a new research path is chosen that allows to study in more detail the early-onset of AD disease and the evolution from MCI to AD by providing precise biomarkers in these patients.

5. CONCLUSIONS

This paper aims at extending the novel concept of pinning controllability under the important requirement of identifying the best driver nodes to functional ($^{18}\text{FDG-PET}$) and structural (MRI) connectivity graphs for CN, MCI, and AD patients. Data indicate:

1. The connections in the structural graphs illustrate the inter-regional covariation of gray matter volumes in different areas.
2. The connections in the functional graphs do not illustrate the correlation in activity. However, they show the correlation in the glucose uptake between different regions.
3. ESI metric has been applied on undirected and unweighted functional graphs. The biggest connected graph has been considered in the functional connectivity graph for AD. For MCI the best driver node is located in the occipital lobe (Occipital-Inf-L), and for AD also in the occipital lobe (Occipital-Sup-R). Early-onset AD can be characterized by changes in functional connectivity in the occipital lobe.
4. ESI metric has also been applied on undirected and unweighted structural graphs. For all CN, MCI, and AD networks, we have found that the most influential node was located in the temporal lobe (Temporal-Pole-Mid-L) which is in agreement with the clinical findings which show that MCI patients who are at risk to develop AD show medial temporal lobe atrophy.
5. In this paper, a novel research path is proposed to apply pinning controllability in disease connectivity networks to provide precise biomarkers for patients who suffer from Alzheimer's disease and control the dynamics of the evolution of the disease.

6. ACKNOWLEDGMENTS

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