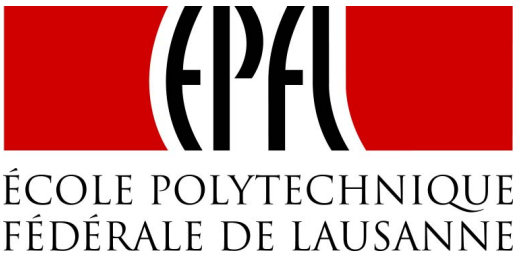

École Polytechnique Fédérale de Lausanne

A Network Tour of Data Science

An exploratory study on the brain *dysconnectome*

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Contents

1 Introduction

Brain imaging and Connectomics: Building a brain network
Neuroimaging techniques represent a non-invasive way to explore brain organization and the interactions between different regions that are functionally specific. In particular, diffusion-weighted imaging techniques and tractography algorithms estimate and characterize the white matter tracts connecting different brain regions. The segmentation into regions and the tracts estimations constitute the brain connectome [1]. The latter is a representation of the human brain as a network in which the nodes are the brain regions and the edges the structural weights estimated on the tracts connecting the regions. The healthy human brain connectome has already been described in the literature and shows specific properties such as rich-club organization [2] and a high small-worldness [3]. On the other hand, the investigation on topological properties of 'disturbed' brain networks has not yet been studied as extensively.

Investigating the brain networks with brain lesions
The brain network can be disrupted following an accident such as a blood vessel obstruction or rupture, both leading to a low blood perfusion of brain areas that eventually die. An example of such accident is a stroke. The created lesions will affect the connectome and will be the cause of evident impairments. The stroke lesion is usually located in a local well defined brain area and restricted to one of the two hemispheres. Until now, the analysis of single-brain lesions has been used in clinical neurology for the localization of brain areas responsible of specific neurological symptoms and behavior. Indeed, this traditional approach allows to localize an area in charge of a specific brain function (and therefore dysfunction), disturbed after the lesion appearance. However, this type of approach can sometimes be flawed because similar symptoms can result from lesions in different brain locations [4]. To overcome this limitation, the relationship between symptoms and behaviors can be further investigated at the whole brain level using the human brain connectome and graph networks tools.

With this project, we aim at exploring the following topics and answering some related research questions and particularly the two following ones:

Characterization of the brain lesion at a network-level - Does a damaged subnetwork affect the global topological brain organization?
The brain lesion can be described as a subnetwork of the connectome, namely the 'dysconnectome'. The latter is based on the original connectome, but it only has the nodes and tracts belonging to the lesion. By investigating the topological properties of these specific subnetworks we may understand their role in the whole brain network. Moreover, using the brain connectome, we could infer whether lesions that are in different sites, but results in similar symptoms are located within the same brain network. This last consideration is supported by the fact that it was shown that lesions causing the greatest number of symptoms lie at the intersection of large white-matter pathways and on hubs that are functionally connected to a large number of brain regions,

Longitudinal study - Can we make inferences on brain reorganization and related clinical improvements from the acute to the chronic phase in stroke patients?
After an accident, such as stroke, the brain undergoes a period of high plasticity where it is able to reorganize itself to try to compensate for the loss of some regions and thus, functions. This reorganization occurs both naturally as well as in response to (motor) learning through rehabilitation. The high plasticity window *closes* after a few months and this represents the begging of the chronic phase. Reorganization is often related to clinical improvement, such as the motor one. We expect that topological network features will reflect the reorganization mechanisms. Moreover, the knowledge on these features and the definition of networks biomarkers could help in predicting recovery, classifying patients and could even support the development of personalized treatments.

2 Methods

2.1 Dataset

In this work we used the whole brain structural connectomes of 62 stroke patients retrieved at 3 weeks and 3 months after stroke occurrence. The connectomes were generated from structural MR images on which a parcellation was applied resulting in 333 cortical and subcortical areas of interest. The structural connectivity was calculated using the mean Fractional Anisotropy (FA) from diffusion images. FA characterizes the white matter integrity. In addition to the connectomes, we also used their respective dysconnectomes, which describe

the disconnected white matter tracts. They were generated from the connectome by only taking as connections those overlapping the lesion mask. Their weights were computed as the sum of points of each weighted streamline going through the lesion.
Moreover, for each subject we had additional information such as their Fugl-Meyer Assesment (FMA) score in both time points (this is an index of motor ability of the upper-limb, widely used to assess stroke patients [5]). In addition, as we knew their lesion location, we could divide them into groups accordingly: 3 subjects had a *Peri-insular* lesion, 16 had it in the *Striatum capsula*, 12 in the *Corona radiata* and 13 in the *Pons*. The remaining 19 patients were grouped as having *other lesions*.

2.2 Dysconnectome properties

With the dysconnectome we introduce a novel method to quantitatively describe the impact of the individual stroke lesion on the whole brain connectome by measuring disconnected white matter pathways.

2.2.1 Dysconnectome and its orders

In addition to the idea of dysconnectome itself, another novelty derives from the concept of disconnection of higher orders, which tries to investigate how the lesion spreads within the network. It has been taken as definition of "lesioned edge" a link which has a positive weight in the matrix D (dysconnectome) and as "lesioned nodes" all the nodes in D adjacent to the lesioned edges. We designed an algorithm, the "kOrderDysconnectome", which by taking as input the binarized adjacency matrices C (connectome) and D (dysconnectome) and the order K, returns as output the matrix D_k. The latter has as many 1s as are the "lesioned edges" and has as many -2s as are the edges in C which start from the damaged nodes and arrive in non-lesioned ones. These last edges are therefore called second-order edges. We can continue to third and fourth order n the same manner.

An example a brain with nodes belonging to different dysconnectome orders can be seen in Fig.1.

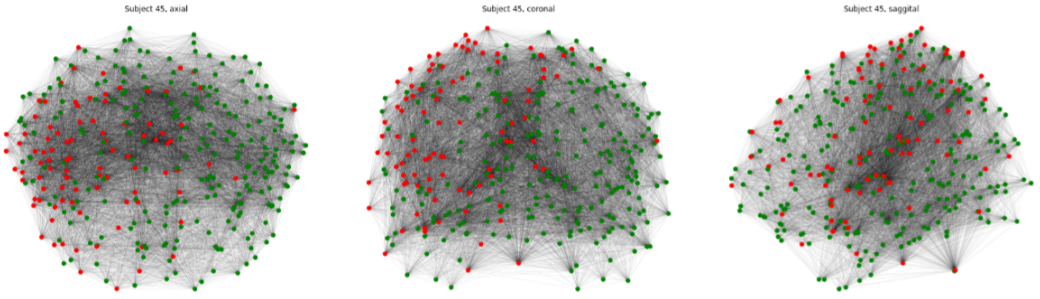


Figure 1: Dysconnectome orders: 3 views of the brain (axial, coronal and sagittal) where the lesioned nodes (first-order dysconnectome) are shown in red, and the nodes of the second-order dysconnectome in green. In this example, when combining first and second order dysconnectom we already retrieve the full connectome.

2.2.2 Network properties

In the first part of this project, we investigate the topological properties of the dysconnectomes. In order to assess the statistical significance of the different network metrics evaluated, we designed a random model distribution to compare them with. This approach of generating random networks is used as part of a nonparametric Monte Carlo sampling test. More specifically, for each subject, 100 surrogate dysconnectomes are defined (a larger number will be used in future work). Each one of these surrogates is created by randomly sampling n from the subject's connectome, where n is the number of edges in the original dysconnectome. This random model has the same density as the original network and partly preserves the topological inherent structure from the connectome. The idea of this testing is to understand whether the topological features observed in the dysconnectome are a mere effect of subsampling the connectome or are intrinsic to the specific localization of the stroke lesion. The measures assessed here were network degree distribution, betweenness centrality, average neighbor degree, closeness centrality, eigenvector centrality, load centrality, clustering coefficient, core number, and the Page Rank index, using a Python package for the study of complex networks [6].
In addition, we computed the density for the first two orders of dysconnectomes as a preliminary study in this direction. We explore the relationship of the network measures with the clinical scores.

2.3 Longitudinal Study

The second part of the project aimed at identifying longitudinal differences in the brain networks (connectome and dysconnectome) both in single-subject as well as in subject-groups terms. In this exploratory step, we wanted to see how the lesion impacts the *healthy* connectome (computed as original, full connectome minus the dysconnectome, and from now on referred to as healthy) and if there are analogies in the way brains reorganize if they have comparable lesions. Similarly to before, our final goal was to correlate structural changes to clinical improvement. In particular, the clinical improvement was computed as:

$$\text{proportional clinical improvement} = \frac{FMA_{chronic} - FMA_{acute}}{FMA_{max} - FMA_{acute}} \tag{1}$$

For this analysis we looked at the changes in the following structural properties between acute and chronic phase for both the healthy connectomes and the dysconnectomes: number of new edges and nodes, density, small-worldness, efficiency and degree normalized by the average degree (this was done to take into account the different sizes of connectome and dysconnectome).
Furthermore, we used the results of the above analysis divided into time points to investigate how the lesion impacts the rest of the brain network. In addition, we looked at the evolution of the hubs and of the regions where the highest differences were observed.

3 Results

3.1 Correlation between dysconnectome and clinical scores

To quantify the direct impact of the lesion on the symptoms, we compared the topological network properties of the lesion to the clinical scores of the patients. For each subject, we correlated the averaged values of the topological features with the clinical scores (Figures 3 and 4). The density of the dysconnectomes correlate with the lesion volume (r=0.91, p=3e-23) (Figure 3) for the two orders of the dysconnectome: a big volume of lesion affects more edges. The density values have a negative association with the clinical scores FMA (r=-0.28,p=0.046 and r=-0.36, p=0.011) (Figure 3). Regarding the network measures, measures of centrality such as the betweenness centrality and the closeness centrality values correlate with the lesion volume in the acute phase (r=-0.37,p=0.028 and r=0.71, p=5e-10) (Figure 4) . When the lesion volume increases, the average betweenness centrality of the dysconnectome decreases and its average closeness centrality increases. It suggest that when the lesion volume increases, the regions of the dysconnectome becomes in average less central. Closeness centrality correlates with the clinical scores: (r=-0.31,p=0.039) with FMUE tc and (r=-0.27,p=0.048) with the percentage of recovery. These results suggest that the topological network properties, and in particular the closeness centrality of the nodes affected by the lesion, are associated to the clinical scores. The centrality of the regions within the brain lesion seem to be a key factor for explaining the clinical scores.
A further analysis was carried out to investigate the relationship between the density of the first two orders of dysconnectome, smallwordness and efficiency with the classification of patients according to whether they are fitters or non-fitters of the Prabhakaran model [7]. The aim was to identify the clinical characteristics of those patients who do not show the expected amount of motor recovery. In the first frame of the Fig. 2 we can see a

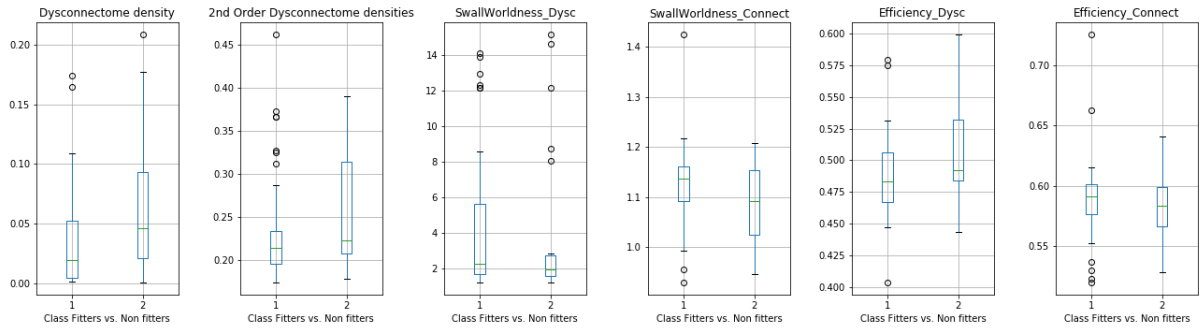


Figure 2: Structural properties of dysconnectome in relation to fitter and non-fitters patients.

statistically significant difference between the densities of the dysconnectomes of the fitters versus those of the non-fitters, with way more variability in the non-fitters as expected. As we also expected for both-fitters and

non-fitters we notice on average an increase in the densities at the transition from the first to the second order of dysconnections. Interesting properties are in the third and forth frames, where it seems that the fitters are more smallworldish, suggesting a better structural organization.

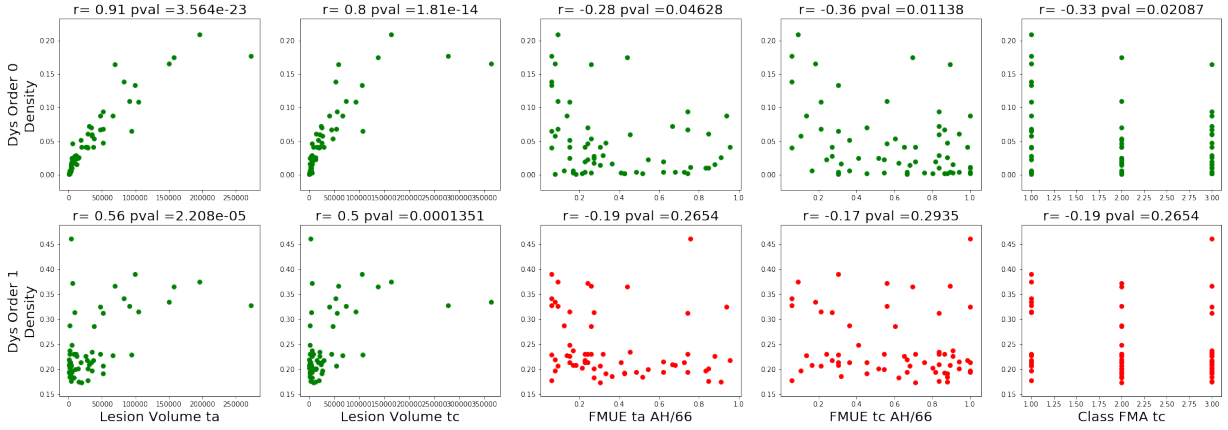


Figure 3: Correlation between the density of 1st and 2nd order dysconnectomes with the clinical scores

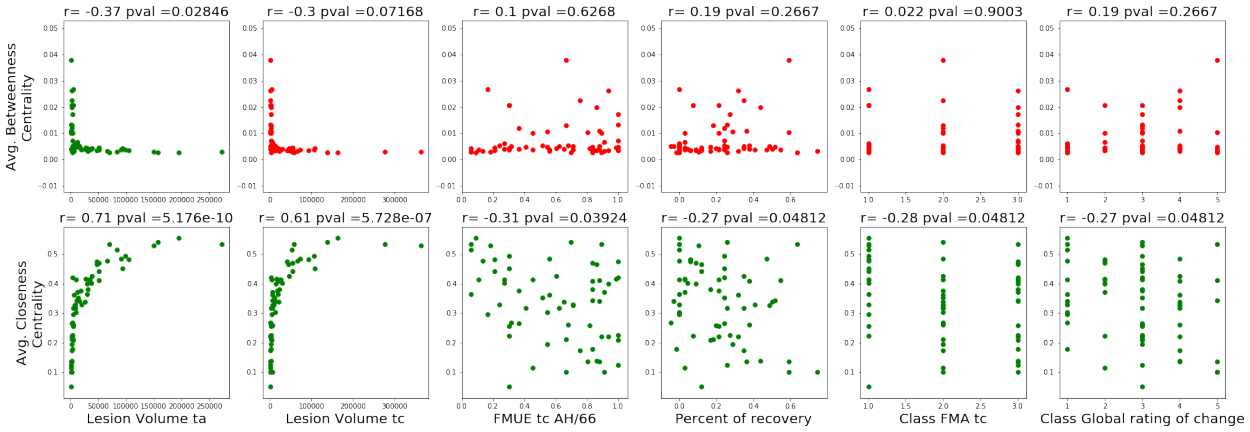


Figure 4: Correlation between centrality measures of the dysconnectomes with the clinical scores

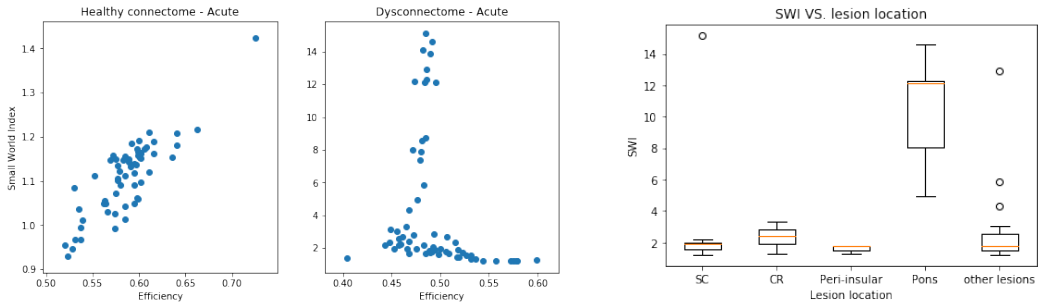
In the line of thinking of dysconnectome small-worldness, we do not find a linear correlation with efficiency (Fig. 5(a)) unlike we can be found in healthy connectomes. Indeed, from the graph we can see that for a constant efficiency, many dysconnectomes have very high small-worldness indexes. Interestingly, by dividing the subjects into groups, we found that subjects having a lesion in the Pons are the only ones presenting this behaviour (Fig. 5(b)). Also, it must be noted that 70% of these subjects were fitters.

3.2 Impact of the lesion on the connectome

To evaluate the impact of the lesion on the healthy connectome, we looked at how its structural properties differed from those of the original connectome. This choice was made since the latter may be considered as a "normal" connectome in the acute phase. There was a significant decrease in density, small-worldness and efficiency, but a significant increase in average degree. In terms of hubs location, there was never a perfect overlap between the networks, and the percentage of positive overlap decreased with time. Indeed, the number of overlapping hubs of the dysconnectome with the connectome was much smaller compared to the overlapping hubs of the healthy connectome, and for the former there was no significant difference in time.

3.3 Longitudinal changes

The next evaluations looked at the differences in structural analysis between chronic and acute graphs for dysconnectomes and healthy connectomes only. The first very basic analyses based on the average change of



(a) SWI over efficiency

(b) SWI for different lesion location

Figure 5: Small-worldness index behavior in the dysconnectome and its relation to lesion location

weighted degree showed that across subjects and nodes there is an overall difference of 5% and a net loss of 2% of connections compared to the initial number of edges. Along the same line we did not see a relevant difference in either the density, the small-world index nor the efficiency in neither graph.

Although the initial analyses suggested small changes on the whole-networks, we were still interested in understanding where they were occurring. For both graphs we found a change in some of the hubs location in time; nonetheless the biggest change in degree did not happen there. In the healthy connectome, the maximal loss or increase in degree was spread over the nodes and over both hemispheres. Moreover, no specific behavior in reorganization was seen in the group analysis. Conversely, the dysconnectome resulted to be more stable in time. First of all the hubs were more constant. Secondly, the maximal changes in degree were observed over the same areas across subjects. These areas were the Thalamus, the Putamen, the Pallidus and the Hippocampus belonging to the controlateral hemisphere (i.e. the one not affected by the lesion). When we grouped the subjects according to their lesion, we found that patients with a Pons lesion had more consistent changes within the group.
From this longitudinal study, we were not able to find any relationship between changes in structural metrics and the clinical improvement computed as in 1.

4 Discussion and conclusion

Evolution of brain networks after stroke
From our analyses we were not able to see significant changes in the connectomes in time. Indeed, the relocation of some hubs, may be an index of brain reorganization; however, because the other topological features remained constant in time the change we are observing may be due to some false positives or may indicate a minor change. Indeed, as referenced in the literature, it has been shown that brain reorganizations occur with functional networks [8] but not yet with structural. In functional brain networks, the edges are computed as the correlation between the hemodynamic signals of the different brain regions. Therefore, changes in functional networks and not in structural ones may suggest that restoring alterations in the white matter tracts require more time (here we only see after 3 months) because of the underlying biological processes. Moreover, a functional reorganization could reflect an adaptive mechanism of using already existing structural rather than developing new- or restoring disrupted structural pathways.

Future work
In further analyses, the topological biomarkers (closeness centrality of nodes affected by the lesion) identified with our preliminary work, as well as the analysis on the dysconnectome and its orders, could be used to classify patients into different stages and help predicting their recovery expectations in the following months. Moreover, a deeper investigation is needed on the patients having a lesion in the Pons as they have shown throughout the analyses some peculiar properties, often not shared by the others subjects.

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