Using Graph Theory to Identify Aberrant Hierarchical Patterns in Parkinsonian Brain Networks

Rafael Rodriguez-Rojas[1-2], Gretel Sanabria[3], Lester Melie[3], Juan-Miguel Morales[1], Maylen Carballo[1], David Garcia[4], Jose A. Obeso[4], and Maria C. Rodriguez-Oroz[4]

[1] International Centre for Neurological Restoration, Havana, Cuba
{rafael,jm,maylen.carballo}@neuro.ciren.cu
[2] "Abdus Salam" International Centre for Theoretical Physics, Trieste, Italy
[3] Cuban Neurosciences Center, Havana, Cuba
{lmelie,gretels}@cneuro.edu.cu
[4] Neuroscience Area, Applied Medical Research Centre, University of Navarra, Spain
{jobeso,dagarcia,mcoroz}@unav.es

Abstract. The topology of complex brain networks allows efficient dynamic interactions between spatially distinct regions. Neuroimaging studies have provided consistent evidence of dysfunctional connectivity among the cortical circuitry in Parkinson's disease; however, little is known about the topological properties of brain networks underlying these alterations. This paper introduces a methodology to explore aberrant changes in hierarchical patterns of nodal centrality through cortical networks, combining graph theoretical analysis and morphometric connectivity. The edges in graph were estimated by correlation analysis and thresholding between 148 nodes defined by cortical regions. Our findings demonstrated that the networks organization was disrupted in the patients with PD. We found a reconfiguration in hierarchical weighting of high degree hubs in structural networks associated with levels of cognitive decline, probably related to a system-wide compensatory mechanism. Simulated targeted attack on the network's nodes as measures of network resilience showed greater effects on information flow in advanced stages of disease.

Keywords: Brain networks, MRI, graph theory, morphometric connectivity.

1 Introduction

The human brain is considered to be one of the most complex systems in nature, structurally and functionally organized into complex and sparse networks. The topology of networks allows efficient dynamic interactions between spatially distinct brain regions, which are thought to provide the physiological basis for high-level information processing [1]. Efforts to understand its intricate wiring patterns and the way these give rise to normal functioning and connectivity abnormalities in neurological and psychiatric disorders, is one of the most challenging areas in modern science.

The mathematical framework of Graph Theory provides powerful tools to deal with intrinsic complexity of brain systems, allowing the extraction of global metrics

J. Ruiz-Shulcloper and G. Sanniti di Baja (Eds.): CIARP 2013, Part II, LNCS 8259, pp. 134–141, 2013.

that capture various aspects of the network's topological organization. However, graph theoretical approaches in neurosciences deals with large and complex neural systems that have revealed non-random but small-world architectures, providing regional specialization with more efficient rates of information transfer [1-3]. This hypothesis has been supported in structural and functional human brain networks studies, over a wide range of scales in space and time.

Small-world networks are characterized by the existence of a small number of nodes with higher connectivity degree, referred to as hub-nodes. Hubs are suggested to play an important role in the overall network organization and can be defined several possible measures of centrality, including degree (number of edges) and betweenness centrality [1]. Detecting hub-regions in a network helps to identify relevant structures subserving specific roles such as motor and cognitive processing, thus providing a link between structure and function [4]. Progress in Graph Theory, combined with advanced neuroimaging techniques like Magnetic Resonance Imaging (MRI), allow us to quantify topological properties of brain systems like basal ganglia – thalamus – cortical circuitry and disturbed functioning that give rise to movement disorders such as Parkinson's disease (PD). Previous functional brain network studies have demonstrated disruption of several large scale brain systems in PD [5-7]. Up to know remains unclear how the affected modular organization of brain network underlies motor and cognitive impairment in PD.

Morphometric-based connectivity has been recently introduced as a measure of structural association between brain regions [8-10]. This concept is defined as the covariance between two anatomical brain areas. Structural networks can then be constructed from morphometric correlations of anatomical metrics like cortical volume, thickness, and surface area. In the present study, we constructed structural networks using average cortical thickness of atlas-based regions, to explore the characteristics of the cortical networks in PD across subgroups at different stages of cognitive impairment, compared to healthy subjects. For the first time we applied graph theoretical approaches to investigate alterations in large-scale morphological brain networks, nodal centrality and network robustness in this neurological pathology.

2 Methods

2.1 Patients and Controls

This research was approved by the Ethics Committee for Medical Research at the Clinica Universidad de Navarra in Spain. All patients provided their written informed consent. All the participants underwent a neuro-psychological assessment, including the Mini-Mental State Examination (MMSE) for global cognitive functions and UPDRS-III scale for motor disabilities. Demographic and clinical data for the study groups are given in Table 1. PD patients were classified in three groups according to cognitive performance: cognitively normal (PDCN); PD with mild cognitive impairment (PDMCI), based on MCI criteria [11]; and with dementia (PDD), based on the DSM-IV-TR manual of mental disorders [12].

Table 1. Demographic and clinical characteristics of the study participants

	HC	PDMCI	PDCN	PDD	test
No.	20	22	28	18	
Sex (M/F)	11/9	15/7	15/13	7/11	N.S[a]
UPDRS III	N.A	32.3±8.5	35.0±12.2	50.0±10.0	P < 0.01[b]
MMSE	29.2±1.1	29.0±1.4	26.4±2.6	18.3±3.8	P < 0.001[b]

N.S: no significant; [a]Chi-square test; [b]Oneway analysis of variance

2.2 MRI Acquisition and Cortical Thickness Measurement

MRI examinations were performed on a 1.5 T Magnetom Symphony scanner (Siemens, Erlangen, Germany). All subjects were investigated with a whole brain T1-weighted coronal oriented Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (repetition time TR = 13 ms; echo time TE = 10 ms; inversion time TI= 1100 ms; flip angle =15; 1 mm isotropic resolution; slice gap = 0 mm). Head motion was minimized with restraining foam pads provided by the manufacturer.

Reformatted T1-weighted MR images were processed using Freesurfer 5.0.0 software package (Massachusetts General Hospital, Harvard Medical School; freely available at http://surfer.nmr.mgh.harvard.edu). Figure 1 (1 to 4) summarizes Freesurfer pipeline, whose technical details have been previously described [13]. After segmentation into gray and white matter, the gray/white and the gray/pial interfaces were tessellated and labelled according to Destrieux sulcogyral-based atlas, which includes 74 regions per brain hemisphere [14]. Cortical thickness, defined as the shortest distance between white and corresponding pial surfaces, was computed for every region. A linear regression was performed at every region to remove the effects of age, gender, age–gender interaction, and mean cortical thickness. The residuals of this regression were then substituted for the raw cortical thickness values.

2.3 Graph Theoretical Approaches

The morphometric network is modeled as an undirected graph, $G_{brain} = [N, W]$ (figure 1.5). N is a set of n=148 nodes determined by the anatomical parcellation and represents the voxels having a non-zero probability of belonging to the cortical tissue. W is the set of w_{ij} edges between each pair of regions i and j. We computed w_{ij} values as the Pearson's product-moment correlation coefficient in corrected thickness values across subjects, removing the influence of all other regions $n \neq (i, j)$. This resulted in a pair of {74 x 74} correlation matrices. Pearson's correlation was adopted instead of partial correlation analysis because the number of nodes exceeds the number of patients. Unweighted binary graphs were generated by thresholding the w_{ij} values based upon the significance of the correlations. Bootstrapping samples (Nboot = 300 samples) of the connectivity matrix were obtained by selecting a random subset of the total number of subjects with replacement to compute the correlation coefficient.

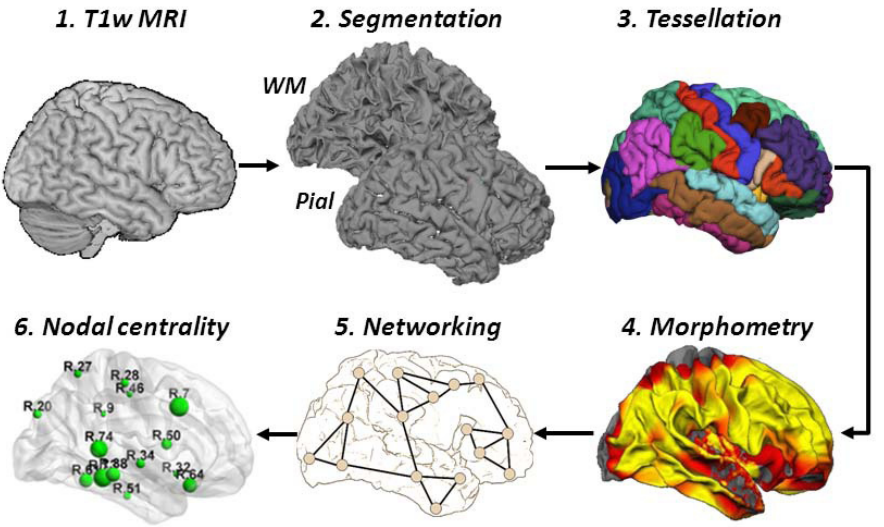

Fig. 1. Pipeline for morphometric-based graph analysis. 1. Acquisition of T1-weighted high resolution MRI; 2. Surface-based segmentation; 3. Atlas-based tessellation and labeling; 4. Calculation of corrected cortical thickness; 5. Schematic representation of the brain network in the form of a graph; 6 Definition of higher-degree connector hubs.

2.4 Nodal Centrality and Network Robustness

The shortest path d_{ij} between any two vertices i and j is defined as the number of edges along the geodesic length connecting them [3]. Degree centrality of a given node $n(i)$ is defined as the number of edges incident to the node. The 'betweenness centrality' $B(i)$ of a $n(i)$ is a global centrality measure of the influence of a node over information flow between other nodes in the network [3]. We measured the normalized betweenness as:

$$B(i) = \Sigma_{j \neq k} \{ n_{jk}(i) / n_{jk} \} \quad (1)$$

where n_{jk} is the number of shortest paths connecting j and k, and $n_{jk}(i)$ is the number of these paths passing through i. The hubs are the regions with higher values of $B(i)$ as seen in figure 1.6. To test differences between groups a nonparametric Kruskal Wallis (KW) statistical test was used, with Bonferroni correction for multiple comparisons.

Small-world networks show a high robustness to random failure of nodes, but are known to be vulnerable to target attack on the hubs [1]. A fault in the system is the removal of any n nodes and all edges connected to these nodes from G_{brain}. To evaluate the attack tolerance of each of the four networks, we removed the nodes and edges from the graph in decreasing order of their betweenness and then measured the changes in the size of the largest connected component.

3 Results

3.1 Nodal Characteristics

Figure 2 shows the strongest hubs in the four sets of undirected graphs, corresponded to healthy volunteers and patients with different levels of cognitive decline. In the control group, regions with $B(i) > 2$ (meaning that these hub regions have at least 2 times the network's average betweenness centrality) included right primary sensorimotor and posterior cingulate areas, and associative temporal regions. Compared with controls, the PD patients showed significant centrality decreases in primary motor cortex, while increases in associative and limbic frontal and occipito-temporal areas are observed (KW test, $p<0.01$). PDD's hubs were predominant in the occipital and parietal regions, with tendency to lose involvement of fronto-temporal areas. Nomenclature of human cortical gyri and sulci can be found in Destrieux et al [14]. Full list of anatomical regions with respective betweenness centrality values are available under request.

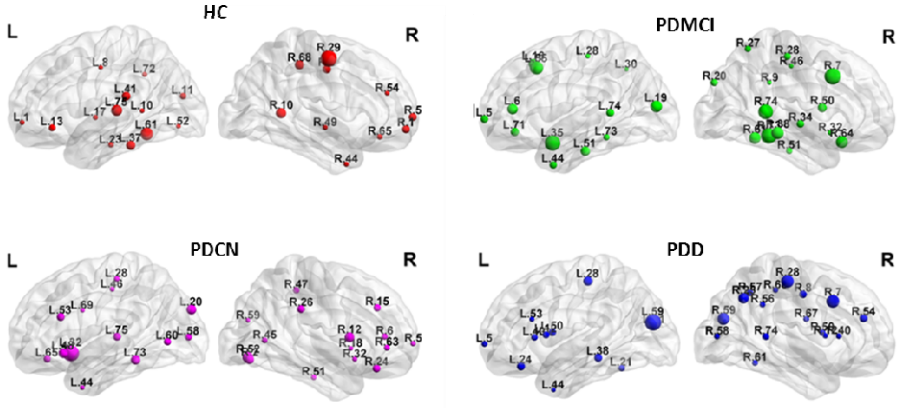

Fig. 2. The structural network cores for each group. Size of spheres indicates normalized betweenness centrality values of each region.

3.2 Reduced Network Robustness in PD

We find that the deletion of connector hubs have distinctly effects on the small-world attributes as a consequence of pathological stages. Figure 3 shows the networks robustness in response to the targeted attack. PDD group was considerably more vulnerable to hubs deletion, with reduction of the largest connected component when at least 15% of the most central nodes and links were removed, and remains noticeably reduced for all thresholds. The structural networks of patients without dementia (PDCN and PDMCI) were as robust as that of controls until the 57% of the most central nodes were attacked. In the range when 57 to approximately 70% of nodes are deleted, these three networks show a cross-linked behavior against attacks. Since that sparsity threshold, resilience to targeted failures are consistent with cognitive decline (HC > PDCN > PDMCI > PDD).

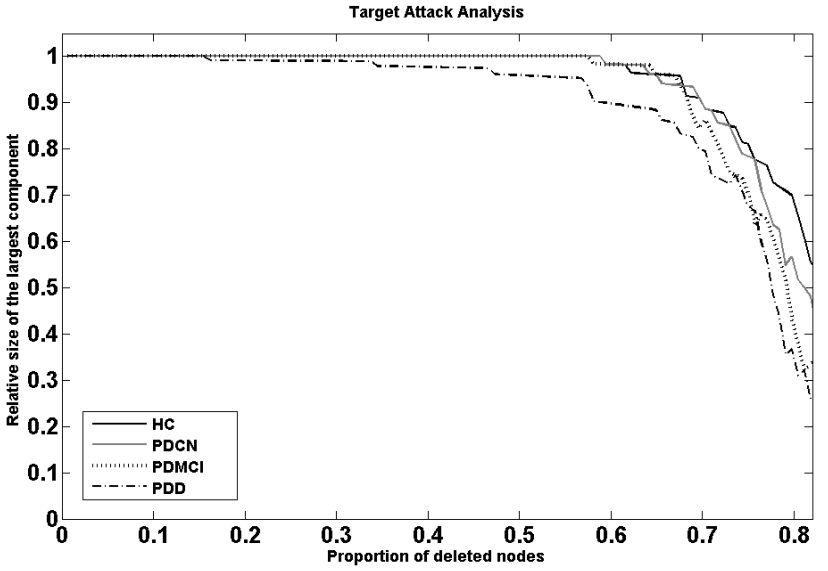

Fig. 3. The graph shows the largest component size of the networks for every group as a function of sparsity threshold. As the proportion of removed nodes increases, the largest component sizes of all groups tend to decrease. The arrow indicates the lowest sparsity threshold (15%) in which all the networks included all connected nodes.

4 Discussion

To our knowledge, this is the first time that graph theory is used to explore the morphological networks in PD and its relation with cognitive decline. We have considered the hypothesis that these covariation patterns reveal information about the dynamics of the brain networks in response to degenerative processes in PD. We have also modeled the vulnerability to targeted attack on the network's hubs in relation to cortical thinning and cognitive impairment.

4.1 Altered Nodal Centrality

Our results point out the degree and distribution of network's hubs as possible biological markers of deficits in cognitive and behavioral functions in PD. The loss of integrative capacities of the precentral regions may reflect altered output through basal ganglia-thalamo-cortical loops, which is consubstantial with PD [15]. The selective damage to high-degree hubs in structural networks should have an outsized impact on the capacity of the network for efficient high-level processing. This could explain the early emergence of motor and cognitive symptoms in the course of PD. During the course to more advanced phases of cognitive impairment, clustering of connector hubs shift to posterior parietal, temporal and occipital regions, including visual and auditory cortices, and to associative and limbic frontal areas (figure 2). This observation fits with the heavy reliance of PD patients on sensory modalities to guide their

actions. Such reconfiguration leads us to speculate that alteration in degree centrality across the brain circuitry may be indicative of system wide compensatory mechanism, in response to the basal ganglia altered output arising from imbalances of dopamine.

In terms of network dynamics, the shift in *B(i)* suggests a reordering in the control of flow of information. However, it is difficult to differentiate between changes resulting from the disease itself as opposed to those that arise as part of a compensatory response. On the other hand, betweenness only takes into account shortest edges, while long range network connections also contribute to global communication patterns. Future studies are necessary to address network-wide integration and its effect over network's efficiency. Our results are in line with recent studies suggesting reduced sensorimotor connectivity and increased functional connectivity in associative and limbic circuits in PD [5-7, 16].

4.2 Topological Vulnerability in PD

Measures of network resilience may be computationally simulated by targeted attack on the network highest-degree nodes. The vulnerability of the network in different stages of disease may then be quantified by comparing its topological or dynamical behavior after the "lesioning". Our observations suggest that pathological attacks on high-centrality nodes have greater effects on information flow in advanced stages of PD than attacks on early phases and healthy controls. These results are consistent with recent inferences about the association between disease stages and thinning of core prefrontal, cingulate, temporal and parieto-occipital regions in PD [17]. More importantly, graphs corresponding to normal or middle cognitive impairment show a tendency to recover resilience capacity after an attack to a high percent of connector hubs, similar to healthy controls. Therefore, this PD related changes in centrality parameters may reflect a less optimal reconfiguration in hierarchical network topology in response to alteration of primary motor and cognitive circuits. Thus, topological organization of network's hubs could provide associations for the understanding of the relationship between network topology and neuropathological state of disease.

5 Conclusions

In the present paper we have shown that combining graph theory and MRI data allows studying the organizational properties of the morphological networks in Parkinson Disease at different stages of cognitive decline. This approach should yield more comprehensive understanding of how structural disruptions in the brain network architecture are associated with functional deficits in PD. Our findings are compatible with the notion that cognitive impairment in PD is associated with disruptions in the integrity of large-scale interconnected brain systems. The graph theory analysis also provides a new way to understand the pathophysiology of specific functional deficits and, possibly, to evaluate disease progression. In a near future, the combination of functional and morphometric-based connectivity in a graph theory framework could explain the nature of dynamical processes taking place on the parkinsonian networks, as well as the causality between network topology and network dynamics.

References

1. Bullmore, E., Sporns, O.: The economy of brain network organization. Nat. Rev. Neurosci. 13, 336–349 (2013)
2. He, Y., Evans, A.: Graph theoretical modeling of brain connectivity. Curr. Opin. Neurol. 23, 341–350 (2010)
3. Stam, C., Reijneveld, J.: Graph theoretical analysis of complex networks in the brain. Nonlinear Biomedical Physics 1, 3 (2007)
4. Fortunato, S., Barthelemy, M.: Resolution limit in community detection. Proc. Natl. Acad. Sci. USA 104, 36–41 (2007)
5. Tessitore, A., Esposito, F., Vitale, C., Santangelo, G., Amboni, M., Russo, A., Corbo, D., Cirillo, G., Barone, P., Tedeschi, G.: Default-mode network connectivity in cognitively unimpaired patients with Parkinson disease. Neurology 79, 2226–2232 (2012)
6. Wu, T., Long, X., Wang, L., Hallett, M., Zang, Y., Li, K., Chan, P.: Functional connectivity of cortical motor areas in the resting state in Parkinson's disease. Hum. Brain Mapp. 32, 1443–1457 (2011)
7. Stoffers, D., Bosboom, J.L., Deijen, J.B., Wolters, E.C., Stam, C.J., Berendse, H.W.: Increased cortico-cortical functional connectivity in early-stage Parkinson's disease: An MEG study. Neuroimage 41, 212–222 (2008)
8. He, Y., Chen, Z., Evans, A.: Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. Cerebral Cortex 17, 2407–2419 (2007)
9. Sanabria-Diaz, G., Melie-Garcia, L., Iturria, Y., Aleman, Y., Hernandez, G., Valdes, L., Galan, L., Valdes-Sosa, P.: Surface area and cortical thickness descriptors reveal different attributes of the structural human brain networks. Neuroimage 50, 1497–1510 (2010)
10. Yao, Z., Zhang, Y., Lin, L., Zhou, Y., Xu, C., Jiang, T.: Abnormal cortical networks in mild cognitive impairment and Alzheimer's disease. PLoS Comput. Biol. 6, e1001006 (2013)
11. Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.: Mild cognitive impairment- beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J. Intern. Med. 256, 240–246 (2004)
12. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, Washington, DC (1994)
13. Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.: Automatically parcellating the human cerebral cortex. Cereb Cortex 14, 11–22 (2004)
14. Destrieux, C., Fischl, B., Dale, A., Halgren, E.: Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. Neuroimage 53, 1–15 (2010)
15. Obeso, J.A., Rodriguez-Oroz, M.C., Benitez-Temino, B., Blesa, F.J., Guridi, J., Marin, C., Rodriguez, M.: Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease. Mov. Disord. 23, S548–S559 (2008)
16. Sharman, M., Valabregue, R., Perlbarg, V., Marrakchi-Kacem, L., Vidailhet, M., Benali, H., Brice, A., Lehericy, S.: Parkinson's Disease Patients Show Reduced Cortical-Subcortical Sensorimotor Connectivity. Movement Disorders 28, 447–454 (2013)
17. Zarei, M., Ibarretxe, N., Compta, Y., Hough, M., Junque, C., Bargallo, N., Tolosa, E., Martí, M.J.: Cortical thinning is associated with disease stages and dementia in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 84, 875–881 (2013)