

SUPPLEMENTARY MATERIAL

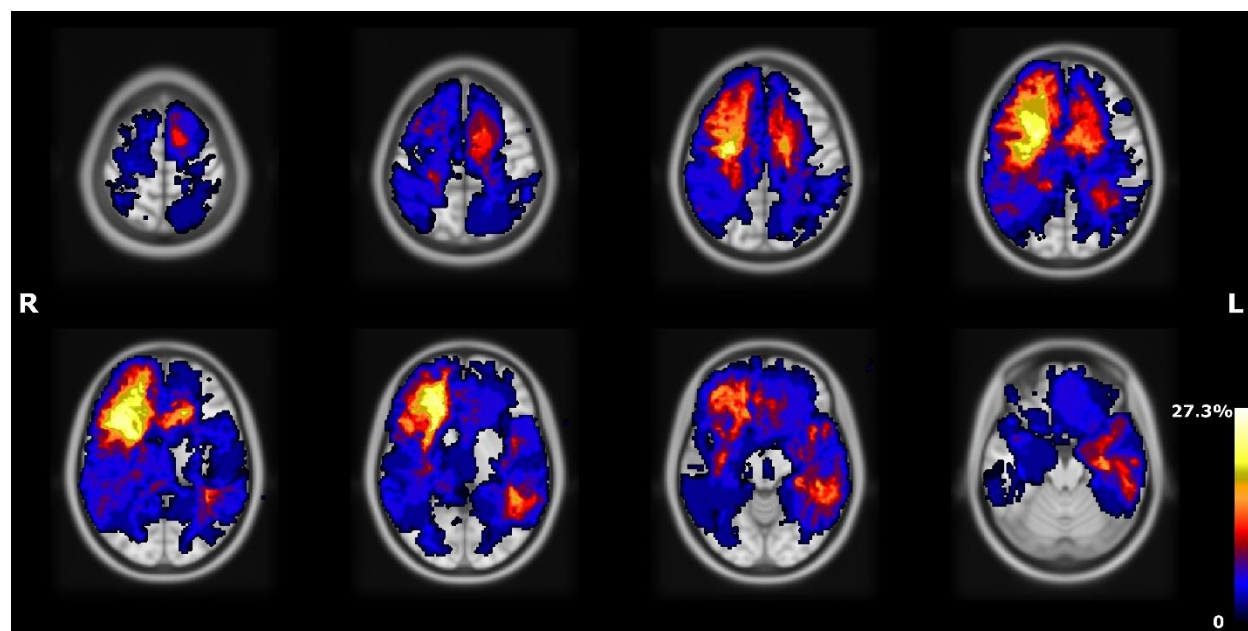
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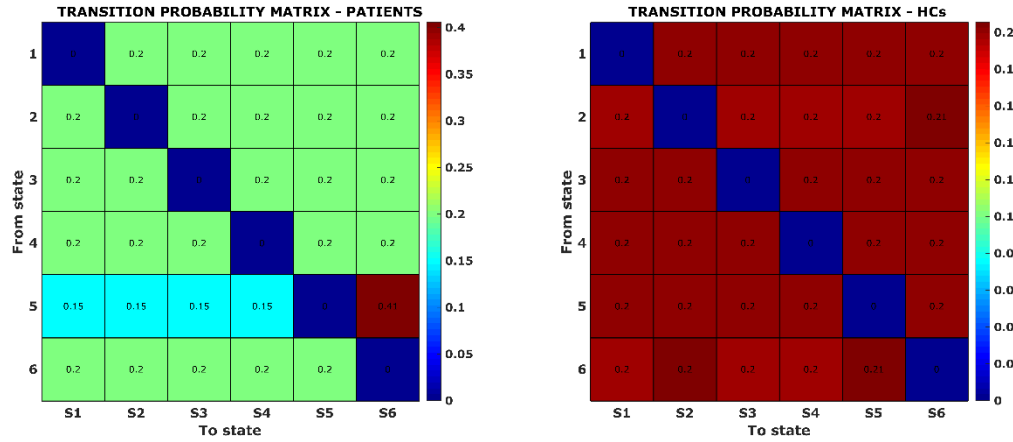
PATIENT ID	AGE	GENDER	HISTOLOGY	IDH1	HEMI	LOBE	T+O VOLUME [cm³]	T VOLUME [cm³]
1	74	M	Diffuse glioneuronal tumour	\	L	T	30	5
2	43	M	Glioblastoma	WT	L	F	81.1	0.4
3	69	M	Glioblastoma	WT	L	T	70.1	66.2
4	67	F	Glioblastoma	WT	L	P	19.4	6.7
5	36	M	Glioblastoma	WT	B	F- CC	128.9	51.4
6	58	F	Glioblastoma	WT	R	F-insular +splenium CC + P-O	76	73.9
7	83	F	Glioblastoma epithelial	WT	L	F-P	60.8	36.6
8	42	M	Glioblastoma	mutant	R	F	139.2	123
9	56	M	Glioblastoma	mutant	L	F	127	88.8
10	32	F	Glioblastoma	WT	R	Thalamic	78.3	53.3
11	64	M	Glioblastoma	WT	B	F-insular + CC	67.9	54
12	75	F	Glioblastoma	WT	L	T	80.4	8.1
13	68	M	Glioblastoma	WT	B	F-T- insular+ cingulate cortex+ splenium CC	134.2	127.5
14	48	F	Glioblastoma	WT	R	T + optic tract	56.4	53.4
15	64	F	Glioblastoma	WT	R	F	12.8	9.3
16	46	F	Glioneuronal neoplasm	mutant	L	F-insular	83.1	83.1
17	77	M	Glioblastoma	WT	L	T	103	85.4
18	57	M	Glioblastoma	WT	L	O-T	50.9	43.1
19	49	F	Glioblastoma	WT	L	T	36.8	34.5
20	74	F	Glioblastoma	WT	L	F	16.4	3.4
21	56	F	Glioblastoma	WT	L	T	6.1	6.1
22	49	M	Glioblastoma	WT	L	T	13.1	7.8
23	57	M	Glioblastoma	WT	R	F	191.6	108.3

24	80	M	Glioblastoma	WT	R	O-T	17.7	17.3
25	54	F	Glioblastoma	WT	L	T	25.7	24.3
26	67	M	Glioblastoma	WT	L	F	49.3	48.1
27	64	F	Glioblastoma	WT	R	T-P	155.9	155.9
28	73	M	Glioblastoma	WT	R	F	122.3	44.7
29	57	F	Glioblastoma	WT	R	F	112.4	99.5
30	50	M	Glioblastoma	N.A.	L	F	95.1	83.3
31	64	F	Glioblastoma	WT	R	F	125.1	62.6
32	73	M	N.A.	N.A.	B	Splenium CC	37.3	36.9
33	70	M	Glioblastoma	WT	L	T	18.8	16.3

Supplementary Table 1: Single patient's demographical and clinical information. Abbreviations: Hemi=involved hemisphere, T+O volume=extent of the tumour+edema segmentation, T volume=extent of the tumour segmentation, CC= corpus callosum, F=frontal lobe, L=left, N.A.= not available, O=occipital lobe, P=parietal lobe, R=right, T=temporal lobe, WT=wild type, \=not measured)



Supplementary Figure 1: Lesion frequency map across patients. Maps are over imposed to the MNI atlas (grey scale). Radiological convention.



Supplementary Figure 2: Transition probabilities from one state (y-axis) to another (x-axis) for the two groups of healthy controls and patients separately.

<i>Jaccard</i>	<i>S1</i>	<i>S2</i>	<i>S3</i>	<i>S4</i>	<i>S5</i>	<i>S6</i>
<i>S1</i>	1	0.45	0.56	0.53	0.54	0.61
<i>S2</i>	-	1	0.61	0.46	0.52	0.45
<i>S3</i>	-	-	1	0.43	0.63	0.50
<i>S4</i>	-	-	-	1	0.44	0.42
<i>S5</i>	-	-	-	-	1	0.77
<i>S6</i>	-	-	-	-	-	1

Supplementary Table 2: The table reports the Jaccard similarity values (Jaccard) between each state modular matrix. This index ranges between 0 and 1, where a similarity of 1 means that the states share the same modular organization.

Comparison between HMM and Sliding Windows

Methods

To compare the results obtained through HMM with the gold-standard approach employed in the literature for dynamic connectivity analyses, we performed a sliding window followed by clustering analysis (SW)¹. In details, we chose a window size of 73 TR (92 seconds) and a step size of 1 TR. Thus, for each subject we obtained 584 windowed FC matrices. For each windowed FC, only the values in the upper triangular part of the matrix were retained after z-Fisher transformation. Considering both the two groups of subjects, we thus obtained a matrix of dimensions 66 subjects $\times$ 584 windows $\times$ 990 correlation values. All subjects were then concatenated prior to performing the clustering analysis, thus obtaining a matrix of dimensions 38544 $\times$ 990.

Then, a K-means clustering was performed on the windowed FC matrices (Euclidean distance, 50 repetitions, number of clusters from 2 to 10). The Silhouette criterion² was employed for the choice of the optimal cluster size. For each cluster centroid the corresponding FC matrix was created and on the same analyses performed on the brain states FC matrices were used. In particular, the FO in each centroid was computed for each subject (FO_SW) and then to compare the FO_SW among the two groups, a Wilcoxon's rank sum test followed by multiple comparison correction ($\alpha=0.05$) was applied. The graph-based analyses and the same statistical tests described before were repeated on the centroids FC matrices.

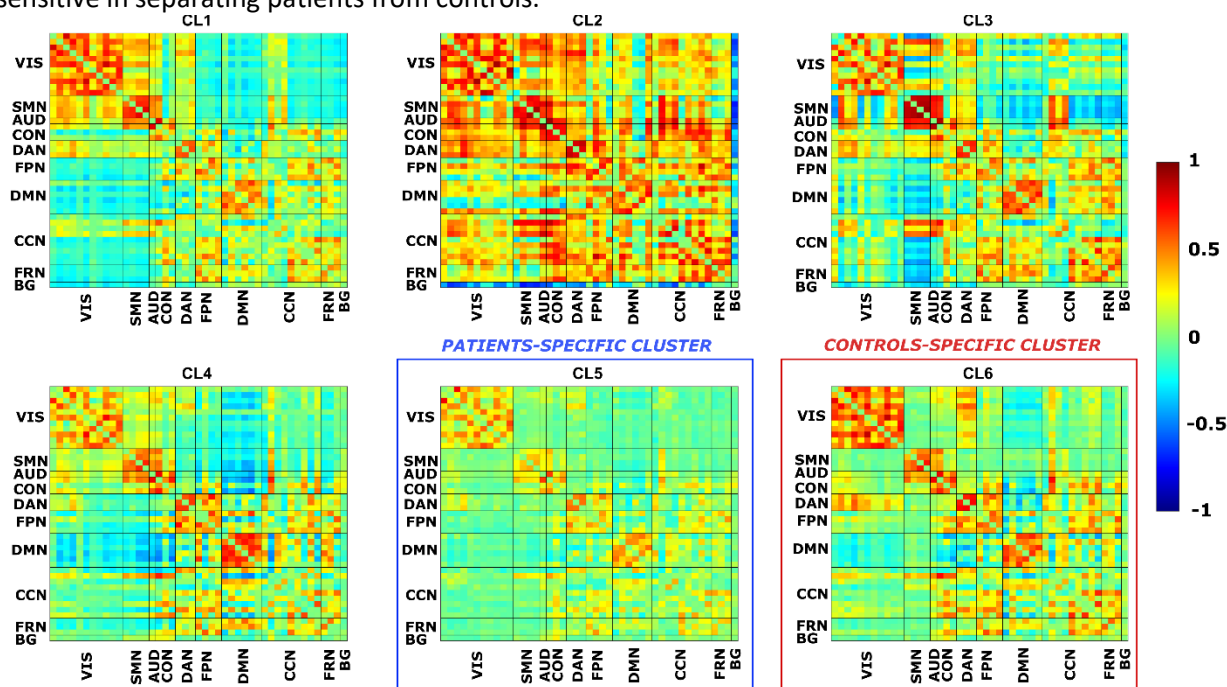
To assess whether the two approaches (i.e., HMM and SW) could give comparable results in terms of connectivity and graph metrics associated to the states or clusters centroids, we matched each HMM state with a cluster centroid on the basis of the associated FC matrix. Specifically, the Pearson's correlation and the structural similarity index between the states FC matrices and the clusters centroids FC matrices were computed.

Results

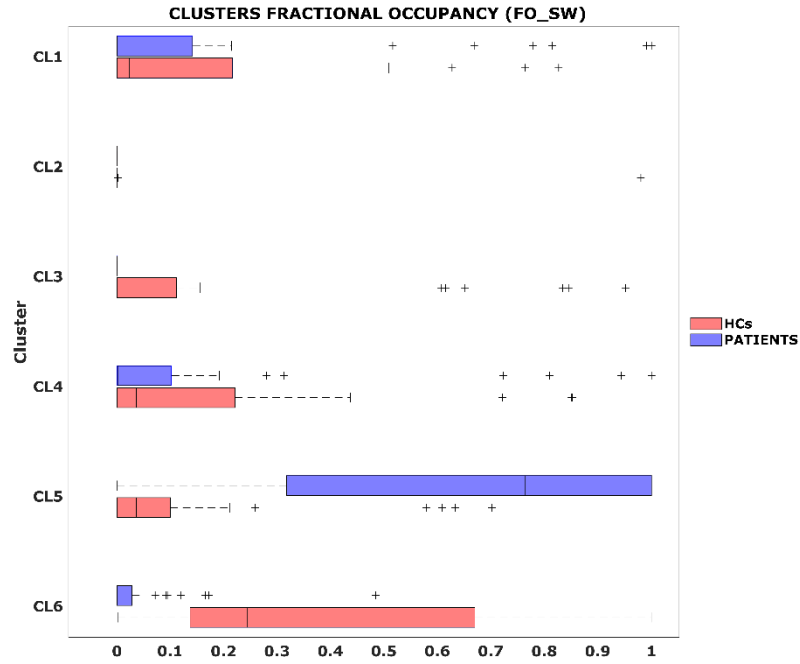
The optimal cluster size resulted to be equal to six, employing the Silhouette criterion, thus six centroids FC matrices were characterized (Supplementary Figure 3).

When we compared the FO in different clusters between the two groups, we found statistically significant differences only in two clusters over six. Cluster 5 was mostly populated by patients, while cluster 6 by HCs (Supplementary Figure 4).

The match between FC matrices obtained with the two approaches (HMM and SW), evaluated through the Pearson's correlation and the structural similarity index (Supplementary Table 3 and 4), pointed out that the pathological state S5 could be clearly associated to cluster 5, while the healthy state S2 and S3 to cluster 2 and 3. For the remaining states, only a weak association was registered. Interestingly, in cluster 5, similar to the pathological S5, a statistically significant decrease in local efficiency and clustering coefficient, but not in the degree and betweenness centrality, was found (Supplementary Figure 5). Thus, while through the HMM analysis we were able to find two pathological brain states, through the SW analysis we could only find one pathological cluster, which probably encapsulated the connectivity features of both S5 and S6. Thus, in contrast to HMM-based analysis, this approach was less sensitive in separating patients from controls.



Supplementary Figure 3: Each panel represents the FC matrix associated to a particular cluster (CL1, CL2, etc.). In both the x- and y-axis, we have the 45 ICs, divided in the 10 functional domains. Warm colors represent high positive correlations values between ICs, whereas cool colors represent high anti-correlations values. We grouped together clusters centroids mostly populated by HCs (red box) and by patients (blue box).



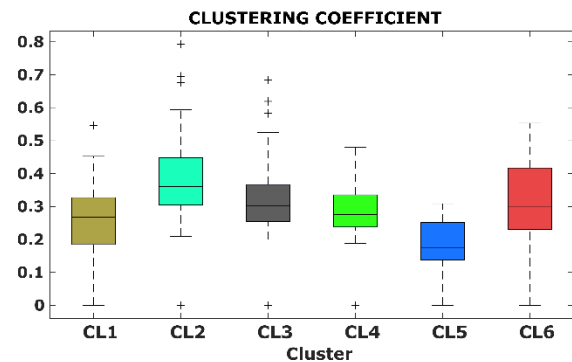
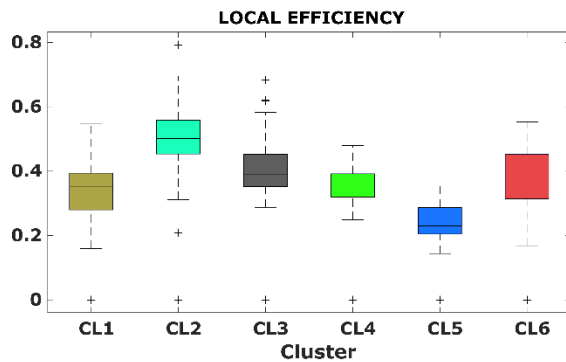
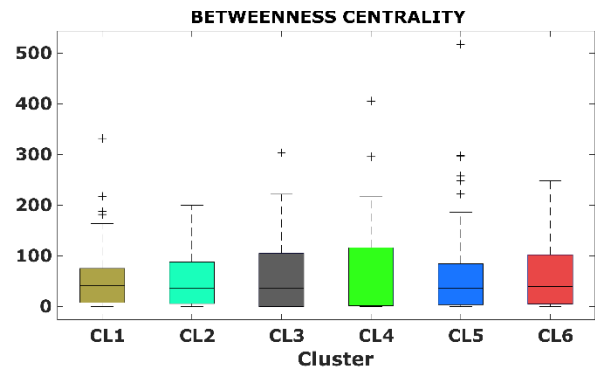
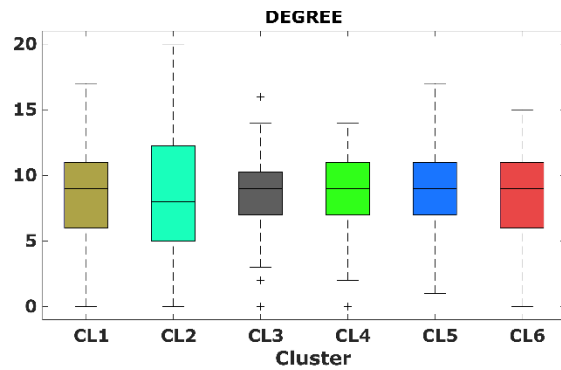
Supplementary Figure 4: The figure reports the distribution in different clusters of fractional occupancy, in blue for patients and in red for HCs. The bottom and top edges of each box indicate the 25th and 75th percentiles. The outliers are represented by the “+” symbol. In each boxplot, the solid line indicates the median.

<i>Corr</i>	<i>S1</i>	<i>S2</i>	<i>S3</i>	<i>S4</i>	<i>S5</i>	<i>S6</i>
CL1	0.58	0.58	0.59	0.59	0.61	0.62
CL2	0.55	0.66	0.62	0.60	0.60	0.58
CL3	0.54	0.61	0.58	0.61	0.61	0.60
CL4	0.49	0.48	0.54	0.44	0.52	0.53
CL5	0.63	0.61	0.67	0.57	0.72	0.68
CL6	0.71	0.68	0.74	0.65	0.73	0.70

Supplementary Table 3: The table reports the correlation (Corr) values between each FC matrix obtained through HMM and each FC matrix obtained through sliding windows. The highest values for each comparison are highlighted in bold.

<i>Ssim</i>	<i>S1</i>	<i>S2</i>	<i>S3</i>	<i>S4</i>	<i>S5</i>	<i>S6</i>
CL1	0.36	0.43	0.37	0.45	0.33	0.34
CL2	0.15	0.30	0.25	0.17	0.13	0.08
CL3	0.29	0.53	0.28	0.44	0.24	0.20
CL4	0.47	0.39	0.36	0.32	0.25	0.38
CL5	0.30	0.29	0.36	0.24	0.41	0.38
CL6	0.44	0.40	0.52	0.28	0.25	0.26

Supplementary Table 4: The table reports the structural similarity (Ssim) values between each FC matrix obtained through HMM and each FC matrix obtained through sliding windows. The highest values for each comparison are highlighted in bold.



Supplementary Figure 5: The two top panels report the distribution of the two metrics of centrality (degree and betweenness centrality), in the form of boxplot, evaluated on the sparsified FC matrices of each cluster centroid (x-axis). In the bottom panels, the distribution of the two metrics of networks segregation (local efficiency and clustering coefficient) are reported.

References

1. Allen, E. A. *et al.* Tracking Whole-Brain Connectivity Dynamics in the Resting State. *Cerebral Cortex* **24**, 663–676 (2014).
2. Rousseeuw, P. J. Silhouettes: A graphical aid to the interpretation and validation of cluster analysis. *Journal of Computational and Applied Mathematics* **20**, 53–65 (1987).